EXERCISE ON NON-INVASIVE VENTILATION (NIV) IN PATIENTS WITH SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) FROM HOSPITAL TO HOME.

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Abstract

Introduction: Patients with severe chronic obstructive pulmonary disease (COPD) experience breathlessness leading to exercise limitation and impacting on Quality of Life (QOL). Pulmonary rehabilitation (PR) may improve QOL, but those with the severest disease are frequently hospitalised and cannot readily access PR. Previous studies have trialled positive pressure as a means of relieving ventilatory load in one off exercise tests, allowing patients with more severe COPD to exercise (Maltais, Reissman and Gottfried, 1995). Other studies have assessed either mixed pathology or patients with stable COPD (Menadue, et al. 2010, Dyer et al. 2011). Therefore there was a need to investigate the feasibility of allowing patients with severe unstable COPD to exercise using non-invasive ventilation (NIV).

Aim: To evaluate the feasibility (including acceptability) of applying NIV during exercise in both the hospital environment and at home with patients who have severe COPD who had been hospitalised for an acute exacerbation with acidotic respiratory failure.

Methods: A mixed methods approach was applied. Patients were recruited when medically stable and randomised into three limbs: 1. Standard Care; 2. Exercise on NIV in hospital for length of admission and 3. Exercise on NIV in hospital and continued at home for three months. Blinding of the participants or researcher was not possible. Quantitative outcome measures were collated for all groups including: six minute walk test (6MWT); St George’s respiratory questionnaire (SGRQ); European quality of life - 5 Dimensions - 5 Levels (EQ-5D-5L); The London Chest Activity of Daily Living Questionnaire (LCADL); Borg breathlessness score (MBORG); Modified Medical Research Council (MMRC) dyspnoea score; activity levels (ActiCal monitor); self-reported medication use, access to healthcare and hospital admissions. Semi-structured interviews were performed with patients in limb three to assess acceptability.

Results: Sample size recruited for the trial was n = 18. At the end of the trial n = 15 remained (n = 6 standard care, n = 5 exercise on NIV in hospital and n = 4 exercise on NIV in hospital and home). Three patients died during the trial. No other participants dropped out of the trial. All outcome measures were completed except the activity monitor (ActiCal). There was a trend for improvement in 6MWT, SGRQ, LCADL and EQ-5D-5L in the exercise on NIV from hospital to home group. Data from the semi-structured interviews revealed that the trial was acceptable to the participants in the exercise on NIV in hospital and home group.

Conclusions: This novel trial has shown that it is feasible and acceptable to patients with severe COPD to exercise on NIV. A further multi-centre RCT is required to achieve sufficient numbers to detect whether there is statistical significance in the primary outcome of the 6MWT, to identify the clinical relevance of any changes, and to evaluate cost effectiveness.
# Contents

Abstract ........................................................................................................................................... 2  
Contents ........................................................................................................................................ 3  
List of Figures ................................................................................................................................. 19  
List of Tables ................................................................................................................................. 21  
Abbreviations ................................................................................................................................. 23  
Glossary .......................................................................................................................................... 29  
Acknowledgements ........................................................................................................................... 35  

## Chapter 1 Background .................................................................................................................. 37  
1.0 Introduction ............................................................................................................................... 37  
1.1 Chronic obstructive pulmonary disease (COPD) .................................................................. 37  
   1.1.1 Definition .......................................................................................................................... 37  
1.2 Diagnosis of COPD .................................................................................................................. 39  
1.3 Severity of COPD ..................................................................................................................... 40  
1.4 Pathophysiology of COPD ....................................................................................................... 40  
   1.4.1 Emphysema: Pathophysiology ......................................................................................... 41  
   1.4.2 Chronic Bronchitis: Pathophysiology .............................................................................. 41  
   1.4.3 Chronic Asthma: Pathophysiology .................................................................................. 41  
   1.4.4 COPD: A multi-system disease ...................................................................................... 41  
   1.4.5 COPD and skeletal muscles .............................................................................................. 42  
   1.4.6 Cardiovascular system ...................................................................................................... 42  
   1.4.7 Skeletal system ................................................................................................................ 43  
   1.4.8 Other considerations ......................................................................................................... 43  
   1.4.9 Conclusions ..................................................................................................................... 43  
1.5 Causes of COPD ....................................................................................................................... 44  
1.6 Incidence (Number of new diagnosis/year) and prevalence (% of population) of COPD ................................................................................................................................. 44  
1.7 Mortality and morbidity of COPD .......................................................................................... 45
2.9.4 How did the individual studies inform the intervention of the planned feasibility study? ................................. 154

2.10 Discussion: Part B ........................................................................................................................................... 156

2.10.1 What was the methodological quality of the individual studies?................................................................. 156

2.10.2 How did the individual studies inform the current study design?................................................................. 157

2.10.3 How did the individual studies inform the planned intervention in the future feasibility study?........... 158

2.11 Conclusion: Part B ........................................................................................................................................... 159

2.12 How did the literature reviews in part A and B combined inform the decisions for the planned feasibility study?.................................................................................................................. 160

2.12.1 Sample characteristics ........................................................................................................................................ 160

2.12.2 Recruitment .................................................................................................................................................. 160

2.12.3 Design .......................................................................................................................................................... 160

2.12.4 Outcome measure .......................................................................................................................................... 160

2.12.5 Exercise type, duration and intensity ........................................................................................................ 161

2.12.6 NIV intervention .......................................................................................................................................... 161

2.12.7 Quality and detail of reporting .................................................................................................................. 161

2.13 Overall conclusion ........................................................................................................................................... 161

Chapter 3 Methodology: Justification ................................................................................................................ 163

3.1 Introduction ...................................................................................................................................................... 163

3.2 Why mixed methods was chosen as a methodology ...................................................................................... 163

3.3 Strengths and weaknesses of quantitative design .......................................................................................... 163

3.4 Strengths and weaknesses of qualitative design ............................................................................................ 164

3.5 The merits and challenges of combining both quantitative and qualitative design .................................... 165

3.6 How to make mixed methods work ............................................................................................................... 166

3.6.1 Rationale for mixing the methods ............................................................................................................. 167
3.6.2 Types of methods ................................................................. 167
3.6.3 Priority given to qualitative or quantitative research .................. 167
3.6.4 Implementation sequence ..................................................... 168
3.6.5 Phase of study in which integration occurred .......................... 168
3.7 Justification of change of primary outcome to feasibility ............... 168
3.8 Explanation of pragmatism: To be able to use the intervention in clinical practice ................................................................. 171
3.9 Conclusion .............................................................................. 171

Chapter 4 Quantitative Methods ...................................................... 172

4.1 Introduction ............................................................................ 172
4.2 Type of study ......................................................................... 172
4.3 Commercial Funding ............................................................... 175
4.4 Ethical Approval .................................................................... 175
4.5 Ethical considerations .............................................................. 176
4.6. Research and Innovation (R & I) ............................................ 176
4.7 NHS Funding .......................................................................... 177
4.8 Choosing the ventilator ............................................................ 177
4.9 Preliminary Equipment Test ...................................................... 178
4.10 Ventilator Settings ................................................................. 178
4.11 Choosing the type of exercise .................................................. 180
4.12 Researcher consideration to reduce bias ................................. 181
4.13 Recruitment preliminary data collection .................................... 182
4.14 Stakeholder involvement and preparation ............................... 182
4.15 Randomisation ..................................................................... 182
4.16 Study Location ..................................................................... 183
4.17 Recruitment screening ............................................................ 184
  4.17.1 Inclusion criterion: ............................................................. 184
  4.17.2 Exclusion criteria: .............................................................. 184
4.18 Recruitment ........................................................................................................... 186
4.19 Baseline assessment ........................................................................................................... 187
  4.19.1 Outcome measures ................................................................................................. 187
  4.19.2 Self-reported symptom diaries .................................................................................... 187
4.20 Allocated treatment ........................................................................................................... 187
  4.20.1 Standard care ............................................................................................................. 187
  4.20.2 Exercise on NIV in hospital .......................................................................................... 188
  4.20.3 Exercise on NIV in hospital and home ........................................................................... 188
4.21 Follow up ......................................................................................................................... 188
  4.21.1 The BODE Index score ............................................................................................... 189
4.22 Outcome measures ........................................................................................................... 189
  4.22.1 Assessment of feasibility ........................................................................................... 192
  4.22.2 Clinical outcomes ....................................................................................................... 192
  4.22.3 The St George’s Respiratory Questionnaire (SGRQ) ...................................................... 196
  4.22.4 London Chest Activity of Daily Living Questionnaire (LCADL) ................................. 196
  4.22.5 The modified BORG Dyspnoea scale (MBORG) .......................................................... 197
  4.22.6 The Modified Medical Research Council Dyspnoea scale (MMRC Dyspnoea scale) .............................................................................................................................. 198
  4.22.7 The Six Minute Walk Test (6MWT) .............................................................................. 198
  4.22.8 EQ-5D-5L .................................................................................................................. 200
  4.22.9 ActiCal Data............................................................................................................... 201
  4.22.10 Daily diary of symptoms and access to health care..................................................... 202
  4.22.11 Ventilator data .......................................................................................................... 203
  4.22.12 Length of stay and therapy time .................................................................................. 203
  4.22.13 Mortality and morbidity data ...................................................................................... 203
4.23 Data Analysis .................................................................................................................. 204
  4.23.1 Feasibility analysis ....................................................................................................... 204
Chapter 5 How rigour and trustworthiness were addressed

5.14 How rigour and trustworthiness were addressed........................................219

5.14.1 Introduction..............................................................................................219
5.14.2 Sampling.................................................................................................219
5.14.3 Triangulation............................................................................................219
5.14.4 Ensuring honesty......................................................................................220
5.14.5 Frequent debriefing sessions.................................................................220
5.14.6 Researcher’s reflective commentary .......................................................220
5.14.7 Credibility................................................................................................221
5.14.8 Member checks.........................................................................................221
5.14.9 Examination of the research findings .......................................................221
5.14.10 Transferability........................................................................................222
5.14.11 Dependability........................................................................................222
5.14.12 Confirmability.........................................................................................222

5.15 Conclusion....................................................................................................226

Chapter 6 Quantitative Results...........................................................................227

6.1 Introduction....................................................................................................227
6.2 Part 1 Feasibility and Acceptability...............................................................227
6.2.1 Introduction..............................................................................................227
6.2.2 Exclusions................................................................................................229
6.2.3 Acceptability and follow up .....................................................................230
6.2.4 Feasibility of the intervention ..................................................................231
6.2.5 Ventilator data..........................................................................................231
6.2.6 Number of sessions prior to discharge .....................................................232
6.2.7 Feasibility of completion of outcome measures .......................................234
6.2.8 SAEs.........................................................................................................236
6.2.9 Hospital Admission data...........................................................................237
6.2.10 Participant diary information....................................................................239
6.2.11 Medication use.......................................................................................239
7.6 What did they not say that I had expected them to? ................................................. 296
7.7 Overall experience ........................................................................................................ 297
7.8 Summary ....................................................................................................................... 298

Chapter 8 Reflexivity ........................................................................................................ 299

8.1 Reflexivity: finding the ‘me’ in the research process ................................................. 299
8.2 Separating the self ......................................................................................................... 300
8.3 How I chose the question? .......................................................................................... 301
8.4 Reflecting on reflecting ............................................................................................... 302
  8.4.1 Tension between researcher and physiotherapist .............................................. 302
8.5 Finding my space as an interviewer? A reflection ...................................................... 304
8.6 Finding my role as analyser ....................................................................................... 306
  8.6.1 Transcribing ........................................................................................................... 306
  8.6.2 Coding .................................................................................................................... 307
  8.6.3 The findings ............................................................................................................ 308
8.7 The integration of the qualitative findings with the quantitative results .................. 308
8.8 Conclusion .................................................................................................................... 308

Chapter 9 Discussion ......................................................................................................... 310

9.1 Introduction .................................................................................................................. 310
9.2 Research Aim: Feasibility and Acceptability ................................................................. 310
  9.2.1 Recruitment sample .............................................................................................. 310
  9.2.2 Inclusion/exclusion criteria ................................................................................... 312
  9.2.3 Access to health care ............................................................................................ 312
  9.2.4 Physiotherapy input .............................................................................................. 313
9.3 Research Aim: Outcome measures and combined results ........................................ 314
  9.3.1 How do the results of the outcome measures compare to the existing literature. .................................................................................................................. 314
  9.3.1a Walking and Activity ......................................................................................... 314
9.3.1b QOL questionnaires ................................................................. 316
9.3.1c Breathlessness measures ......................................................... 317
9.3.2 Summary .................................................................................... 318
9.4 What might the findings and results mean? .................................. 318
  9.4.1 What may have contributed to this trend for improvement in
  quantitative results and qualitative findings? .................................... 318
9.5 Strengths of the study ................................................................. 319
9.6 Problems and limitations of the research .................................... 321
9.7 Implications of findings for further research ................................. 325
9.8 Implications of findings for clinicians now .................................... 326
9.9 Implications for patients .............................................................. 326
9.10 Clear vision of the future RCT ...................................................... 326
9.11 Outline of the future research protocol and justification provided
  by feasibility study ............................................................................ 329
  9.11.1a Study Ethics and procedure .................................................. 329
  9.11.1b Justification ........................................................................... 329
  9.11.2 Study objective and null hypothesis ....................................... 329
    9.11.2a Study objective ................................................................. 329
    9.11.2b Null hypothesis ............................................................... 329
  9.11.3 Study Design ......................................................................... 329
    9.11.3a Design ............................................................................. 329
    9.11.3b Justification ..................................................................... 329
  9.11.4 Research Team ...................................................................... 330
    9.11.4a Justification ..................................................................... 330
  9.11.5 Equipment ............................................................................ 331
    9.11.5a Justification ..................................................................... 331
  9.11.6 Recruitment ........................................................................... 331
    9.11.6a Screening ........................................................................ 331
**Reference List**

<table>
<thead>
<tr>
<th>Appendix</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendix 1 Literature Review Part B: Excluded studies</td>
<td>426</td>
</tr>
<tr>
<td>Appendix 2a Ethical Approval University Hospitals Bristol</td>
<td>431</td>
</tr>
<tr>
<td>Appendix 2b Ethical Approval University Hospital Bristol Amendment</td>
<td>435</td>
</tr>
<tr>
<td>Appendix 2c Ethical Approval University of Western England</td>
<td>437</td>
</tr>
<tr>
<td>Appendix 3 Participant Information Sheet</td>
<td>439</td>
</tr>
<tr>
<td>Appendix 4 Consent to study form</td>
<td>448</td>
</tr>
<tr>
<td>Appendix 5 Research and innovation permission</td>
<td>450</td>
</tr>
<tr>
<td>Appendix 6 Intellectual property contract</td>
<td>452</td>
</tr>
<tr>
<td>Appendix 7 Philips-Respironics Trilogy 100 specification</td>
<td>483</td>
</tr>
<tr>
<td>Appendix 8 Preliminary Trilogy CPET</td>
<td>484</td>
</tr>
<tr>
<td>Appendix 9 Letter to GP</td>
<td>487</td>
</tr>
<tr>
<td>Appendix 10 Trial inclusion and exclusion document</td>
<td>488</td>
</tr>
<tr>
<td>Appendix 11 Participant Diary</td>
<td>489</td>
</tr>
<tr>
<td>Appendix 12 SOP Exercise plan</td>
<td>491</td>
</tr>
<tr>
<td>Appendix 13 SOP Issuing a ventilator</td>
<td>493</td>
</tr>
<tr>
<td>Appendix 14a SGRQ Permission</td>
<td>496</td>
</tr>
<tr>
<td>Appendix 14b SGRQ Questionnaire</td>
<td>497</td>
</tr>
<tr>
<td>Appendix 15 LCADL Questionnaire</td>
<td>503</td>
</tr>
<tr>
<td>Appendix 16 Modified Borg dyspnoea scale</td>
<td>505</td>
</tr>
<tr>
<td>Appendix 17 MMRC Dyspnoea scale</td>
<td>506</td>
</tr>
<tr>
<td>Appendix 18 SOP 6MWT</td>
<td>507</td>
</tr>
<tr>
<td>Appendix 19 Interview Guide</td>
<td>513</td>
</tr>
<tr>
<td>Appendix 20 Interview transcriptions</td>
<td>514</td>
</tr>
<tr>
<td>Appendix 21 Baseline severity data</td>
<td>544</td>
</tr>
<tr>
<td>Appendix 22 6MWT Raw data</td>
<td>545</td>
</tr>
</tbody>
</table>
# List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>The overlap of disease with different pathophysiology within a COPD diagnosis</td>
<td>38</td>
</tr>
<tr>
<td>1.2</td>
<td>Spirometry demonstrating post bronchodilator FEV1 and FVC in two male patients of similar age and height, one with COPD and one patient without COPD.</td>
<td>39</td>
</tr>
<tr>
<td>1.3</td>
<td>COPD disease trajectory</td>
<td>47</td>
</tr>
<tr>
<td>1.4</td>
<td>Cycle of dyspnoea and activity avoidance (Adapted)</td>
<td>52</td>
</tr>
<tr>
<td>1.5</td>
<td>COM-B system of behaviour change Reproduced with permission of BioMed Central</td>
<td>67</td>
</tr>
<tr>
<td>1.6</td>
<td>Pressure (P) volume (V) curve of the respiratory system for a patient with dynamic lung hyperinflation</td>
<td>69</td>
</tr>
<tr>
<td>2.1</td>
<td>Literature search flow diagram</td>
<td>96</td>
</tr>
<tr>
<td>2.2</td>
<td>Flow diagram of the results of the literature search of part B</td>
<td>123</td>
</tr>
<tr>
<td>3.1</td>
<td>MRC Process for developing and evaluating complex interventions. Key elements of the development and evaluation process</td>
<td>169</td>
</tr>
<tr>
<td>4.1</td>
<td>Schematic of the research process</td>
<td>174</td>
</tr>
<tr>
<td>4.2</td>
<td>The Trilogy 100 (Philips-Respironics)</td>
<td>177</td>
</tr>
<tr>
<td>4.3</td>
<td>A) The Comfort Gel full face mask (Philips-Respironics) and B) Swift Fx nasal pillows (ResMed)</td>
<td>179</td>
</tr>
<tr>
<td>4.4</td>
<td>Diagram of the timing of outcome measure assessment</td>
<td>191</td>
</tr>
<tr>
<td>4.5</td>
<td>ActiCal Device</td>
<td>201</td>
</tr>
<tr>
<td>5.1</td>
<td>Phases of thematic analysis (TA) (Braun and Clarke, 2006)</td>
<td>215</td>
</tr>
<tr>
<td>6.1</td>
<td>The consort diagram</td>
<td>228</td>
</tr>
<tr>
<td>6.2</td>
<td>Bar chart of the number of concordance days with the ActiCal device across groups</td>
<td>235</td>
</tr>
<tr>
<td>6.3</td>
<td>6MWT means of groups. (B-Baseline, DC-Discharge, M1-Month one, M2-Month two, M3-Month three) presented with SDs.</td>
<td>254</td>
</tr>
<tr>
<td>6.4</td>
<td>6MWT total scores measured over all time points, for all participants in the standard care group, exercise on NIV in hospital and home group and exercise on NIV in hospital and home group. (B-Baseline, DC-Discharge, M1-Month one, M2-Month two, M3-Month three)</td>
<td>256</td>
</tr>
</tbody>
</table>
Figure 6.5 SGRQ results of the 3 groups mean score. (B-Baseline, DC-Discharge, M1-Month one, M2-Month two, M3-Month three)..........................257
Figure 6.6 Graph demonstrating the mean SGRQ impact scores by group. (B-Baseline, DC-Discharge, M1-Month one, M2-Month two, M3-Month three) with SDs. .................................................................258
Figure 6.7 SGRQ mean activity scores across the groups. (B-Baseline, DC-Discharge, M1-Month one, M2-Month two, M3-Month three) with SDs. ........................................................................................................259
Figure 6.8 SGRQ mean symptom score. (B-Baseline, DC-Discharge, M1-Month one, M2-Month two, M3-Month three) with SDs ..........................................................260
Figure 6.9 Graph of LCADL results mean scores by group. (B-Baseline, DC-Discharge, M1-Month one, M2-Month two, M3-Month three) with SDs .................................................................261
Figure 6.10 MMRC Dyspnoea mean score by group. (B-Baseline, DC-Discharge, M1-Month one, M2-Month two, M3-Month three) with SDs ..........................................................261
Figure 6.11 Mean MBORG breathlessness scores at rest. (B-Baseline, DC-Discharge, M1-Month one, M2-Month two, M3-Month three) with SDs ..........................................................262
Figure 6.12 EQ-5D-5L mean utility scores. (B-Baseline, DC-Discharge, M1-Month one, M2-Month two, M3-Month three) with SDs ..........................................................264
Figure 6.13 EQ-5D-5L mean group visual analogue scores (VAS) scores. (B-Baseline, DC-Discharge, M1-Month one, M2-Month two, M3-Month three) with SDs ..........................................................266
Figure 6.14 A box-plot graph to demonstrate the total daily step count between groups from discharge to month three.........................................................267
Figure 7.1 The experience of living with severe COPD ..........................................................272
Figure 7.2 The acceptability of the research and intervention ..........................................................280
Figure 7.3 Directions for clinical practice ..................................................................................290
Figure 9.1 Diagram of the future RCT ..................................................................................328
## List of Tables

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>NICE guideline 2010 of COPD severity</td>
<td>40</td>
</tr>
<tr>
<td>1.2</td>
<td>Management of COPD: Multidisciplinary approach</td>
<td>54</td>
</tr>
<tr>
<td>1.3</td>
<td>The costs of treatment of COPD (Patel and Baxter, 2014)</td>
<td>57</td>
</tr>
<tr>
<td>2.1</td>
<td>Key search terms</td>
<td>94</td>
</tr>
<tr>
<td>2.2</td>
<td>Review of SRs using the PRISMA checklist for the reporting of SRs</td>
<td>97</td>
</tr>
<tr>
<td>2.3</td>
<td>Evaluation of the quality of the SRs using the Critical Appraisal Skills Programme (CASP) tool for SRs</td>
<td>109</td>
</tr>
<tr>
<td>2.4</td>
<td>How the SRs may inform the proposed research study design</td>
<td>113</td>
</tr>
<tr>
<td>2.5</td>
<td>How did the SRs inform the proposed intervention</td>
<td>116</td>
</tr>
<tr>
<td>2.6</td>
<td>Search terms for literature review Part B</td>
<td>122</td>
</tr>
<tr>
<td>2.7</td>
<td>The description of the included studies including reporting any statistical improvement</td>
<td>125</td>
</tr>
<tr>
<td>2.8</td>
<td>The quality assessment of the individual studies</td>
<td>142</td>
</tr>
<tr>
<td>2.9</td>
<td>Combined information that informed the design of the planned feasibility study from the reviewed individual studies</td>
<td>152</td>
</tr>
<tr>
<td>2.10</td>
<td>Combined information to inform the intervention of the planned feasibility study</td>
<td>154</td>
</tr>
<tr>
<td>4.1</td>
<td>A summary of the outcome measures used in NIV on exercise in COPD</td>
<td>193</td>
</tr>
<tr>
<td>5.1</td>
<td>Adapted 15 point checklist of criteria for good thematic analysis (TA) (Braun and Clarke, 2006)</td>
<td>224</td>
</tr>
<tr>
<td>6.1</td>
<td>Reasons for patient exclusions (n = 30)</td>
<td>229</td>
</tr>
<tr>
<td>6.2</td>
<td>Other reasons patients were not included (n = 15)</td>
<td>230</td>
</tr>
<tr>
<td>6.3</td>
<td>Ventilator settings (mean ±SD) used during the trial</td>
<td>231</td>
</tr>
<tr>
<td>6.4</td>
<td>Table of acute hospital treatment received data</td>
<td>233</td>
</tr>
<tr>
<td>6.5</td>
<td>SAEs for all three groups</td>
<td>237</td>
</tr>
<tr>
<td>6.6</td>
<td>Median number of hospital admissions in all groups within the six months pre-trial, in-trial time and six months post-trial</td>
<td>238</td>
</tr>
<tr>
<td>6.7</td>
<td>Median length of stay (days) of hospital admissions between groups within the six months pre-trial, in-trial time and within the six months post-trial</td>
<td>238</td>
</tr>
</tbody>
</table>
Table 6.8 The median days increase in total patient reported extra medication use between groups over the three month trial period ............... 240
Table 6.9 Table of GP access: Recorded by participants from hospital discharge to month three ................................................................. 240
Table 6.10 Baseline characteristics. Data are shown as mean ±SD (95% CI) or median (IQR range) ............................................................. 243
Table 6.11 Other severity factors .............................................................................................................................................................................. 244
Table 6.12 Table of Mean BODE scores at baseline and % chance of mortality at 52 months. Data are mean ±SD ........................................... 245
Table 6.13 Smoking and illegal drug use within the group .............................................................................................................................. 246
Table 6.14 Body Mass Index (BMI) of the groups (mean ±SD) (World Health Organisation (WHO), 2000) ......................................................... 248
Table 6.15 Social Isolation ....................................................................................................................................................................................... 250
Table 6.16 Table of deprivation ............................................................................................................................................................................ 252
Table 6.17 Median daily step count over the three months following discharge .......................................................................................... 268
Table 6.18 Summary table of the outcome measure results in each group from baseline to month three ....................................................................... 269
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A&amp;E</td>
<td>Accident and Emergency</td>
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<td>ABG</td>
<td>Arterial Blood Gas</td>
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<td>AE</td>
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<td>Atrial Fibrillation</td>
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<td>Australian New Zealand Clinical Trials Register</td>
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<td>Ambulatory Oxygen Therapy</td>
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<tr>
<td>AT</td>
<td>Anaerobic Threshold</td>
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<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
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<td>American Thoracic Society</td>
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<tr>
<td>BiPAP</td>
<td>Bi-level Positive Airway Pressure</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index (kg.m(^2))</td>
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<td>British Thoracic Society</td>
</tr>
<tr>
<td>CAL</td>
<td>Chronic Airflow Limitation</td>
</tr>
<tr>
<td>CASP</td>
<td>Critical Appraisal Skills Programme</td>
</tr>
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<td>Cochrane Central Register of Controlled Trials</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>Cumulative Index to Nursing and Allied Health Literature</td>
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<td>Cardiac Output</td>
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<td>CO(_2)</td>
<td>Carbon Dioxide</td>
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<td>Chronic Obstructive Pulmonary Disease</td>
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<td>Continuous Positive Airways Pressure</td>
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<td>Chronic Respiratory Questionnaire</td>
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<tr>
<td>Acronym</td>
<td>Full Form</td>
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<td>DH</td>
<td>Department of Health</td>
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<tr>
<td>DLH</td>
<td>Dynamic Lung Hyperinflation</td>
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<td>Excerpta Medica Database</td>
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<td>European Quality of Life - 5 Dimensions - 5 Levels</td>
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<td>ESWT</td>
<td>Endurance Shuttle Walk Test</td>
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<tr>
<td>FEV$_1$</td>
<td>Forced Expiratory Volume in One Second</td>
</tr>
<tr>
<td>FiO$_2$</td>
<td>Fraction of inspired Oxygen</td>
</tr>
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<td>FTE</td>
<td>Full-Time Equivalent</td>
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<tr>
<td>FVC</td>
<td>Forced Vital Capacity</td>
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<td>GOLD</td>
<td>Global Initiative for Obstructive Lung Disease</td>
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<td>General Practitioner</td>
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<td>Null Hypothesis</td>
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<td>Water</td>
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<td>Hospital Anxiety and Depression Scale</td>
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<td>Haemoglobin</td>
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<td>Helium</td>
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<td>Health Related Quality of Life</td>
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<td>Interleukin 6</td>
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<td>IMT</td>
<td>Inspiratory Muscle Training</td>
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<td>IPA</td>
<td>Interpretive Phenomenological Analysis</td>
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<td>IQR</td>
<td>Interquartile Range</td>
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<td>Incremental Shuttle Walk Test</td>
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<td>Intention To Treat</td>
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<td>Intensive Therapy Unit</td>
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<td>LCADL</td>
<td>London Chest Activity of Daily Living Scale</td>
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<td>LILACS</td>
<td>Latin American and Caribbean Health Science</td>
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<td>LOS</td>
<td>Length Of Stay</td>
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<td>Long Term Oxygen Therapy</td>
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<td>LVRS</td>
<td>Lung Volume Reduction Surgery</td>
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<td>MAU</td>
<td>Medical Assessment Unit</td>
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<td>MBORG</td>
<td>Modified BORG Dyspnoea Score</td>
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<td>MCID</td>
<td>Minimum Clinically Important Difference</td>
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<td>Medical Literature Analysis and Retrieval System Online</td>
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<td>METS</td>
<td>Metabolic Equivalents (oxygen consumption at rest)</td>
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<td>MI</td>
<td>Myocardial Infarct</td>
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<td>MID</td>
<td>Minimal Important Difference</td>
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<tr>
<td>MMRC</td>
<td>Modified Medical Research Council</td>
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<tr>
<td>MRC</td>
<td>Medical Research Council</td>
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<td>MSK</td>
<td>Musculoskeletal</td>
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<td>National Health Service</td>
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<td>NIV</td>
<td>Non-Invasive Ventilation</td>
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<td>NMES</td>
<td>Neuro-Muscular Electrical Stimulation</td>
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<tr>
<td>NS</td>
<td>Non Significant</td>
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</table>
OHS  Obesity Hypoventilation Syndrome
OSA  Obstructive Sleep Apnoea
O₂  Oxygen
PaCO₂  Partial Pressure of Arterial Carbon Dioxide (kPa)
PaO₂  Partial Pressure of Arterial Oxygen (kPa)
PAV  Proportional Assisted Ventilation
PEDro  Physiotherapy Evidence Database
PEEP  Positive End Expiratory Pressure
PEEPᵢ  Intrinsic Positive End Expiratory Pressure
PEEPᵢ,dyn  Dynamic Intrinsic Positive End Expiratory Pressure
P_mask  Mask Pressure
P_oэ  Oesophageal Pressure
P_pl  Pleural Pressure
PR  Pulmonary Rehabilitation
PRISMA  Preferred Reporting Items for SRs and Meta-Analyses
PS  Pressure Support (On inspiration)
PsychINFO  Psychological Information Database
PTP_di  Pressure/Time Products of Transdiaphragmatic Pressure
PTP_ga  Pressure/Time Products of Gastric Pressure
PTP_oes  Pressure/Time Products of Oesophageal Pressure
PVD  Peripheral Vascular Disease
QALY  Quality Adjusted Life Year
QOL  Quality Of Life
R & I  Research and Innovation
RCT  Randomised Controlled Trial
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>REC</td>
<td>Regional Ethics Committee</td>
</tr>
<tr>
<td>RLU/s</td>
<td>Relative Light Units/Second</td>
</tr>
<tr>
<td>ROS</td>
<td>Reactive Oxygen Species</td>
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<tr>
<td>RR</td>
<td>Respiratory Rate</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SaO₂</td>
<td>Saturation of Arterial Blood with Oxygen (read from artery)</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SGRQ</td>
<td>The St George’s Respiratory Questionnaire</td>
</tr>
<tr>
<td>SIGN</td>
<td>Scottish Intercollegiate Guidelines Network</td>
</tr>
<tr>
<td>SMD</td>
<td>Standardised Mean difference</td>
</tr>
<tr>
<td>SpO₂</td>
<td>Saturation of Arterial Blood with Oxygen (read from pulse)</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
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<tr>
<td>SR</td>
<td>Systematic Reviews</td>
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<td>S/T</td>
<td>Spontaneous Timed</td>
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<td>SV</td>
<td>Stroke Volume</td>
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<tr>
<td>Ti</td>
<td>Inspiratory Time</td>
</tr>
<tr>
<td>TA</td>
<td>Thematic Analysis</td>
</tr>
<tr>
<td>Tₑ</td>
<td>Expiratory Time</td>
</tr>
<tr>
<td>Tlim</td>
<td>Limit of Tolerance</td>
</tr>
<tr>
<td>UAE</td>
<td>Unsupported Arm Exercise</td>
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<tr>
<td>UHBristol</td>
<td>University Hospitals Bristol NHS Foundation Trust</td>
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<tr>
<td>UMIN</td>
<td>University Hospital Medical Information Network</td>
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<tr>
<td>UWE</td>
<td>University of the West of England</td>
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<tr>
<td>Vₐ</td>
<td>Alveolar Ventilation</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Score</td>
</tr>
</tbody>
</table>
VC  Vital Capacity
VD  Physiological Dead Space
VCO₂ Volume of CO₂ (breathed out)
VE  Expired Minute Ventilation
VL  Ventilatory Limitation
VO₂ Oxygen Uptake (L.min⁻¹)
VO₂max  Maximum Oxygen Uptake
VO₂peak  Peak Oxygen Uptake
VO₂Resp  Resting Oxygen Uptake
VT  Tidal Volume
WHO World Health Organization
WLpeak  Peak Workload
Wmax  Maximum Workload
6MWT Six Minute Walk Test
12MWT Twelve Minute Walk Test
Glossary

**Acid base balance**: Blood acidity increases when the level of acidic compounds in the body increase or when the level of alkaline compounds in the body decrease (both caused by intake or production, or decreased through elimination). Blood alkalinity increases with the opposite processes. The body's balance between acidity and alkalinity is referred to as acid-base balance (Levitzky, 1991). The acidity or alkalinity of any liquid is shown on the pH scale. The blood's acid-base balance is meticulously controlled because even a slight variation from the normal range can damage organs. The aim of acid-base balance is to achieve a stable concentration of hydrogen ions in body fluids (Mosby, 2012).

**Acidosis**: Increased acidity in the blood and tissues caused by an increased hydrogen ion concentration. This causes a fall in pH to less than 7.35. If the pH of arterial blood falls below 6.8 there is irreversible cell damage and death (Levitzky, 1991).

**Accessory muscles**: These are additional muscles that assist with inspiration. They include the external intercostals, sternomastoids, trapezium, pectoralis minor and the scalene muscles (Dempsey et al., 2006).

**Airway Obstruction (airflow obstruction)**: In COPD the airways can collapse on exhalation because of a loss of stable alveolar walls, preventing air from moving out of the lungs. Additionally there may be chronic inflammation and mucus causing a blockage to the airway. In the case of COPD pathology the airway obstruction is chronic and not, or only partially, reversible. The amount of obstruction is measured by Spirometry (Mitchell, 2015).

**Anaerobic threshold (AT)**: The point during cardiopulmonary exercise test beyond which the demand of the muscles for oxygen exceeds the amount delivered to them, so that they start to add aerobic with anaerobic uptake (Dempsey et al., 2006).

**Alveolar ventilation (VA)**: Is the volume of air that reaches the alveoli and is available to take part in gas exchange (movement of oxygen into the blood and carbon dioxide from the blood). When VA is low this is referred to as hypoventilation (Dorland, 2011).
Carbon dioxide (CO$_2$): The waste gas breathed out in expiration (Mosby, 2012). CO$_2$ is essential for regulating breathing levels and maintaining body pH (Mosby, 2012). PaCO$_2$ is the partial pressure of CO$_2$ in the arterial blood, the overall blood gas pressure applied by CO$_2$. The normal level of CO$_2$ is 4.7-6.0kPa (kilopascal). High CO$_2$ levels are referred to as hypercapnia. If the CO$_2$ exceeds the normal level blood becomes more acidic (Frew and Doffman, 2008).

Carbon dioxide output (VCO$_2$): The volume of CO$_2$ (mL/min) breathed out through the lungs (Mosby, 2012).

Cardiac output: This is the volume of blood pumped by the heart per minute and is the product of the amount of blood per heart beat (called the stroke volume) multiplied by the number of heart beats in a minute (heart rate (HR)) (Aliverti and Macklem, 2008).

Cellular respiration: For muscles to contract they need energy, which they get by burning fuel. Carbohydrate is the fuel which is ‘burnt’ using O$_2$. The waste products produced are CO$_2$ and water (H$_2$O) (Levitzy, 1991).

Continuous Positive Airways Pressure (CPAP): is a mild positive pressure which splints open the airways decreasing breathing effort and allowing time for gas exchange (Kinnear, 2008).

Dead space ventilation (Vd): Not all of the air that passes the lips reaches the alveolar unit where gas exchange happens. Part of the gas from each breath remains in the conducting airways (trachea and bronchi) and therefore does not participate in gas exchange (Laszlo, 1994). Physiological dead space (Vd) is the anatomical dead space and areas of lung ventilated but not perfused so no gas exchange occurs (Laszlo, 1994).

Dynamic lung hyperinflation (DLH): This is a temporary increase in operating lung volumes above their resting values, caused by a limitation in expiratory flow (O’Donnell, Revill and Webb, 2001).

End-expiratory lung volume: The volume of air remaining in the lung at the end of spontaneous expiration. If increased this volume can contribute to gas trapping and DLH (O’Donnell, Revill and Webb, 2001).
**Exacerbation:** Increase in severity of disease and/or signs and symptoms (Kim *et al.*, 2004).

**Expiration:** Breathing out, the movement of air out of the lungs (Mosby, 2012).

**Forced Expiratory Volume in one second (FEV<sub>1</sub>):** The volume of gas exhaled in the first second following full inspiration. It is a sign of airway obstruction.

**Forced Vital Capacity (FVC):** The greatest volume of gas that can be exhaled following full inspiration by breathing out as vigorously and quickly as possible.

**Golgi tendon organ:** Is a neurotendinous organ (spindle) within the muscle sensing changes reported from the tendon regarding muscle tension and inhibits movement if tension is high to protect against injury. (American Thoracic Society (ATS), 1999)

**Humoral stimulus:** Is when a hormone is released in response to change in the blood or other body fluids (ATS, 1999).

**Hyperpnoea:** Increased depth and rate of breathing in response to exercise (Dempsey, 1985).

**Hypoventilation:** This is when ventilation is low caused by either a reduced respiratory breathing frequency (RR) or by reduced depth of breathing. It causes an increased amount of CO₂ in the blood (Frew and Doffman, 2008).

**Inspiration:** Breathing in, the movement of air into the lungs (Mosby, 2012).

**Inspiratory capacity (IC):** The maximum amount that can be inspired at the end of a tidal expiration (Laszlo, 1994).

**Inspiratory Pressure Support (IPS):** Positive pressure via a face mask to increase depth of breathing (Tidal volume (V<sub>T</sub>)) (Kinnear, 2008).

**Maximum Oxygen uptake (VO₂max):** Oxygen uptake (VO₂) is the volume of oxygen (mL/min) taken up from the lungs into the blood and utilized in metabolism in the body primarily, in mitochondria (Laszlo, 1994). The highest value of oxygen that could be used during a cardiopulmonary exercise test, rarely achieved in clinical practice. A VO₂max of < 80% predicted is abnormal. The lower the VO₂max the worse the outcome. VO₂peak is the highest value of oxygen consumption observed during an exercise test. VO₂Resp is the highest value of oxygen...

**Minute Ventilation (VE):** (L/min) sum of the volume of all the breaths in one minute. It is the product of the frequency (f) and depth of breathing (TV) (Dempsey *et al.*, 2008).

**Mitochondria:** Is a membrane bound organelle found in cells. These structures are sometimes described as "the powerhouse of the cell" because they generate most of the cell's supply of adenosine triphosphate (ATP) used as a source of energy. In addition to supplying cellular energy, mitochondria are involved in other tasks such as cell signalling, cellular differentiation, cell death, as well as maintaining the control of the cell cycle and growth (Allaire *et al.*, 2004).

**Muscle dysfunction:** Is defined as:

"the loss of at least one of the two main muscle properties: Strength and endurance. The former corresponds to the capacity to develop a short maximal contractile effort, whereas the latter is characterized by the ability to maintain a submaximal exercise load throughout a more prolonged period of time".

(Gea, Agusti and Roca, 2013, p.1222)

**Normal Quiet Breathing (NQB):** Normal breathing at rest/ relaxed breathing (Laszlo, 1994).

**Non-invasive ventilation (NIV):** Provides both inspiratory positive pressure and a continuous splinting (expiratory) pressure via a face mask (Kinnear, 2008).

**Oxygen:** O2 gas essential for the body to convert into energy for use in cell metabolism, essential for cell, tissue and organ life (Mosby, 2012). The partial pressure of O2 (PaO2) is the amount of overall blood gas pressure applied by O2. Normal PaO2 is 10.7-13.4kPa (Frew and Doffman, 2008).

**Parenchyma:** The working parts of the lung only related to gas exchange: alveoli, terminal bronchioles and vessels. However the term may include any form of lung tissue including bronchioles, bronchi and interstitium (Mattison and Christensen, 2006).

**PEEPi:** Intrinsic Positive Expiratory End Pressure (AutoPEEP) is incomplete expiration prior to the initiation of the next breath causing progressive air trapping.
(hyperinflation). This accumulation of air increases alveolar pressure at the end of expiration (Fleury, 1985).

**pH**: A figure stating the acidity or alkalinity of a solution on a scale on which seven is neutral, lower values are more alkaline. On an arterial blood gas (ABG) the normal pH is 7.35 (Mosby, 2012).

**Pleural Pressure (P_{pl})**: The pressure surrounding the lung within the pleural space (Laszlo, 1994).

**Polycythaemia**: Excessive haemoglobin and haematocrit within the red blood cells. The symptoms can be fatigue, high blood pressure and headaches. It can cause blood clots causing cerebral vascular attack (stroke), myocardial infarction (MI) (heat attack), deep vein thrombosis (leg/arm clot) and pulmonary embolism (Lung clot) (Mosby, 2012).

**Proportional Assisted Ventilation (PAV)**: Mode of ventilation via a face mask which provides inspiratory flow and volume to meet the demands of increased ventilation despite any changes in lung compliance or resistance (Hernandez et al., 2001).

**Pulmonary hypertension**: This is when the pressure in the blood vessels in the lungs (the pulmonary vasculature) is abnormally high. The pulmonary vasculature carries blood that is low in oxygen through the pulmonary arteries from the right side of the heart to the lungs. At this location red blood cells collect oxygen. The blood is then pumped back to the left side of the heart and around the body. With pulmonary hypertension the higher pressure in the blood vessels means the right side of the heart needs to work harder to pump the blood. Chronically this causes the right side of the heart to fatigue with this extra work, and pumps less effectively. The symptoms include dyspnoea, swollen ankles, fatigue, dizziness and chest pain (British Lung Foundation (BLF), 2013).

**Positive End Expiratory Pressure (PEEP)**: Applied positive pressure from a ventilator to maintain airways pressure above atmospheric pressure to stop end expiratory alveolar collapse and improve respiratory gas exchange.

**Respiratory Acidosis**: Uncompensated respiratory acidosis is when the arterial blood pH is less than 7.35 and the partial pressure of carbon dioxide (PaCO₂)
greater than 6kPa in an ABG (BTS, 2002). This condition is caused by low $V_A$ (shallow breathing). This causes $\text{PaCO}_2$ build up, which subsequently combines with water in the body to make carbonic acid, therefore reducing plasma pH. Respiratory acidosis can be caused by medullary trauma, neuromuscular disease, spinal injuries, chest injury, pneumonia, pulmonary oedema, COPD, and cardiac arrest (Mosby, 2012).

**Respiratory failure:** is defined as:

> "the failure to oxygenate the blood to achieve an arterial partial pressure of oxygen ($\text{PaO}_2$) > 8kPa whilst breathing room air at sea level (fractional inspired oxygen concentration; $\text{FiO}_2 = 0.21$). It is further sub-classified into two types, which describe the adequacy of ventilation in clearing carbon dioxide from the blood. There are two types:

Type 1: Respiratory failure without ventilatory failure and $\text{PaO}_2 < 8.0kPa$ with $\text{PaCO}_2 < 6.5kPa$

Type 2: Respiratory failure with ventilatory failure and $\text{PaO}_2 < 8.0 \text{kPa}$ with $\text{PaCO}_2 > 6.5 \text{kPa}$"

(Burt and Arrowsmith, 2009, p. 475).

**Tidal volume ($V_T$):** size of each breath or the volume of gas inspired or expired during an unforced full breathing cycle (Kinnear, 2008).

**Ventilatory Drive** (respiratory drive, or respiratory control): Process by which detected changes in the body’s hydrogen, through changes in pH and $\text{PCO}_2$ levels, are responded to by the central nervous system’s stimulation of the rhythm, effort and rate of breathing (Levitzsky, 1991).

**Ventilatory limitation (VL):** In lung disease a person will stop exercising because of VL. This is normally experienced as severe breathlessness. The person stops before maximum cardiac capacity is reached ($\text{HR} < 80\%$ predicted) (O’Donnell and Webb, 2008).

**Vital Capacity (VC):** The maximum amount of gas that can be exhaled after a maximum inhalation or inhaled following a maximal exhalation (Laszlo, 1994).

**Work load** (Maximum workload ($W_{\text{max}}$), peak workload ($W_{\text{peak}}$)): The effort during exercise testing or training. Can relate to HR, $\text{CO}_2$, metabolic equivalent of resting $\text{O}_2$ consumption (METS) and other physiological products.
Acknowledgements

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My completion of this project could not have been accomplished without the funding and support of Philips-Respironics and the NHS funded Clinical Academic Training Programme. The project relied upon the willingness and support of my Therapy management team and colleagues within the Respiratory Medicine team and Home NIV team, thank you all.
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Chapter 1 Background

1.0 Introduction

The purpose of this chapter is to provide the background to the research idea, subsequent research project and thesis. The chapter addresses the following topics:

- Introduces the epidemiology of Chronic Obstructive Pulmonary Disease (COPD) and how it impacts on the lives of patients with the condition.
- Examines the treatment options available to these patients with focus placed on discussing Pulmonary Rehabilitation (PR), including the content and structure of such intervention programmes.
- Discusses the pathophysiology of COPD and why exercise is limited.
- Explains the problems with access to PR and identifies other possible forms of delivery. One realistic treatment option discussed is non-invasive ventilation (NIV).
- Describes the history of NIV and how it is currently used and the potential for it to be used to assist PR.
- The chapter ends by summarising the thesis structure.

1.1 Chronic obstructive pulmonary disease (COPD)

1.1.1 Definition

COPD is an umbrella term used to describe numerous chronic conditions including chronic bronchitis, emphysema, chronic obstructive airways disease and chronic airflow limitation (CAL) (National Institute of Health and Care Excellence (NICE), 2010). This is illustrated in Figure 1.1
COPD is distinguished by damage to the small and large airways and lung parenchyma (lung tissue) and its vasculature, caused by chronic inflammation (NICE, 2010; O’Donnell, Revill and Webb, 2001). This causes non-reversible progressive airflow obstruction (see Glossary, p.25) demonstrated by a decline in lung function tests over time (Jones and Ostrem, 2011; NICE, 2010).

Impairments caused by COPD include airflow obstruction (difficulty exhaling air), which, in more advanced disease, occurs even during normal quiet breathing (see Glossary, p. 32); increased work of breathing; deconditioning; and skeletal muscle dysfunction (see Glossary, p. 32) (O’Donnell, Revill and Webb, 2001). This causes the symptoms of worsening breathlessness, chronic productive cough, and limited exercise tolerance (NICE, 2010) and these contribute to a negative impact on psychological state and social engagement (British Thoracic Society (BTS), 2013; O’Donnell, Revill and Webb, 2001).
1.2 Diagnosis of COPD

Diagnosis is made from a combination of clinical judgements from the patient’s presentation including patient subjective history, reported symptoms, physical assessment and spirometry testing to confirm airflow obstruction (NICE, 2010). COPD usually only occurs in people over 35 years of age and many people are not diagnosed until after they are 50 years old (NICE, 2010).

Airflow obstruction is defined as a decreased FEV₁/FVC ratio after bronchodilators (where FEV₁ is forced expired volume in 1 second and FVC is forced vital capacity, see Glossary, p. 31). If FEV₁/FVC is less than 0.7 or if FEV₁ is ≤ 80% of the predicted normal this is indicative of airflow obstruction (NICE, 2010). This is the current working definition of COPD but it is considered to be flawed and could lead to misdiagnosis, which is why history and symptoms must also be considered (Rennard et al., 2013; Qaseem et al., 2011). The differences between normal spirometry and a patient with COPD are demonstrated in figure 1.2.

![Spirometry graph](image)

**Abbreviation key:** COPD Chronic obstructive pulmonary disease, FEV₁ Forced expiratory volume in one second, FVC Forced vital capacity.

**Figure 1.2** Spirometry demonstrating post bronchodilator FEV₁ and FVC in two male patients of similar age and height, one with COPD and one patient without COPD.

Figure reproduced with permission from Dr Adrian Kendrick, Association of Respiratory Technology and Physiology, NIV course, Holiday Inn, Birmingham, COPD presentation, October 2014.
1.3 Severity of COPD

The patient must present with clinical symptoms for a diagnosis of 'mild' COPD and all diagnosed cases must have $\text{FEV}_1/\text{FVC} < 0.7$. See Table 1.1 for NICE (2010), definition of disease severity.

**Table 1.1 NICE guideline 2010 of COPD severity**

<table>
<thead>
<tr>
<th>$\text{FEV}_1$ (% predicted)</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 80</td>
<td>Mild</td>
</tr>
<tr>
<td>50-79</td>
<td>Moderate</td>
</tr>
<tr>
<td>30-49</td>
<td>Severe</td>
</tr>
<tr>
<td>&lt; 30 or &lt; 50 but with additional respiratory failure (see glossary, p. 34)</td>
<td>Very Severe</td>
</tr>
</tbody>
</table>

**Abbreviation key:** $\text{FEV}_1$ Forced expiratory volume in one second

1.4 Pathophysiology of COPD

Traditionally COPD was seen as a disease that predominantly affected the respiratory system (Calverley and Walker, 2003). However it is now known that COPD affects the skeletal muscles, the cardiovascular system and contributes to depression, weight loss and osteoporosis (Anderson and MacNee, 2009; Norwood and Balkissoon, 2005; Sin, 2003; Biskobing, 2002; Prescott et al., 2002). This is an important consideration because disability experienced does not always correspond with $\text{FEV}_1$ (Doherty, 2008). A more comprehensive assessment of severity would also include frequency of exacerbations, dyspnoea level, exercise capacity, six minute walk test (6MWT), body mass index (BMI) and evaluation of heart failure (NICE, 2010). Additionally $\text{FEV}_1$ within large powered studies has not been demonstrated to respond to medication including inhaled bronchodilators and steroids (Tashkin, Celli and Senn, 2008; Calverley, Anderson and Celli, 2007).

COPD includes three different subgroups of emphysema, chronic bronchitis and chronic asthma that overlap to a different degree in each patient, previously demonstrated in figure 1.1 (ATS, 1995). The pathophysiology of each subgroup is described below.
1.4.1 Emphysema: Pathophysiology

This is defined by abnormal, permanent widening of air spaces distal to the terminal bronchioles, with additional obliteration of alveolar walls (Mattison and Christensen, 2006). The natural elasticity of the lungs is also lost causing hyperinflation and elimination of the alveolar walls. This leads to reduced gas exchange because of a decrease in the alveolar surface area (Mattison and Christensen, 2006).

1.4.2 Chronic Bronchitis: Pathophysiology

Chronic inflammation causes an increase in mucus production, a normal defensive response. This leads to an increase in the number of goblet cells that secrete mucus, further contributing to hyperplasia of the mucus gland and resulting in infections (Innes et al., 2006). This all leads to narrowing of the small airways and airway obstruction.

1.4.3 Chronic Asthma: Pathophysiology

Pathophysiological there is smooth muscle constriction combined with inflammation of the bronchi (Fanta, 2009). Some patients may have allergic asthma which means that their airways react to allergens or irritants. In response to the allergen there is a release of histamine and prostaglandin, which cause constriction of the smooth muscle in the airway, inflammation of mucosa and increased secretion, all leading to airway obstruction (Frew and Doffman, 2008). When there is little or no reversibility of obstruction on lung function testing then asthma has evolved to become a diagnosis of COPD.

1.4.4 COPD: A multi-system disease

More recent thought is that COPD is actually a multi-system disease (Decramer et al., 2008). This is because COPD is not just associated with airway obstruction but is also an inflammatory process (Jones and Ostrem, 2011). COPD is a catabolic process and individuals are at risk of becoming underweight, which is a poor prognostic clinical feature (Chailleux, Laaban and Veale, 2003). It is well documented that COPD is associated with not only pulmonary but systemic inflammation. A systematic review (SR) by Gan et al. (2004) demonstrated increased levels of systemic inflammatory markers including C-reactive protein, IL-6 and fibrinogen in patients with COPD compared to controls. Exacerbations
further enhance this inflammation contributing to other systems being exposed to inflammation (Agusti et al., 2012). A fuller exploration of COPD pathophysiology is beyond the scope of this thesis. The reader is directed towards Calverley and Walker (2003) for a more comprehensive overview.

1.4.5 COPD and skeletal muscles

Quadriceps muscle dysfunction has been identified in patients with COPD even at the early stages of the disease (Seymour et al., 2010). This is a term used to describe the decreased muscle strength, decreased endurance and increased fatigability of the muscle (Mador, Bozkanat and Kufel, 2003; Gosselink, Troosters, Decramer, 1996). Additionally, quadriceps strength and rectus femoris muscle cross-sectional area are significantly reduced (Shrikrishna et al., 2012). Fatigue is also increased in patients with COPD compared to age matched controls (Mador et al., 2000), fatigue will be discussed further in section 1.10.3, fatigue and reduced activity in COPD. Exacerbations worsen quadriceps strength and this can persist up to one month post discharge (Crul et al., 2007; Pitta et al., 2006: Spruit et al., 2003). There are many potential causes of the decline in muscle function. Genetics, smoking, lack of oxygen (O₂), increased carbon dioxide (CO₂) leading to a pH imbalance and acidosis (these terms are explained in the Glossary on p.25, also refer to acid base balance for further information, p.28), testosterone and vitamin D deficiency have all been implicated (Barreiro and Gea, 2014). Other contributing factors to decreased quadriceps strength and reduced muscle mass are systemic inflammation, co-morbidities, exacerbations, reduced physical activity, the ageing process and medication (Shrikrishna et al., 2012; Gea, Martinez-Llorens and Barreiro, 2014; Gayan-Ramirez and Decramer, 2013; Gea, Augusti and Roca, 2013; Pitta et al., 2006; Spruit et al., 2003; Decramer, 1996). Whilst debate surrounds the cause of the changes to lower limb muscle, what is clear is that muscle strength, in particular the quadriceps, is an important systemic marker in COPD and weakness is associated with increased mortality and healthcare utilisation (Decramer et al., 1997; Swallow et al., 2007).

1.4.6 Cardiovascular system

Cardiovascular disease is more prevalent in patients with COPD than the general population (Mapel, Dedrick and Davis, 2005). Cardiovascular disease increases in severity with increasing severity of COPD (Sin and Man, 2005; Anthonisen et
It is difficult to isolate the cause of cardiovascular disease in COPD, as smoking is a confounding causal factor for both conditions (Maclay and MacNee, 2013). Other proposed causes include physiological stress on the cardiovascular system caused by low O₂ levels (Maclay and MacNee, 2013). Evidence suggests these causes relate to abnormalities of the vascular wall, and changes in cellular production, sympathetic nerve supply, atherosclerosis and heart rate (HR) (Kameda et al., 2003; Savransky et al., 2007; Aoki et al., 2001).

1.4.7 Skeletal system

Osteoporosis is a disease caused by low bone mass and destruction of the bone tissue (World Health Organisation (WHO), 1994). Osteoporosis traditionally was thought to be a later stage disease caused by smoking, steroid use, vitamin D deficiency and inactivity (Lehouck et al., 2011; Riancho et al., 1987, Seeman et al., 1983), however, research is now focusing on the presence of osteoporosis in mild cases of COPD, suggesting that physiological changes from COPD may also contribute (Bolton et al., 2009; Bolton et al., 2004). Cross-sectional population studies have demonstrated a greater prevalence of bone mineral loss in patients with COPD compared to age matched controls (Iqbal et al., 1999; Engelen et al., 1998). As the severity of COPD advances the number of patients with osteoporosis increases (McEvoy et al., 1998). The exact mechanisms for osteoporosis are unclear but it is possible systemic inflammation plays a part (Bolton et al., 2009).

1.4.8 Other considerations

Significant pathophysiology separate to the respiratory effects and co-morbidities also contribute to the severity of the disease (Jones and Ostrem, 2011). Patients with greater than two co-morbidities have a greater chance of repeated hospital admissions and may die earlier than other patients with COPD who do not have co-morbidities (Yohanne and Alexpoulos, 2014; Sode, Dahl and Nordestgaard, 2011).

1.4.9 Conclusions

Patients with COPD have a multi-system pathology (Sinden and Stockley, 2010). It is not always clear whether symptoms are caused as a direct result of COPD pathology or as a consequence of inactivity and medication. What is clear is that
outcomes for patients with COPD worsen through inactivity (Garcia-Aymerich et al., 2006). Therefore it is important that interventions consider COPD as a multi-system pathology and look at interventions that can act on multiple systems. There is little that can be done to improve lung function so interventions which seek to encourage activity should be further developed. However COPD patients may find it difficult to exercise for pathophysiological reasons, and these will be explored in the next section.

1.5 Causes of COPD

COPD is mostly caused by tobacco smoke in the western world (Pauwells and Rabe, 2004), however 20% of cases are not caused by smoking. Whilst smoking rates have declined in developing countries, they are increasing in developing countries and this means that the future prevalence of COPD may rise as smokers develop the disease (Mannino and Buist, 2007). Conversely the link between COPD and smoking is not completely understood, because only a minority of heavy smokers will go on to develop significant disease (Mannino, Brown and Giovano, 1997; Lacasse, Brooks and Goldstein, 1995). Controversially modern researchers report that COPD may in some cases have little to do with cigarette smoking. Recent research has been investigating other causes. Current research is looking at the possibility of a COPD gene (Berndt, Lerne and Shapiro, 2012). It has been argued that a large cause of COPD worldwide is the burning of biomass fuels for cooking (Salvi and Barnes, 2009). Another cause of 1-2% of emphysema is a genetic lack of alpha-1 antitrypsin, a protein that inhibits neutrophil elastase, which protects the lungs (Strange, 2013).

1.6 Incidence (Number of new diagnosis/year) and prevalence (% of population) of COPD

Globally the incidence rate is unknown as most data relates to high income countries (Gershon et al., 2010). The incidence of COPD in England is 2.0 per 1000 people per year (Simpson, Hippisley-Cox and Sheikh, 2010).

COPD has a prevalence rate of 1.6% globally (Menezes et al., 2008). Data from the quality and outcomes framework (QOF) report the prevalence of diagnosed COPD as 1.6% in England. Approximately 900,000 people have been diagnosed
with COPD in England and Wales, although it is thought that there are considerably more undiagnosed (NICE, 2010; Healthcare Commission, 2006). A study undertaken in 2006 demonstrated a prevalence of spirometry-diagnosed COPD at 13.3% within the 8215 participants (Shahab et al., 2006). There are estimated to be 2.8 million people with undiagnosed COPD in the UK (British Lung Foundation (BLF), 2007). 10% of patients with COPD are first diagnosed when they attend hospital as an emergency (National Health Service (NHS) Medical Directorate, 2012).

Prevalence is increasing in women while it has levelled out in men (Global Initiative for Obstructive Lung Disease (GOLD) 2016; NICE, 2010). COPD is also more common in more disadvantaged areas (Department of Health (DH), 2011b; NICE, 2010). Prevalence increases with age and it is not commonly seen in people under 35 years of age (Pauwells and Rabe, 2004).

1.7 Mortality and morbidity of COPD

COPD is associated with high mortality and morbidity rates (Mathers and Loncar, 2006; Jemal et al., 2005). Globally COPD is the fourth leading cause of death and is predicted to be the third by 2030 (Mathers and Loncar, 2006), and it kills more people each year than any other non-communicable chronic disease (Jamal et al., 2005). COPD is the fifth most common reason for death in England and Wales, causing more than 25,000/year (DH, 2011b). Death rates for COPD in the UK are higher than the European and European Union averages (NHS Medical Directorate, 2012). The disease is the second leading cause of emergency admission in the UK and patients with COPD occupy over one million 'bed days' yearly in hospitals in the UK (NICE, 2010).

1.8 Economic Cost

There is a high medical and social economic cost. COPD is challenging to diagnose, medications are expensive, repeated worsening flare ups are costly and there are social costs from patients not being able to work and having increased social care needs (Simeons, 2010).

The medical cost is high because of the need for substantial and ongoing medical treatment. The total annual cost of COPD to the NHS is estimated to be over £800
million for direct healthcare costs, which equates to £1.3 million per 100,000 people (Health Care Commission, 2006).

In the late 1990s, 24 million working days per year were lost due to COPD, and the cost of lost productivity has been estimated at around £2.7 billion (DH, 2010b). 44% of people diagnosed with COPD are below the retirement age, 24% of these are unable to work because of their symptoms, and a further 9% are limited at work because of COPD (DH, 2010a). The number of lost working days through people of working age caring for patients with COPD is unknown (Britton, 2003). There are other social costs related to decreased quality of life (QOL). Restricted mobility leads to social isolation and the development of psychological conditions (DH, 2010b). A BLF survey found that 90% of participants felt that they could not contribute to society (BLF, 2007).

There is limited evidence about the overall costs of treating COPD exacerbations or ‘flare ups’. This is because there is a discrepancy on what constitutes an exacerbation, how this may be recorded, and variability in possible treatment (Simoens, 2010). A study in the NHS demonstrated that the total primary care cost associated with acute exacerbations of chronic bronchitis in the COPD-diagnosed population was £35.7 million (McGuire et al., 2001) compared to total annual cost of COPD at £491,652,000 direct costs and £982,000 indirect costs (24 million lost work days) (Healthcare commission, 2006). The cost of COPD per patient per year is £819.42 (54% hospital care, 18.6% medication, 16.4% General Practitioner (GP) visit, 57% Accident and Emergency (A&E) visit and 5% laboratory tests) (Britton, 2003). Punekar, Shukla and Mullerova (2014) suggest from their observational study that the overall cost increases with increasing disease severity. It is thought that to reduce the cost of this disease future management should focus on prevention of exacerbations requiring hospitalisation (Punekar, Shukla and Mullerova, 2014).

1.9 The clinical course of COPD

The clinical course of COPD over time is progressive because it causes increasing airflow obstruction, demonstrated in declining lung function and an abnormal inflammatory reaction in the lungs to noxious gases (GOLD, 2015; Fletcher and Peto, 1977). Severity is also affected by co-morbidities, age, and systemic changes (Jones and Ostrem, 2011; Decramer et al., 2008).
1.9.1 Early symptoms

The initial symptoms are often an unproductive cough and breathlessness (Georopoulos and Anthonisen, 1991). However most patients do not present at their GP until their breathlessness is disrupting activities of daily living (Pauwells and Rabe, 2004). The breathlessness on exertion results in less everyday activity. The continued inactivity causes deconditioning of muscles and further inactivity leading to social isolation (GOLD, 2015; Decramer, Rennard and Troosters 2008). This is discussed further in section 1.10 on living with the disease. As the disease progresses, weight loss and anorexia are common symptoms (Schols et al., 1993). In advanced COPD patients commonly develop cor pulmonale, an alteration of right cardiac ventricular function, with right ventricular dilation and hypertrophy as a result of secondary pulmonary hypertension (Calverley, 1996). The presence of right sided heart failure decreases the 5 year survival rate to only 27-33% (MacNee, 1994).

1.9.2 Exacerbation

COPD has a fluctuating progressive trajectory (Murray, Kendall, Boyd and Sheikh, 2005) caused by repeated exacerbations (Pauwels et al., 2001). See figure 1.3 for a diagram of the disease course.

![Figure 1.3 COPD disease trajectory](http://www.ncbi.nlm.nih.gov/pubmed/?term=lehman+2004+Dec+Br+J+Gen+Pract#)
Exacerbations are defined as an acute onset of continued worsening of symptoms beyond those normally experienced that need additional medical treatment (GOLD, 2015; Burge and Wedzicha, 2003). However, every patient’s symptoms are different, making it difficult to standardise classification of an exacerbation. This has implications for the way the illness may be coded, leading to a discrepancy in hospital data (Lopez-Campos, Caleu and Quintana-Gallego, 2013; Stein et al., 2010). As COPD progresses the frequency and severity of exacerbations increases (Burge and Wedzicha, 2003). COPD patients typically suffer from one to four exacerbations per year, with the frequency of exacerbations increasing with the severity of COPD (Simeons, 2010).

Exacerbations are correlated with persisting deteriorating symptoms and health-related QOL, increased healthcare consumption and death (BTS, 2013). Exercise ability and physical activity are reduced during and after an exacerbation, causing skeletal muscle dysfunction, especially of the legs (BTS, 2013). Severe exacerbations present with Type II respiratory failure and an acidotic pH on arterial blood gas (ABG). If not corrected this can lead to cell death and organ failure (Calverley and Gorini, 2008).

1.9.3 Respiratory failure

During acute respiratory failure, respiratory rate (RR) increases causing expiratory time to decrease which adds to an increase in lung volume and intrinsic positive end expiratory pressure (PEEPi) (see Glossary, p. 33), which can lead to decreased cardiac output (see Glossary, p. 30) (Fleury et al., 1985). For patients in uncompensated respiratory failure, who do not respond to standard care of oral steroids, antibiotics and bronchodilators it has been recommended that NIV (see Glossary, p. 32) is used (NICE, 2010; Royal College of Physicians, 2008; BTS, 2002).

1.10 Living with the disease

As the symptoms worsen, QOL is impaired and sleep may be disturbed (Calverley and Walker, 2003). Patients become unable to carry out everyday activities, including work and participating in social activities, leading to reduced social interaction. Anxiety and depression may emerge as the patient becomes
increasingly isolated and physically disabled by their disease (BTS, 2013; Wagena et al., 2005).

1.10.1 Stigma

In one interview study participants with COPD expressed a prevalence of blame towards them related to their smoking. This was experienced from others including health care workers and inwardly they blamed themselves (Berger, Kapella and Larson, 2011). Symptoms of COPD can be embarrassing for patients to deal with publicly, extending to their medications including inhaler use and O₂ outside of the home (Johnson et al., 2007; Earnest, 2002). Patients with COPD are particularly embarrassed by their physical limitations especially to do with falling behind others (Berger, Kapella and Larson, 2011). Stigmatisation may contribute to social isolation and depression, further contributing to inactivity (Berger, Kapella and Larson, 2011).

1.10.2 Anxiety and depression

A recent literature review of the prevalence rate of anxiety within the COPD population identified rates between 6-74% (Yohannes, Willgoss and Baldwin, 2010). It has been suggested that the vast variation in prevalence rate may have been because of poor methodological quality of the studies and the differences in the objective measures used, with up to 13 different types used, including the Hospital Anxiety and Depression Scale (HADS) and the Anxiety Based Interview Schedule (Vogele and von Leupoldt, 2008). An alternative suggestion is that it is difficult to distinguish between symptoms of anxiety and those of respiratory disease. The presence of anxiety (assessed by HADS and Spielberger State Trait Anxiety Inventory) and COPD is associated with reduced functional status and QOL (St Georges Respiratory Questionnaire (SGRQ), lower walking distance (6MWT) and lower ergometer peak workload (WL_peak) (Giardino et al., 2010; Di Marco et al., 2006). Anxiety can also lead to more utilisation of health services, increased risk of exacerbation and readmission to hospital (Laurin et al., 2012; Laurin et al., 2009). There is little research investigating anxiety and physical activity in patients with COPD, however one study found an association between increased anxiety and increased activity levels (Nguyen et al., 2013). It is unclear whether the anxiety caused the increased levels of activity or being more active made the participants more anxious (Nguyen et al., 2013). In depth interviews
with patients with COPD showed that some participants were afraid of carrying out activity for fear of the breathlessness it may cause and thus avoided activities. Planning their days to avoid activities however made them feel more frustrated and anxious (Willgoss et al., 2010).

The prevalence of depression in patients (assessed using the Centre for Epidemiological Studies Depression score; Geriatric Depression Scale; Geriatric Mental State Schedule; Brief Assessment Schedule Depression Cards) with COPD is reported as between 10-42% (Maurer et al., 2008; van Manen et al., 2002; Lacasse, Rousseau and Maltais, 2001; Yohannes et al, 2000). The prevalence is so variable because of the different use of outcome measures and variation of disease severity in the studies. Depression is almost twice as likely to occur in patients with COPD compared to an aged matched cohort (Ng et al., 2007). Depression is undertreated in patients with COPD, with an estimate that only one third of patients with depression receive the correct treatment (Kunik et al., 2005; Kim et al., 2002). Depression leads to lower treatment adherence, reduced walking distance (12 minute walk test (12MWT) and decreased QOL (Hopkins Symptoms Checklist-20; Medical Outcome Short Form - 36) (Felker et al., 2001; Bosley et al., 1996; Light et al., 1985).

Depressed patients with COPD have a diminished daily and maximum exercise capacity when compared to non-depressed patients with COPD (di Marco et al., 2014). Anxiety and depression cause decreased QOL and decreased concordance with medication (Yohannes, Wilgoss and Baldwin, 2010). Patients with anxiety and depression have a greater chance of re-hospitalisation and mortality (Ng et al., 2007; Gudmundsson et al., 2005; Dahlen and Jansen, 2002). Harris et al., (2008) reported that patients with COPD who scored highly for anxiety and depression were more likely to report breathlessness and to be afraid of exercise, regardless of their Medical Research Council (MRC) breathlessness score.

1.10.3 Fatigue and reduced activity in COPD

Fatigue is the second most common symptom in patients with COPD after dyspnoea (Blinderman, Homel and Billings, 2009). Fatigue is more prevalent in patients with COPD than in the general population (Lewko, Bidgood and Garrod,
2009) and leads to an increased hospitalisation risk (Paddison et al., 2013). This fatigue could make participating in physical activity more difficult.

QOL and exercise tolerance are commonly reduced and physical activity levels are lower compared with those of healthy people of a similar age (Menadue et al., 2014; Pitta et al., 2005). The literature demonstrates that reduced activity in patients with COPD leads to reduced exercise capacity, less QOL, higher use of healthcare including hospital admissions and reduced life expectancy (Watz et al., 2008; Garrod et al., 2006; Pitta et al., 2006; Garcia-Aymerich et al., 2006).

Exacerbations have a detrimental effect on physical activity. This is because there is less time spent by a patient outdoors immediately prior to an exacerbation and for up to five weeks after an exacerbation (Pitta et al., 2006; Donaldson et al., 2005). Physical activity deteriorates with disease progression (Watz et al., 2009).

1.11 Dyspnoea - breathlessness

Breathlessness is defined as:

“A subjective experience of breathing discomfort that is comprised of qualitatively distinct sensations that vary in intensity”


Dyspnoea is the main symptom of COPD (Viegi et al., 2007) and is more common in severe disease (Killian et al., 1992). Patients frequently describe their dyspnoea as a sense of increased effort to breathe, heaviness, air hunger, gasping and suffocation (Strang, Ekberg-Jansson and Henoch, 2014; Simon, 1989). Patients with COPD often experience anxiety in combination with their breathlessness (Strang, Ekberg-Jansson and Henoch, 2014). This experience is greater than in other pathologies (Pantilat et al., 2012; Bausewain et al., 2010; Gore et al., 2000). In interviews with patients with very severe COPD the fear of breathlessness meant that the participants did not take part in usual activities or leave the house. Shortness of breath, fatigue and a lack of energy were reported as making it impossible for the participants to perform their activities of daily living (Stranng, Ekberg-Janssson and Henoch, 2014).
1.11.1 Patient Management of Breathlessness

Dyspnoea can lead to a cycle of activity evasion, deconditioning and reduced participation in activities (Garrod et al., 2006). This is illustrated in figure 1.4.

![Cycle of dyspnoea and activity avoidance (Adapted)](image)

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**Figure 1.4 Cycle of dyspnoea and activity avoidance (Adapted)**


Interviews with patients with severe COPD demonstrated that patients used individual strategies to manage their breathlessness including slowing the pace of activities, sitting down for activities, controlled breathing exercises and activity avoidance (Dunger et al., 2015; Stranng, Ekberg-Jansson and Henoch, 2014).

The importance of exercise as an intervention will be discussed later (section 1.15.2 Why PR is beneficial), but it seems appropriate that interventions should seek to address the anxiety and symptoms of becoming breathless on exercise, as this may encourage the patient to participate in exercise.
1.12 Social Deprivation

COPD is related to poverty with an increased prevalence in lower socio-economic groups. Factors associated with poverty include poor diet, damp housing and increased frequency of chest infections (Russell et al., 2011). Deprivation has been linked with increased mortality in outpatients with COPD after one year (Collins et al., 2010). There is also an increased risk of exacerbation and admission to hospital with lower social economic status (Calderon-Larranaga et al., 2010; Healy, 2003). Smoking is associated with deprivation leading to overall worse outcomes (Shohaimi et al., 2013; Osman et al., 2007).

1.13 Treatment and management of COPD

1.13.1 Introduction

A number of national and international respiratory societies have developed guidelines for the management of COPD. The Global Initiative for Chronic Obstructive Pulmonary Disease (2015) guidelines are internationally recognised and were developed jointly by the National Heart Lung and Blood Institute and the WHO to increase awareness of COPD (GOLD, 2015). Additional guidance was developed by the International Primary Care Respiratory Group based on five recommendations but with the aim of being more appropriate to the primary care physician (Jones and Ostrem, 2011; Bellamy et al., 2006).

Although there is no known cure for COPD (Jones and Ostrem, 2011) the main effective interventions in the treatment of COPD exacerbations are increased doses of inhaled bronchodilators, systemic corticosteroids, antibiotics and NIV for respiratory failure (NICE, 2010). Advice on smoking cessation is also important (Willems et al., 2004; Scanlon et al., 2000) as 33% of all COPD patients in the UK continue to smoke (NICE, 2010). The management recommendations for each stage of disease severity is demonstrated in table 1.2 (GOLD, 2015).
Table 1.2 Management of COPD: Multidisciplinary approach


<table>
<thead>
<tr>
<th>Stage of COPD Severity: GOLD</th>
<th>Lung Function</th>
<th>Management</th>
<th>Clinician</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild: GOLD I</td>
<td>FEV₁/FVC &lt; 0.7 and FEV₁ &gt; 80% of predicted with or without symptoms</td>
<td>Spirometry testing Smoking cessation Vaccination Flu/pneumonia</td>
<td>GP Physiologist Respiratory nurse Physiotherapist</td>
</tr>
<tr>
<td>Moderate: GOLD II</td>
<td>FEV₁/FVC &lt; 0.7 and FEV₁ 50-80% of predicted</td>
<td>Short-acting bronchodilators PR Nutritional advice</td>
<td>GP Pharmacist Physiotherapist Diabetician</td>
</tr>
<tr>
<td>Severe: GOLD III</td>
<td>FEV₁/FVC &lt; 0.7 and FEV₁ 30-50% predicted</td>
<td>Long acting bronchodilators and inhaled corticosteroids PR</td>
<td>Respiratory consultant GP Physiotherapist</td>
</tr>
<tr>
<td>Very Severe: Gold IV</td>
<td>FEV₁/FVC &lt; 0.7 and FEV₁ &lt; 31% of predicted or presence of respiratory failure or right sided heart failure</td>
<td>O₂ Therapy Surgery End of life management</td>
<td>GP Thoracic Surgeon Palliative care Social services</td>
</tr>
</tbody>
</table>

**Abbreviation Key:** GOLD Global Initiative for chronic obstructive lung disease, FEV₁/FVC Forced expiratory volume in one second/ forced vital capacity, O₂ Oxygen

### 1.14 Medication

Maintenance medication consists of both short and long acting bronchodilators and inhaled steroids to relieve the symptoms of airways obstruction where it is still reversible (NICE, 2010). It is now thought these should be initiated at the very early stages of disease (Jones and Ostrem, 2011).
1.14.1 Long term O\textsubscript{2} therapy (LTOT) and ambulatory O\textsubscript{2} (AOT)

There are two well publicised RCTs demonstrating that 15 hours per day of LTOT improves survival in patients with COPD and hypoxaemia (low concentration of O\textsubscript{2} in the blood, (Mosby, 2012; Medical Research Council Working Party, 1981; Nocturnal oxygen therapy group, 1980). LTOT is indicated in patients with a PaO\textsubscript{2} < 7.3kPa, peripheral oedema (seen as swollen ankles), pulmonary hypertension (pulmonary artery wall damage causing right sided heart failure, see Glossary, p.33) and polycythaemia (Increased quantity of haemoglobin (Hb) in the blood, this can thicken the blood, see Glossary, p. 33) (BTS, 2015). However the effects of LTOT on QOL are inconclusive. In one trial there were no statistically significant changes in QOL (SGRQ) scores demonstrated in patients with COPD six months after starting LTOT (Okubadejo et al., 1996) compared to a trial by Borak et al. (1996) which demonstrated a significant improvement in mood after one year of initiating LTOT. From the literature one study undertook in-depth interviews with people who had been carers of recently deceased patients with COPD, reported that although LTOT improved symptoms and mobility in the home, the cylinders used meant that the patients did not like to be far from their O\textsubscript{2} source and felt restricted (Elkington et al., 2004).

AOT is used during exercise and activities of daily living (BTS, 2015). The addition of AOT during exercise can improve exercise tolerance and dyspnoea during exercise programmes. It is recommended for use if patients decrease their SpO\textsubscript{2} during exercise training (BTS, 2015; Bradley et al., 2007; Nonoyama et al, 2007; Bradley and O'Neill, 2005), however the disadvantages of using the O\textsubscript{2} cylinders may outweigh the benefits. A large double blinded placebo controlled RCT involving n = 139 participants with stable COPD with PaO\textsubscript{2} > 7.3kPa comparing O\textsubscript{2} via cylinder with air via a cylinder at 6L/minute for use on any activity that provoked dyspnoea. The study demonstrated no improvements in dyspnoea, QOL or functional capacity with the use of O\textsubscript{2} (Moore et al., 2011). Additionally at the end of the trial, when surveyed, 50% of the participants reported difficulties using the equipment and 46% of the O\textsubscript{2} group reported that they would prefer to stop using the O\textsubscript{2} altogether. Some participants felt embarrassed using the cylinders and were anxious of becoming dependent on them. Interestingly the use of the air cylinders provided similar comments. Therefore it may be the weight and type of cylinder that limited beneficial use (Moore et al., 2011).
When considering interventions for patients with severe COPD, it is therefore important that the intervention improves QOL and does not add to the burden of disease, whilst maintaining activity levels. If an intervention is proven to decrease hospital admissions and length of stay then this may have a positive effect on improving QOL. PR is an intervention that can improve health status and walking distances (McCarthy et al., 2015). PR will be discussed in depth in the next section.

1.15 Pulmonary Rehabilitation (PR)

1.15.1 What is PR?

PR describes programmes that are designed to provide a structure for the delivery of physical training sessions for patients with COPD. PR also includes education sessions on disease, nutrition and medication. The primary aim of PR is to improve the symptoms of patients with COPD (BTS, 2013).

1.15.2 Why is PR beneficial?

There is very good quality evidence to support the effectiveness of exercise training within PR on exercise capacity (BTS, 2013). The most recent SR included 65 RCTs involving 3822 participants with COPD for meta-analysis (McCarthy et al., 2015). This demonstrated that PR in comparison to usual care offered clinical and statistical improvements in 6MWT and health-related QOL including dyspnoea, fatigue and emotional function (McCarthy et al., 2015). The limitations of most of the studies are that they were all unblinded due to the nature of the intervention, potentially leading to bias, and most of the sample were men which may not be reflective of today’s COPD population (McCarthy et al., 2015; NICE, 2010). The current evidence supports the use of PR in patients with COPD, however more research is needed into the content and structure of PR.

Dyspnoea and health status is also improved by PR, with a meta-analysis of twenty trials using SGRQ (McCarthy et al., 2015). The minimal clinically important difference (MCID) was defined as the smallest difference in a measurable clinical parameter that indicates a meaningful change in the patient’s condition (either better or worse) decided by the patient, clinician or researcher (Kiley et al., 2005). The meta-analysis demonstrated that the weighted mean difference was greater than the MCID of 4 units for total, symptoms, impact and activity domains.
(McCarthy et al., 2015). The weighted mean difference is often used in meta-analysis when comparing the average difference between the treatment group and the control group across studies. Within mean weighted analysis some of the studies contribute more to the average than others (Cochrane Library, 2012). Physiological benefits of exercise training in rehabilitation of patients with COPD include reduced HR, minute ventilation (Ve) (see Glossary, p. 32) and acidosis, and superior action of mitochondrial enzymes (see Glossary, p. 32) with increased capillary concentration in trained muscles (Cassaburi et al., 1997). More recently research has identified that PR decreases the frequency of hospital admissions following an exacerbation (Puhan et al., 2011). PR may improve activity levels, as demonstrated by a recent SR, but further evidence is needed because of a lack of comparison control groups (Cindy et al., 2012). A large RCT also demonstrated improvement in psychological health with improvements in anxiety and depression (Griffiths et al., 2000).

PR also appears to represent good value for money compared to many drug treatments (see table 1.3).

**Table 1.3 The costs of treatment of COPD (Patel and Baxter, 2014)**

<table>
<thead>
<tr>
<th>Ranking (cost)</th>
<th>Treatment</th>
<th>Cost (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Telehealth</td>
<td>92,000</td>
</tr>
<tr>
<td>2.</td>
<td>Triple Therapy</td>
<td>7,000-187,000</td>
</tr>
<tr>
<td>3.</td>
<td>Long acting Beta-agonist medication</td>
<td>8,000</td>
</tr>
<tr>
<td>4.</td>
<td>Tiotropium (bronchodilator to relax smooth muscle in airway, opening the airway)</td>
<td>7,000</td>
</tr>
<tr>
<td>5.</td>
<td>PR</td>
<td>2,000-8,000</td>
</tr>
<tr>
<td>6.</td>
<td>Smoking cessation support with medication</td>
<td>2,000</td>
</tr>
<tr>
<td>7.</td>
<td>Flu vaccination</td>
<td>1,000 (in at risk population)</td>
</tr>
</tbody>
</table>

**Abbreviation Key:** PR Pulmonary rehabilitation, QALY Quality adjusted life year.
There are many problems with medication including non-adherence (Rand et al., 1995; Dolce et al., 1991), side effects (Calverley et al., 2007; Reilly, 2014) and poor administration techniques (Vincken, Dekhuijzen and Barnes, 2013). Therefore PR provides a more cost effective treatment, although despite the benefits and low cost of PR it is still under-utilised in patients with COPD (see section 1.15.10) (Yohannes and Connolly, 2004; Brooks et al., 2007; Puhan et al., 2011).

1.15.3 What should the duration of the training programme be?

Three studies have assessed rehabilitation duration and demonstrated greater improvement in health status and function in the groups carrying out rehabilitation of a longer duration (Berry et al., 2003; Foy et al., 2001; Swerts et al., 1990). Longer training duration may be more beneficial for the patients with more severe disease who are more deconditioned. One RCT indicated that 18 months duration of a supervised exercise programme may be more beneficial than three months. The study demonstrated improvements in self-reported disability scores and physical function compared to three months (Berry et al., 2003). Therefore it is recommended that PR duration be longer than three months if costs allow (BTS, 2013), however a longer training programme may have a cost and resource implication which has not been evaluated.

1.15.4 How many sessions should there be?

The BTS PR quality standards (2014) suggest that based on available evidence, programmes should consist of a minimum of two supervised sessions per week for at least six weeks. The most beneficial number of supervised sessions during a programme of PR has not been confirmed in the literature. McCarthy et al. (2015) SR and Griffiths et al. (2000) RCT supported the benefits of PR incorporated two supervised sessions and either a third supervised or unsupervised exercise session.

1.15.5 Type of training

It has been suggested that the exercise component of PR may consist of strength and endurance training in the form of progressive muscle resistance exercises and aerobic training (BTS, 2013). Lower limb endurance training commonly includes either walking or cycling. This is to target lower limb weakness that may
be associated with a poor prognosis (Swallow et al., 2007). Walking and cycling may be easily reproduced in an outpatient environment although they may not be considered as enjoyable by some patients as other pursuits, which may lead to a reduction in motivation, which in turn can lead to reduced exercise tolerance (ATS and ERS, 2006). One RCT considered Nordic walking as an alternative means of delivering PR in a three month programme. The Nordic walking group improved their 6MWT distance compared to baseline and control group, this was sustained at six to twelve months post completion of the course (Breyer et al., 2010).

Another possible means of exercise is Tai Chi Qigong which incorporates breathing and whole body movement. An RCT compared Tai Chi Quigong with a walking group and a control group. Tai Chi increased the mean 6MWT distance from 298 to 349 m. This was significantly greater than the walking or control group (Chan et al., 2013), however a limitation was the high drop-out rate in the control group. A potential problem with more specialist exercise regimens are that they often need skilled practitioners to deliver and may require space or equipment not readily available.

In summary, the exercise component of PR may consist of progressive muscle resistance exercise and aerobic training. This could include cycling or walking. A patient’s preference for exercise should be considered when planning the exercise to facilitate motivation to exercise.

1.15.6 Training Intensity

It is recommended that the exercise programme should also be individualised in terms of training intensity. Vallet et al., (1997) carried out an RCT demonstrating the importance of individualised training for patients with chronic airflow limitation (CAL) (synonymous with COPD). In this study, patients with COPD were randomly allocated to four weeks of individualised ($n = 12$) or standardised ($n = 12$) stationary bike training. The individualised training was carried out at the individually measured gas exchange threshold (anaerobic threshold), and in the standardised group was carried out at 50% of the calculated maximal HR reserve. The results demonstrated that the target training level was similar between the two groups, however there were greater physiological improvements demonstrated in the individualised group (greater submaximal cardiorespiratory responses with lower ventilation). Therefore the results of this study suggest that
Individualised training may lead to greater physiological improvements than standardised programmes.

The BTS PR guidelines (2014) recommend a minimum target intensity of 60% peak work rate, however the optimum intensity is unknown. The recommended duration of the exercise is between 30 - 60 minutes per session. Some patients with severe disease may not be able to exercise for 30 minutes and shorter sessions will still be beneficial (BTS, 2013). Although there is weak evidence for resistance training it can be used within PR programmes. Muscles trained should include quadriceps, with individualised weights of two to four sets of 10 - 15 repetitions (BTS, 2013; O’Shea, Taylor and Paratz, 2009; Houchen, Steiner and Singh, 2009). To achieve the physiological benefits, patients need to train at a level which exceeds their anaerobic threshold (see Glossary, p. 29). High-intensity exercise training may produce greater physiological improvement compared with lower-intensity exercise training in people with COPD (Gimenez et al., 2000; Casaburi et al., 1991).

Severe COPD patients are unable to train at this level due to ventilatory limitation (VL) (Casaburi, et al., 1997). Some individuals may have difficulty performing exercise at an adequate intensity for the required duration (Maltais et al., 1997) and may not achieve the same benefit from exercise training as those without a significant VL to exercise, particularly if peripheral muscle strength is relatively preserved (Garrod et al., 2006; Plankeel, Mcmullen and MacIntyre, 2005; Troosters, Gosselink and Decramer, 2001).

In summary, the literature has suggested that the exercise intensity should be 60% of peak work rate for durations between 30 - 60 minutes, but shorter sessions may also be beneficial. Some patients may have very severe lung disease and be deconditioned so they may be unable to train at a high intensity or for a long period of time. Therefore the exercise component of PR should be individualised in terms of the intensity and the duration of training.

1.15.7 Activity

It is recommended that all adults should take 150 minutes of moderate intensity aerobic exercise per week to maintain a healthy lifestyle (WHO, 2010). The DH (2009) recommended this to be five sessions of 30 minutes of activity a week.
Individuals hindered by illness and disease are advised to carry out as much physical activity as their health allows (WHO, 2010). The GOLD strategy (2015) recommended that patients with COPD should participate in daily physical activity, although the details of this are not described.

A study undertaken in Sweden demonstrated that patients with COPD carry out less than the recommended physical activity levels compared with patients with other conditions and the healthy population (Arne et al., 2009). Katajisto et al. (2012) carried out a study which sent out a postal questionnaire to 719 patients with COPD to establish their activity levels and exercise participation. The study had a good response rate (87%) and found that, as anticipated, activity and exercise decrease with disease severity. Interestingly the reported barriers to exercise were dyspnoea (66%), pain (36%), other illness (42%), dislike of strenuous exercise (20%) and poor weather (17%). Although the research relied on self-reported data and did not encompass very severe patients (65% predicted of FEV1/FVC), it did demonstrate that dyspnoea was the main barrier to exercise and this needs to be addressed to enable patients to be active.

Whilst it is recommended that patients with COPD need to train at a certain intensity to gain optimum physiological benefit, studies suggest that patients may gain health benefits participating in activity. One study explored the relationship between baseline activity and mortality, demonstrated that a small increase in physical activity in people who are sedentary may have similar health benefits to a greater change in the more physically active population (Minton et al., 2013).

1.15.8 How should PR be evaluated?

NICE (2010) quality standards for COPD advised that PR is evaluated by a validated outcome measure, for example the 6MWT. The BTS Quality standards for PR (2014) suggested that PR is evaluated by, as a minimum, measures of exercise capacity, other body systems (for example, physical activity) and health status. The research recommendation of the BTS (2013) regarding PR evaluation suggested that measures should evaluate other body systems, not just the respiratory system. The BTS (2013) suggested that research was needed into the use of physical activity measures to evaluate PR. The outcome measures used need to be easy for clinicians to carry out in clinical practice and not expensive so as to be available for local hospitals and centres. The majority of the
recommended evaluation of PR is therefore through quantitative outcome measures. However, as PR is individualised it would seem important to capture some rich data about the acceptability and perceived benefits of the intervention in the form of qualitative research.

In summary, the exercise component of PR should be evaluated by both HRQOL measures and exercise capacity. Outcomes measuring activity levels following PR are under researched and need to be evaluated. Qualitative information would be useful to inform clinicians of acceptability of PR to patients. This would help inform exercise programmes to improve adherence and ensure they remain patient focused.

1.15.9 Who should be offered PR?

It has been recommended that PR should be offered to all patients with COPD with a MRC breathlessness score of > 3 (NICE, 2010). PR is also recommended for patients with moderate to severe COPD, or those who have mild lung function but experience shortness of breath on activity, including patients who have been hospitalised for an exacerbation (BTS, 2013; NICE, 2010). The contraindications to PR are those patients who have had a recent Myocardial Infarction (MI), unstable angina or who are unable to walk (BTS, 2013).

1.15.10 PR attendance

Approximately 33% of patients offered PR refuse to attend and a further 33% fail to complete due to sickness, reduced motivation, depression or logistical problems (BTS, 2011; Keating, Lee and Holland, 2011; Taylor et al., 2007; O'Shea, Taylor and Paratz, 2007; Fischer et al., 2007; Arnold, Bruton and Ellis-Hill, 2006). Therefore it is estimated that less than 5% of the patients with COPD who would benefit from PR actually receive it (Brooks et al., 2007; Yohannes and Connolly, 2004). This is problematic as patients who are less active are more commonly admitted to hospital and more likely to relapse following discharge (Garcia-Aymerich et al., 2006; Kim et al., 2004). It is important to consider different ways of administering PR to patients with severe COPD. This could include the timing of PR, the environment in which PR is delivered and also adjuncts to exercise that may relieve dyspnoea allowing patients to train.
The NICE COPD guidelines (2010) state that PR should be available for all who need it. Problems with incompletion of PR include accessibility in rural areas, waiting lists and problems with logistics including hospital transport. It is often house bound patients with very severe COPD who are unable to access or complete the PR course (Harris, Hayter and Allande, 2008; Sabit et al., 2007).

1.15.11 Post exacerbation PR

The BTS quality standards for PR (2014) suggested that patients should be referred to PR on discharge from hospital following an exacerbation and attend within one month of hospital discharge.

Often research on PR is carried out with the stable COPD population, however more recently research has focused upon rehabilitation post exacerbation. One Cochrane review aimed to assess the effects of ‘early’ PR within three to eight days after COPD exacerbations (Puhan et al., 2011). The review considered nine RCTs involving 432 participants. The programmes had variable participant completion rates of 40-94%. PR significantly reduced the number hospital admissions and also reduced mortality, although the effect of the intervention may have been overestimated due to the small sample size of the trials. Nevertheless, no study reported any serious adverse events (SAE) with the intervention. There were also statistically and clinically significant improvements in SGRQ and Chronic Respiratory Questionnaire (CRQ) and 6MWT, although there was a considerable difference in mean results between the trials in 6MWT (mean difference 77.70m, 95% Confidence Interval (CI) (12.21-143.20).

An RCT undertaken by Ko et al., (2011) compared early post-exacerbation PR within two to three weeks of hospital discharge with usual care. HRQOL as measured by SGRQ (the higher the score the worse the HRQOL experienced) was improved in the post-exacerbation PR group (mean total score ±standard deviation (SD) 40.15 ±19.10 versus 46.91 ±18.21 in the usual care group, with a statistical significance of p = 0.01 and 42.3 ±20.06 in the post exacerbation PR group versus 51.44 ±18.98 in the usual care group with a statistical significance of p = 0.01 at three and six months respectively). There were no differences between usual care and the post exacerbation group in SGRQ scores observed at 12 months post discharge.
Behnke et al. (2003) compared two groups of patients after recovery from an exacerbation of COPD requiring a hospital admission. The two groups were a control group (n = 14) with no exercise and an intervention group (n = 12) that performed a 10-day walking training in the hospital, followed by 18 months of supervised individualised training at home. The exercise was initiated at four to seven days after hospital admittance. The results showed that during the 18-month period patients in the training group showed a reduced frequency of hospital admissions (total, n = 3 versus n= 14, p = 0.026; disease-related, n = 3 versus n = 12, p = 0.050) and administered less short-acting β2-agonists than the control group - (mean [95% CI]), 2.4 [1.4 - 3.4] versus 5.7 [4.2 - 7.2] puffs per day, p < 0.001). The results also showed improved walking distance, with decreased levels of breathlessness, and improved HR QOL in all domains of CRQ. However the control group showed a deterioration in CRQ scores over all domains with a worsening of the reported fatigue score (mean ±SD) from 16.7 ±1.6 at baseline to 23.7 at 18 months for the rehabilitation group compared to 13.9 ±1.1 at baseline and 11.2 ±1.3 at 18 months for the control group. The six minute treadmill walk test demonstrated a significant improvement from baseline to 18 months in the rehabilitation group (p < 0.001) compared to the control (rehabilitation group baseline walking distance was 273m improving to 597m at 18 months versus baseline measure of 226m decreasing to 208 at 18 months in the control group).

The literature therefore suggests that it may be advantageous to begin the exercise component of PR in hospital following an exacerbation of COPD. The literature suggests exercising post exacerbation is safe and beneficial to patients with COPD.

1.15.12 Home based exercise

Traditionally PR takes place in an outpatient clinic either at a hospital or in the community, for example a community centre. But home PR needs to be considered due to the poor uptake of outpatient PR discussed earlier (see section 1.15.10, PR attendance). There was one UK-based study looking at home PR but this was in the form of brief advice after a one hour outpatient attendance and not comparable to a formal supervised exercise programme at home (White et al., 2002).
Home based rehabilitation programmes may offer an alternative way of delivering PR in patients with severe COPD who can not access PR. However most of the literature in support of PR is based on supervised outpatient programmes (BTS, 2013). The evidence surrounding home PR is conflicting.

A randomised, placebo-controlled trial of patients with COPD (n = 60) with MRC Grade 5 who were housebound due to their breathlessness demonstrated there was no benefit from supervised exercise training in their home (Wedzicha et al., 1998).

In a large retrospective observational study (n = 146/450) of patients with COPD graded as MRC 5, but who were able to attend and complete outpatient PR, gained the same significant improvement (p < 0.0005) in incremental shuttle walk test (ISWT) compared to patients who had MRC grade of 3 who completed the same outpatient PR (n = 103/450) (Evans et al., 2009). The ISWT results of patients graded MRC 5 increased by 54m (CI 43 - 64) post PR compared with MRC grade 3 participants increased by 63m (CI 50 - 75). However more unstable patients (exacerbation in last 3 months) were excluded and the drop out number was high (n = 55) and this consisted of participants with worse lung function, 16% were MRC grade 5 compared with 8% grade 4, thus severity of disease may be a barrier to outpatient PR.

There have been four studies that attempted to make a comparison between hospital and home based rehabilitation (Guell et al., 2008; Maltais et al., 2008; Puente-Maestu et al., 2000; Strijbos et al., 1996), however on review they evaluated supervised versus non-supervised rather than home versus outpatient location. The studies demonstrated that it was safe to carry out home based rehabilitation in patients with COPD. None of the home based programmes were completely carried out at home. Some of the self-management, monitoring and education sessions were carried out in the hospital (Guell et al., 2008; Maltais et al., 2008; Puente-Maestu et al., 2000). Only one study was a powered non-inferiority study (Maltais et al., 2008; BTS, 2013). All of the other studies were underpowered to have detected any statistically significant differences between the supervised and unsupervised groups.

One small numbered study did include regular home visits from clinicians to supervise exercise (Strijbos et al., 2008). This compared a 12 week hospital
programme \((n = 18)\) with a 12 week supervised home programme \((n = 17)\) and a control group \((n = 15)\) of no rehabilitation. Both PR groups demonstrated improvement in maximal work level and walking distance, but the hospital PR group only improved their maximal work load (see Glossary, p. 35) on an exercise cycle test up to six months after the programme. In contrast the home group continued to improve their maximum work level and walking distance up to 18 months after the programme. This may be because they were accustomed to exercising in their own environment unlike the hospital based patients. However a possible limitation of the study was it did not interview the participants to understand why they had continued or not continued with the exercise. This may have offered more understanding of why the improvements were maintained at 18 months.

Murphy, Bell and Costello, (2005) provided supervised home rehabilitation immediately on discharge demonstrating improvements in walking distance, leg strength and QOL compared to usual care. Therefore there may be some benefit for patients exercising at home who are unable to access PR, but the fear of exercise and dyspnoea they experience may still prevent them from training and achieving health benefits.

A well cited RCT (Griffiths et al., 2000) demonstrated that the positive effects of PR deteriorate over time and in the PR treatment group were only marginally better than the control group at one year. One possible reason for this may be that patients do not continue an exercise programme over time. Therefore it could be speculated that a possible benefit of home based rehabilitation may be that patients develop ways of exercising in their own environment that are easier to maintain.

In conclusion, the effects of outpatient PR reduce over time, so one suggestion is to base the exercise rehabilitation in the patient’s home environment to facilitate continued exercise at home following cessation of the programme. A home based programme may mean that it is accessible to patients with severe lung disease and housebound patients can be included.
1.16 PR and Behaviour change interventions.

Whilst there are clear short term benefits of PR the longer term benefits are unclear and studies suggest they only last for one year (Guell et al. 2000; Troosters et al. 2000; Hill et al. 2008). Therefore it is appropriate to consider methods of delivering PR that ensure uptake and adherence to longer term physical activity. A theoretical underpinning of behaviour change in PR interventions may be important in creating and supporting effective behaviour change. Behaviour change can be defined as a:

"Coordinated set of activities designed to change specified behaviour patterns"

(Michie, van Stralen and West, 2011, p.1).

There are many frameworks of behaviour change interventions. Michie, van Stralen and West (2011) produced from their SR of behaviour change frameworks an accessible and complete model of behaviour change called the COM-B system see (figure 1.5).

![Figure 1.5 COM-B system of behaviour change Reproduced with permission of BioMed Central](image)

This model has the potential to be useful when designing and evaluating interventions.

A recent SR considered studies that used interventions to increase physical activity in patients with COPD (Wilson et al., 2015). It is uncertain what length,
intensity and method of delivering the intervention is needed to facilitate change in physical activity behaviour in COPD. The review included \( n = 20 \) studies including \( n = 31 \) physical activity interventions varying in type, timing and duration of intervention. The range of exercise duration was 150-180 minutes per week. Most included moderate aerobic exercise for physical activity and included behaviour advice, self-monitoring and goal setting for activity behaviour. Most of the studies used a pedometer or accelerometer to measure activity. Unfortunately because of the wide variety of interventions and outcome measures a meta-analysis for type of intervention or outcome assessment was not feasible. For a sub-group \( n = 7/16 \) demonstrated between group differences in favour of a walking based intervention.

It is challenging for patients with COPD to carry out physical activity for many complex reasons. To enable an intervention to change behaviour in regards to exercise and activity it is important that these reasons are understood. As part of this exploration it is valuable to review physiologically what may contribute to those causes.

**1.17 The pathophysiology of COPD and exercise**

One of the most debilitating aspects of COPD is that it hinders a patient’s ability to exercise. The physiological response of patients with COPD to exercise is complex. The main difference is that people with normal lungs stop exercising because of cardiovascular limitation, but there are several possible theories suggesting that VL, causing dyspnoea, is the reason for cessation of exercise in patients with COPD. VL is described as when the patient can no longer exercise due to breathlessness (Mador *et al*., 2000; Polkey *et al*., 1995). VL is a complicated response related to pathophysiological mechanisms in the lungs, peripheral muscles and psychological factors relating to motivation and dyspnoea. This section of the theses will address some of the key suggested causes of VL, however due to the extensive physiology literature surrounding this debate a full review is beyond the scope of this thesis.

Garcia-Rio *et al.* (2009) described an association between Dynamic Lung Hyperinflation (DLH) (see Glossary, p. 30) and reduced daily activity regardless of severity, however, there are studies that found no relationship between DLH and muscle load and breathlessness (Freedman, Lane, Guz, 1987; Potter,
Olafsson and Hyatt, 1971). DLH resulted in a biomechanical disadvantage, shortening the inspiratory muscles and results in breathing at higher absolute lung volumes compounding breathlessness sensations (Gorini et al., 1996). Patients with DLH will be positioned physiologically at the top of the curve and thus disadvantaged by limited lung compliance to respond to exercise. See Figure 1.6 demonstrating this physiological disadvantage.

![Figure 1.6](Image)

**Abbreviation Key:** Pressure P (cmH₂O), Volume V (L)

*Figure 1.6 Pressure (P) volume (V) curve of the respiratory system for a patient with dynamic lung hyperinflation*

Figure reproduced with permission from Dr Adrian Kendrick, Association of Respiratory Technology and Physiology, NIV course, Holiday Inn, Birmingham, COPD presentation, October 2014.

COPD patients with DLH are unable to increase their tidal volumes (Vₜ) (see Glossary, p. 34) in response to amplified ventilatory drive on exercise (see Glossary, p. 34) (O’Donnell, Revill and Webb, 2001). This means that there is alveolar hypoventilation (see Glossary, p. 25 on alveolar ventilation (Vₐ)). Therefore the body responds by increasing the RR leading to shortening of the inspiratory muscles (O’Donnell and Webb, 2008).

Another possible suggestion as to why patients with COPD were unable to exercise was because the diaphragm becomes fatigued. Aliverti et al. (2004)
suggested that diaphragm fatigue was caused by expiratory muscle activity. This activity negatively affects the cardiovascular system and the interaction between the respiratory and peripheral muscle systems (Aliverti et al., 2004; Potter, Olaffson, Hyatt, 1971). This may have caused diaphragm fatigue but this had not been demonstrated conclusively at the point of VL (Mador et al., 2000; Polkey et al., 1995).

Patients with COPD often have reduced elasticity and compliance of the lung parenchyma. There is also a chronic change in the diameter of the airways (Decramer et al., 2012). These pathological changes may mean that patients with COPD are unable to use effectively a feedback system from receptors within the lung parenchyma (stretch) (see Glossary, p. 32), airway receptors (flow), muscle spindles (tension) and Golgi tendon organs (tension) (see Glossary, p. 31) in the chest wall (Remmers and Bartlett, 1977). These combine with neural humoral stimuli related to tissue CO₂ yield causing an exact homeostatic reduced expenditure exercise hyperpnoea (see Glossary, p. 31) (Dempsey, 1985). Therefore the patient is unable to respond to the exercise as efficiently with increased Vₜ, vital capacity (VC) (see Glossary, p. 34) and expiratory flow rates (Powers and Howley, 1997).

O'Donnell, Revill and Webb (2001) found that COPD patients who stopped exercising because of dyspnoea had significantly greater resting airflow limitation and thoracic hyperinflation than those who stopped for leg discomfort. Therefore the patients with more severe lung disease are more limited by breathlessness on exercise. DLH creates a mismatch between drive to breathe and incapacity to meet ventilator requirements. O'Donnell, Hamilton and Webb (2006) referred to this as neuro-muscular uncoupling of the ventilation system. This leads to circumstances where, despite putting in the most forceful of inspiratory effort, minimal air goes into the lungs on inspiration. This causes the patient to experience intolerable breathlessness (O'Donnell and Webb, 2008).

An alternative hypothesis was that over time COPD causes increased energy demands and a decrease in the available O₂. This was argued to be primarily caused by excessive recruitment of the expiratory muscles (Aliverti and Macklem,
The theory was that energy demands increased because of the high O\textsubscript{2} cost consumed by the respiratory muscles (VO\textsubscript{2 Resp}) (see Glossary, p. 31, maximum O\textsubscript{2} uptake) of breathing in COPD. In normal subjects this is 1 – 3mL\textsubscript{O\textsubscript{2}}/L but in patients with COPD it is 6.3 - 16.4mL\textsubscript{O\textsubscript{2}}/L (Levison and Charnick, 1968). Patients with COPD recruited their expiratory muscles during exercise to improve their V\textsubscript{E}, however, this was futile due to high pleural pressures (P\textsubscript{pl}) (see Glossary, p. 33) limiting potential expiratory flow. Patients who do successfully recruit their expiratory muscles have an increased VO\textsubscript{2 Resp}. If this is subtracted from VO\textsubscript{2max} (maximum volume of O\textsubscript{2} that can be used) (see Glossary, p. 31) then there is very little energy left for peripheral muscles and other body tissues. In the patients who did not recruit their expiratory muscles the respiratory muscles took 17% of VO\textsubscript{2max} compared to 53% in patients who used their expiratory muscles (Babcock et al., 2002). Although the patients who did not recruit their expiratory muscles had better exercise tolerance their resting lung function worsened. Aliverti et al. (2008) hypothesised that patients with COPD learn to de-recruit their abdominal muscles as their disease progresses, but this causes DLH. Overall an imbalance may be present between energy provision and use causing VL.

A different theory that investigated why COPD patients stop exercising considered that pathophysiological consequences of COPD are not just confined to the lungs (Decramer et al., 2005). Respiratory impairment is not enough to explain exercise limitation in COPD (Debigare and Maltais, 2008). There was only a weak link between lung function and exercise tolerance, implying that other systems must be involved (O'Donnell, Lam and Webb, 1999). COPD may be associated with weight loss and muscle dysfunction (Decramer et al., 2005). Chronic inflammation may lead to muscle dysfunction because there was evidence of local inflammation in the muscle of patients with COPD including cytokines, macrophages and T-Cells, and these may have contributed to the pathogenesis of skeletal muscle (Montes de Oca et al., 2005). Leg discomfort was often stated as a reason for stopping exercise (Debigare and Maltais, 2008; Gosselink, Troosters and Decramer, 1996). Killian et al. (1992) studied the influence of leg muscles on exercise intolerance in COPD. They concluded that leg discomfort was a frequent exercise-limiting symptom when cycling, however in the study by O'Donnell, Revill and Webb (2001) only n = 18 of 105 patients stopped exercising because of leg
discomfort, much less than the n = 61 of 105 patients who stopped because of breathlessness. Hamilton et al. (1996) evaluated the relationship between the perception of leg fatigue, work capacity and muscle strength in both normal participants and patients with COPD. They concluded that weaker patients had leg fatigue and reduced peak exercise capacity. They also found that quadriceps strength determined exercise capacity independent of lung function.

In contrast Mahler and Wells (1988) demonstrated that their participants (n = 153) with mild COPD stopped with leg symptoms whereas those with severe disease stopped because of dyspnoea. A smaller (n = 84) but more recent study reported that breathlessness limited exercise as opposed to leg fatigue following walking. A comparison between those patients who stopped because of dyspnoea compared to leg discomfort revealed no difference in age or FEV₁. The participants in the study that reported dyspnoea performed less well in the interval walking test than those who reported leg discomfort (Man, Soliman and Gearing, 2003).

The response to sub-maximal exercise could have been shaped by the strength and aerobic capacity of the leg muscles. Lower limb atrophy in patients with COPD ranges from 21 - 45% of muscle bulk (Vermeeran et al., 2006; Schols et al., 1993) and muscle limb weakness is established in patients with COPD (Bernard et al., 1998; Killian et al., 1992). Evidence has suggested that patients with COPD have weaker leg muscles that fatigue more quickly than the muscles of healthy people (Debigaire and Maltais, 2008). There is also a reduction in the number of Type I muscle fibres that provide a slow contraction action and are very resistant to fatigue. There is a reduction in the cross sectional area of both Type I and Type II (the faster acting) muscle fibres and also contractile protein deficiency. The resulting muscle inefficiency contributes to exercise limitation (Gosker et al., 2002; American Thoracic Society, 1999b; Bernard et al., 1998). Similarly, there is lower myosin and oxidative enzyme activity (Gosker et al., 2002; Maltais et al., 2000) affecting muscle endurance (Allaire et al., 2004). This suggested that patients with COPD have muscle changes that influenced their deconditioning, making it more difficult to rehabilitate them. However it might be too simplistic to consider physiological causes of breathlessness in isolation. It is also important
to consider how psychological factors may influence dyspnoea on exercise. Dyspnoea is a complex multidimensional experience that is very individual hence why patients with the same pathology perceive it differently.

Traditionally dyspnoea was viewed as a simple concept measured by numerical scoring. The understanding of dyspnoea has progressed and there is a growing body of literature citing psychological factors as impacting on the perception of dyspnoea including emotion, anxiety, previous experience, attributions and context. More recently a school of thought has suggested interpreting dyspnoea was similar to how we view the complexity of pain (Lansing et al., 2009). The Lansing et al. (2009) model of different breathlessness sensations and causes fits more easily with the complexity of dyspnoea experienced by patients with COPD.

This model of Lansing, et al. (2009) reflects 3 specific qualities of dyspnoea gathered from previous research literature (Harver et al., 2000; Schwartzstein, 1998; Banzett et al., 1996; Elliott et al., 1991; Simon et al., 1990; Banzett et al., 1989). The three suggested descriptors are:

1) Air hunger: This is driven by brainstem motor control and is an automatic stimulus of breathing, not caused by a mismatch between drive and ventilation. This would be similar to the dyspnoea experienced for physiological reasons previously discussed.

2) Tightness sensation: This relates to bronchospasm and is a result of bronchoconstriction of the airways. It is a localised sensation to the chest (Moy et al., 1998).

3) Work: Increased work of breathing is influenced by an increased motor command in response to an activity or exercise. The increased motor commands influence the muscle afferent pathways and perceived cortical command, leading to an increase in $V_E$.

The first two dyspnoea descriptors seem to relate more to the physiological causes previously discussed, however the sensation of work seems to fit in more with voluntary interaction. This would seem to relate more to motivation and emotions. Carrieri-Coleman et al. (1996) identified a relationship between the
affective dimension and sensory dyspnoea. They identified that supervised exercise training can decrease dyspnoea-related anxiety in the same individuals, even if the same intensity of breathing is sustained. Leopold et al., (2009) used cards conveying a negative affective state or those with a positive affective state during cycle ergometry in patients with COPD. A higher level of dyspnoea was expressed by the group viewing the negative affective cards, although this was not significant. As the sample was elderly with more co-morbidities it may be that both groups exposed were more deconditioned. This research was further developed by Jannsons et al., (2011) who evaluated dyspnoea-related fear before and during PR and demonstrated that those with increased baseline anxiety and dyspnoea-related fear had a higher baseline dyspnoea score. This was the group who also had the steepest improvement in dyspnoea during PR. However in these studies there was no validated measure for dyspnoea-related fear.

This section has demonstrated that there are numerous interconnecting physiological causes that may contribute to dyspnoea limiting exercise. These include DLH, respiratory and peripheral muscle dysfunction, and pulmonary gas exchange deficits causing arterial hypoxaemia (O'Donnell and Webb, 2008; Aliverti and Macklem, 2008). It would seem sensible to conclude that all systems play a role because of the multi-system pathology of COPD.

Exercise is important for maintaining activity levels (Decramer et al., 2005). Therefore it is important to consider treatments that encourage exercise and treatments that may overcome both the pathophysiological changes and the psychophysiological changes in patients with COPD that prevent them exercising. Adjuncts to exercise will be considered in the next section.

1.18 Are there any methods or adjuncts that could improve PR?

1.18.1 Lung volume reduction surgery (LVRS)

LVRS is a proven palliative procedure for patients with COPD who have emphysema in the upper lobes of the lungs. This surgery removes 20 – 30% of each lung’s most damaged segments. This reduces dead space (see Glossary, pp. 30 dead space ventilation) and gas trapping (see Glossary, p. 31 end expiratory lung volume) allowing for improved breathing biomechanics on exercise (Ernst and Anantham, 2011). When comparing LVRS and three months
of PR to three months of PR alone there were improved benefits in static lung function, gas exchange and QOL with a trend for improved walking distance in the group that received both LVRS and PR (Criner et al., 1999). In another study exercise endurance and QOL significantly improved at 24 months post-operative procedure compared to the control group (Fishman et al., 2003). However LVRS is a highly selective treatment, therefore it is not suitable for all patients with severe COPD. There is also a risk of post-operative mortality (7.9%) and post-operative complications are at > 50% (DeCamp et al., 2008). Thus this kind of surgical management is not necessarily appropriate and the high risk of the procedure may outweigh the benefits. Therefore there is a need to look at other low risk and low selection criteria interventions that may act as an adjunct for PR.

1.18.2 Inspiratory muscle training (IMT)
IMT attempts to improve respiratory muscle strength and endurance. IMT uses devices that permit inhalation against resistance at a certain threshold. A pilot study (n = 36) of patients with COPD demonstrated that the use of IMT in addition to an exercise programme led to greater improvement in walk test distance than those who undertook exercise alone (Winer, Azgad and Ganam, 1992). Similarly, another pilot study (n = 32) found that IMT led to greater improvement in cardiopulmonary exercise test parameters after an exercise programme (Wanke et al., 1994).

Two subsequent RCTs in patients with COPD found no additional benefit from IMT with exercise compared to exercise alone in regards to dyspnoea experienced by the participants or performance. (Berry et al., 1996; Larson et al., 1999). The positive studies in favour of IMT have limitations due to small samples, no randomisation, not blinded, there was a high participant drop-out rate and a lack of detail of the intervention and exercise training (Wanke et al., 1994; Weiner, Azgad and Ganam, 1992). IMT is not recommended as a routine adjunct to PR (BTS, 2013).

1.18.3 Other Adjuncts
Other adjuncts have been advocated including hormonal supplements, nutritional supplements and heliox (80% Helium, 20% O₂) but are not currently recommended with PR due to a lack of appropriate evidence (BTS, 2013). There
may also be evidence for the addition of neuro-muscular electrical stimulation (NMES) of the quadriceps if there is available expertise. Some patients, with low BMI and with evidence of quadriceps weakness, that are unable or unwilling to participate in PR could be considered for NMES (BTS, 2013; Vivodtzed et al., 2006).

In conclusion, PR seems to be supported by evidence in patients with very severe COPD. The problem of access to PR and fear of participation in exercise because of the sensation of dyspnoea means that many patients with severe COPD are unable to use this intervention. Adjuncts to PR have been considered but are not currently recommended due to a lack of appropriate evidence (BTS, 2013). Thus there is a need to consider other ways of providing exercise to this group of patients. Exercise on NIV may provide a means for enhancing the ability for these patients to engage with exercise.

1.19 Non-invasive ventilation (NIV)

It is relevant to this study to understand how NIV was established as a treatment for COPD. Non-invasive ventilation methods have been key to the history of respiratory care, although having early origins, they were initially superseded by invasive methods. In the last 30 years the use of NIV ventilation has escalated globally in both acute and chronic use, for multiple pathology and novel uses. This is because there are disadvantages to using invasive ventilation (ventilating via an endotracheal tube) that may often be avoided with NIV, this will be further discussed in section 1.19.2 The birth of NIV.

1.19.1 Negative pressure ventilation

The first well recognised feasible way of sustaining life in patients unable to breathe independently was by the use of negative pressure applied with tank ventilation, developing into the iron lung (Simonds, 2001; Woolam, 1976a; Drinker and Mckhann, 1929). Cuirass jackets eliciting negative pressure were created in the 1930s (Woolam, 1976b). The emergence of ventilation occurred during the polio epidemic of the 1940s-1950s (Colice, 1994; Morch, 1990; Lassen, 1956). Iron lung ventilation was rolled out all over the UK and former Empire (Simonds, 2001). Unfortunately, despite the use of the iron lung, mortality remained high. Therefore new ways of ventilating patients were trialled including manual
intermittent positive pressure ventilation. This doubled the chance of survival and led to the replacement of negative pressure ventilation with positive pressure (Young and Sykes, 1994). This was soon superseded by more advanced ways of invasive ventilation (Pierson, 1990).

By the 1970s ventilation was a routine part of intensive therapy unit (ITU) management for all pathologies requiring support to the respiratory system. Invasive ventilation became more sophisticated and improved with the introduction of novel ways of taking physiological measures e.g. ABG analysis (Pierson, 1990). However, awareness of the complications of invasive mechanical ventilation and artificial airways led to investigations into ventilatory support with fewer side effects (Tremblay and Slutsky, 2006; Slutsky, 2005; Pierson, 1990; Stauffer and Silvsetri, 1982).

1.19.2 The birth of NIV

Searching for new methods of ventilation led to a renewed interest in NIV and mask ventilation was successfully used with continuous positive airways pressure (CPAP) to treat obstructive sleep apnoea (OSA) (Sullivan et al., 1981). In 1987 Delaubier et al. used NIV to treat a young man with Duchenne’s muscular dystrophy. The arrival of NIV as a treatment for chronic hypercapnic respiratory failure changed the normal trajectory of neuromuscular and chest wall diseases (Lobato and Alises, 2013; Piper and Sullivan, 2006). NIV functioned to reduce the work of breathing of the respiratory muscles by decreasing the RR and increasing TV leading to an improvement in VA (Elliott, 2005). It can be applied with a nasal or full face mask without reducing the defence of the airway. This method can be used safely outside of the ITU (Plant, Owen and Elliott, 2000). Initially volume modes were used to ventilate patients but this then changed to inspiratory pressure modes. This was further developed into Bi-level inspiratory positive airways pressure (BIPAP) (Respironics) made up of two pressures inspiratory positive airways pressure (IPAP) to change the depth of breathing and expiratory positive airways pressure (EPAP) was added to treat a collapsing/floppy upper airway in sleep or overtake resistance in the breathing tube to allow for mask leak ventilation (Simonds, 2001). This also allowed for a patient to spontaneously trigger a breath, in spontaneous timed (S/T) mode, rather than the machine triggering and generating a controlled breath (Elliott, 2009). This allowed for more
comfort and concordance with the device (Simmonds, 2001). More recently research has considered its use in other conditions. Obesity hypoventilation syndrome (OHS) required treatment with NIV. This was caused by obesity leading to extra work for the diaphragm meaning hypoventilation can result. OHS is commonly diagnosed in addition to OSA and COPD, referred to as crossover syndrome. This mixed pathology often meant patients needed a mix of inspiratory and expiratory pressures called hybrid modes to treat their symptoms. More recently NIV has been used to palliate the respiratory symptoms in Motor Neuron Disease (MND), which commonly include breathlessness on lying flat and during sleep caused by poor innervation to the respiratory muscles causing hypoventilation (NICE, 2010).

NIV using inspiratory Pressure Support (IPS) was a mode of ventilator support that demonstrated pioneering positive results when treating COPD patients with acute respiratory failure (Plant, Owen and Elliott, 2000). NIV enabled patients not to be intubated and suffer the potential risk of nosocomial infections and complications arising from the use of paralysing agents. This is because NIV allows for speaking, swallowing and airway defence mechanisms, for example preserved cough (Nava and Hill, 2009; Elliott, 2005). Two meta-analyses confirmed the effectiveness of NIV in acute exacerbations of COPD (Lightowler et al., 2003; Peter et al., 2002). It improved survival and also decreased length of hospital stay (Ram et al., 2004a).

The use of NIV for chronic hypercapnia is controversial. Long term RCTs are currently being undertaken across Europe, including the UK version ‘The Hot study’, but results are yet to be published. Results to date have been variable. One study suggested a marginal improvement in survival but this decreased after three years (McEvoy et al., 2009).

Researchers have used the knowledge of the therapeutic effects of NIV and applied this to investigate the benefits of using NIV during exercise in patients with COPD. NIV may offload the respiratory muscles, improving the experience of dyspnoea during exercise and allowing patients to train at a higher intensity, gaining health benefits.
Patients using NIV to exercise

Physiological studies have researched the addition of positive pressure via a face mask to patients with COPD when exercising. Initial studies focused on CPAP to unload the respiratory muscles (Petrof, Calderini and Gottfried, 1990; O'Donnell, Sanii and Younes, 1988; O'Donnell et al., 1988). This applied Positive end expiratory pressure (PEEP) (See Glossary p. 34), which acts to splint open the airways, reducing the work of breathing (Lopes, Nery and Sousa, 2011). It was thought that CPAP lowered the inspiratory threshold load on the inspiratory muscles in hyperinflated patients (Ambrosino and Strambi, 2004). This rectified the PEEPi, improving neuromuscular coupling, therefore lessening dyspnoea, and increasing exercise tolerance (Lougheed, Webb and O'Donnell, 1995).

O'Donnell, Sanii and Younes (1988) demonstrated that CPAP applied to patients with COPD significantly improved submaximal endurance time by 48% (mean time 8.82 minutes in the CPAP group compared to 5.98 minutes in the control group) and reduced dyspnoea scores compared to the control group at iso-time in the CPAP group to BORG score of 5.5 compared to 7.83 in the control group. This same research group confirmed that CPAP counterbalanced PEEPi during cycling (O'Donnell et al., 1988). They hypothesised that inspiratory muscle performance determined exercise endurance and that CPAP may relieve dyspnoea by unloading the overburdened respiratory muscles. They suggested a connection between elevated inspiratory muscle action, increasing central command output and creating dyspnoea (Leblanc et al., 1988). A further supporting study on patients with COPD demonstrated that CPAP maintains oxygenation and decreases the pressure time interval of the respiratory muscles, thus reducing the O$_2$ consumption of the muscles (Petrof, Calderini and Gottfried, 1990).

A recent study using CPAP on COPD patients climbing stairs did not support these previous results. The findings demonstrated no improvement in lung hyperinflation, deoxygenation, hypoventilation, blood lactate production, dyspnoea or completion time (Walterspacher et al., 2013), however the patients carried the CPAP up the stairs, which may have added to their muscle burden. The patients were not screened for DLH so may not have been physiologically disadvantaged to benefit, as in other studies (Soares, Oliveira and Franca, 2008).
Nevertheless the patients in the study by Walterspacher et al. (2013) did develop significantly less limb discomfort when on CPAP. They hypothesised that the CPAP caused a decreased work of breathing, boosting peripheral blood flow and therefore improving oxygenation of the limb muscles (Romer and Polkey, 2008; Petrof, Calderini and Gottfried, 1990).

Overall the existing evidence suggests that CPAP may be beneficial in some patients with severe COPD, however CPAP did not influence $V_T$ and whilst aiding inspiration it may add to inspiratory load and increased respiratory effort if the pressure is too high (Keilty, 1994).

**1.19.4 Using the mode of pressure support (PS) to exercise**

IPS is a type of mechanical ventilation that can effectively aid breathing when applied non-invasively to patients with respiratory failure. PS is a pressure-targeted mode where the patient initiates each breath which is supported by a pre-set pressure (Kinnear, 2008). NIV is a combination of PS and PEEP synchronised with the inspiratory effort of the patient (Simonds, 2001). NIV works acutely to reduce inspiratory effort and dyspnoea while increasing $V_A$ (Plant, Owen and Elliott, 2000). Other studies have used the mode of proportional assisted ventilation (PAV) (see glossary, p. 33), which provides partial ventilatory assistance providing changing inspiratory flow and pressure in proportion to the patient’s effort (Ambrosino and Strambi, 2004).

Maltais, Reissman and Gottfried (1995) studied PS versus no PS in patients with COPD on an exercise bike. PS increased $V_E$ through changes to both $V_T$ and RR. Physiologically this was unrelated to reductions in inspiratory effort, evidenced by oesophageal and transdiaphragmatic pressure-time intervals. Dyspnoea significantly improved when PS was used and deteriorated on removal. Slowing of the maximal muscle relaxation of skeletal muscle is an early marker of fatigue (Kyroussis et al., 1996). When PS was applied to COPD patients during treadmill walking, oesophageal maximum relaxation rate was significantly lower than walking without IPS. This therefore suggests that IPS unloads inspiratory muscles counteracting fatigue. This was further validated in study by Kyroussis et al., (2000) involving patients with severe COPD who exercised on a treadmill. Unsupported oesophageal and transdiaphragmatic pressure rose early in exercise and remained high until dyspnoea stopped exercise. When the patients
walked the same distance with NIV a reduction was observed in the inspiratory and expiratory time products throughout the walk. Therefore it would seem PS substantially unloads all parts of the respiratory muscle pump (De Backer et al., 2010).

Another theory of how PS may physiologically aid exercise in COPD was investigated by Polkey et al. (1996). Patients with severe COPD exercised on a treadmill with and without PS. Plasma lactate levels were compared for both walks. The walk with PS showed no difference in lactate levels compared to the unsupported walk, however, patients were able to walk for longer with PS.

Hernandez et al. (2001) trial involved a sample of patients with severe COPD who exercised using proportional assisted ventilation (PAV); a mode of ventilation that provides a level of support irrespective of any changes in lung compliance or resistance. They showed similar improvements in exercise duration, $V_T$ and $V_E$, with improvements in ABG and dyspnoea, however there also seemed to be an overall improved breathing pattern. Therefore it could be that NIV regulates and paces breathing as well as offloading the respiratory muscles.

An alternative hypothesis on how NIV may delay VL was offered. The theory is that using NIV during training of patients with COPD led to unloading of the respiratory muscles. This may minimise the impact of increased respiratory muscle blood flow, enabling more effective physiological adaptations of the peripheral muscles. This results in less perceived leg effort, increased leg oxygenation, decreased exercise lactate and improved exercise tolerance (Borghi Silva et al., 2010; Borghi Silva et al., 2008). This hypothesis was based on the work by Harms et al. (1997) on the use of NIV during exercise in normal subjects which showed that respiratory muscle effort improved blood flow distribution. The growth of inspiratory muscle strength in the NIV group may be accounted for by the decreasing of mechanical load and a pause in the onset of respiratory muscle fatigue (Polkey et al., 1996; Nava et al., 1993) causing a reduction of inspiratory muscle metaboreflex activity. It is possible that increased walking distance was caused by improved respiratory muscle strength contributing to less leg fatigue. The decrease in lactate/speed ratio also advocates better oxidative capacity of the exercising muscles, and possible true beneficial physiological adaptations (Borghi Silva et al., 2010). Alternatively there have been some studies
demonstrating negative results when ventilation is applied during exercise (Highcock, Shneerson and Smith 2003; Revill, Singh and Morgan, 2000).

In the prospective randomised study carried out by Revill, Singh and Morgan (2000) the effect of AOT versus PS on an endurance shuttle walk was evaluated. The participants (n = 10) with severe COPD (FEV$_1$ < 40% predicted) performed the endurance shuttle walk test under five test conditions: baseline walk (no support); PS at 14cmH$_2$O, PEEP set < 3cmH$_2$O from a portable ventilator (HIPPY, Friday Medical, U.K.) using a full face mask (over nose and mouth); sham PS < 8 cmH$_2$O PEEP < 3cmH$_2$O; AOT at 2L/min; and sham O$_2$ (carrying the portable cylinder but breathing in air). The results demonstrated a significant improvement in the mean walk time compared to baseline (172 seconds) with the addition of AOT (242 seconds) but a worsening in time with the HIPPY ventilator (84 seconds). The authors concluded that a more powerful machine, in terms of inspiratory flow, is required to support exercise when higher levels of ventilation are reached. Therefore inspiratory flow needs to be considered and assessed when choosing a ventilator to support the exercise programme.

Highcock, Shneerson and Smith (2003) evaluated three different makes of ventilator (BiPaP S/T 30, Nippy 2 and VPAP ST using bi-level mode). No details were given to EPAP values, only that they were set as a minimum. The average IPAP pressure used was 12.2cmH$_2$O on (n = 8) patients with COPD (severity FEV$_1$/FVC < 70% predicted) whilst exercising during a submaximal treadmill exercise. The participants walked to exhaustion with each of the ventilators, and one with just breathing through a mouthpiece, in a random order. As a control four treadmill walks were performed unaided. The mean distance of the unaided walks were 259m, mouthpiece alone was 211m, and only 145m with the addition of the ventilators. There was no difference found between each make of ventilator, however the V$_T$ and V$_E$ achieved were greater in the ventilator walks. The authors did attempt to apply a control walk and counteract learnt behaviour of walks by using multiple walks. The authors attempted to reduce bias with randomisation, although blinding of participants and researchers was not attempted.

The negative results of this study may have been because the pressure, circuit and equipment were inadequate to meet the inspiratory flow rates or pressure needed to offload the respiratory muscles to result in physiological change.
The circuit used in Highcock, Shneerson and Smith’s (2003) study used an inefficient expiratory valve so up to 60% of expired air may remain in the circuit at the end of expiration (Lofaso et al., 1996). Therefore the authors’ conclusions were that exercise capacity in patients with COPD was not improved with the addition of ventilatory support using a mouth piece and whisper valve in the circuit (Highcock, Shneerson and Smith, 2003). The authors commented on asynchrony between patient and ventilators as the patients were breathing out before the ventilator had achieved the set IPAP. The ventilators used in that study are now dated and modern ventilators are more sensitive and have improved synchronisation with patients. The disease severity of the participants in the Highcock, Shneerson and Smith’s (2003) study was not very severe. Although the authors did consider whether their exercise was limited by breathlessness and excluded participants if they could walk for more than 10 minutes on the treadmill at their individual maximum speed. There was also only a 30 minute rest in-between walks. The number of participants recruited in these negative studies are small but comparable with those recruited in the positive studies.

Recent studies have considered upper limb exercise in COPD with the use of NIV compared to unsupported exercise. NIV improved unsupported arm exercise (UAE) endurance time possibly because of reduced dyspnoea and perceived exertion, and improvement in oxygenation (Menadue et al., 2010; Menadue et al., 2009). Physiologically during UAE some accessory muscles (see Glossary, p 29) have two jobs of executing the upper limb activity, as well as helping inspiration. Consequently some of the ventilator load is shifted to the diaphragm and abdominal muscles. Previously arm elevation was shown to increase inspiratory muscle work in patients with chronic respiratory failure (Poggi et al., 2006). The reduction in dyspnoea that was observed with NIV during UAE suggests that NIV may have improved exercise performance by unloading the inspiratory muscles. The added EPAP used in Poggi, et al.’s (2006) study has been shown to counterbalance PEEPi (Nava et al., 1993). The decrease in perceived dyspnoea may have allowed patients to exercise for longer, although both groups stopped because of arm tiredness. This may again relate to the competition for blood flow between muscles of locomotion and respiratory muscles (Debigare and Maltais, 2008).
1.19.5 NIV on exercise conclusion

Overall the evidence has suggested that the use of NIV during exercise in COPD may be beneficial. NIV may reduce breathlessness during exercise as a result of one or more physiological processes, allowing for higher levels of exercise intensity. It would seem that only suggesting that physiological factors influence dyspnoea on exercise may be too simplistic. Dyspnoea is an individual experience developing from physiological, psychological and social factors. Given that there is a multi-factorial reason as to why patients with COPD could not exercise, it would seem feasible to suggest that the reason NIV allowed patients with COPD to exercise harder and for longer was also multi-factorial. On reviewing the methodological quality of the studies the biggest problem was the small sample sizes used and lack of RCTs (De Backer et al., 2010).

1.20 Current political health climate in the UK

It is important to consider how the current political health climate influenced the environment in which the current research was carried out to enable the results to be interpreted in context. The NHS was driven by a government target which sought to decrease waiting times to under four hours in A&E departments and facilitate the flow of patients through the hospital system (DH, 2002; DH, 2000). Additionally there had been government and health guideline drives to move care provision back into the community (DH, 2014; DH 2010c; National Collaborating Centre for Chronic Conditions, 2004). This policy had impacted upon COPD patients because it had driven early discharge schemes for patients admitted with exacerbations. This potentially meant that patients spent less time in the hospital and were less at risk of developing hospital acquired infections. An SR concluded that 30% of patients admitted with a COPD exacerbation were considered for early discharge (Ram et al., 2004b). A SR and two audits demonstrated that early discharge was safe and effective, mortality and re-admission rates were the same for both groups of patients (Ram et al., 2004b; Candy et al., 2005; Quantill et al., 2003). Early discharge schemes could potentially affect the amount of time available for recruitment and establishing an exercise on NIV intervention, however these schemes are aimed at patients who are less acutely unwell (for example, do not have a pneumonia or respiratory failure treated with NIV). Therefore the patients with more severe COPD treated with NIV have a longer...
hospital stay which allows for a longer duration for recruitment and immediate initiation of exercise on NIV post exacerbation. These severe patients are also identified as those less able to access or partake in community PR.

COPD patients with severe and end-stage COPD previously received very little palliative input (Curtis, 2008; Gardiner et al., 2010). Hospice and palliative care services were primarily offered to patients with cancer because the prognosis of COPD is difficult to predict (Pountney, 2006). NICE (2011) guidance has recommended an improved palliative care service for patients with COPD. Within the last five years palliative input for COPD patients has improved within Bristol. There has been a drive for improved completion of advanced care decisions, ‘do not resuscitate’ forms and palliative symptom control forms. This has also included an increase in referral to palliative care for patients with severe COPD who have had repeated admissions. If someone is referred to palliative care services it often means that the level of active care is reconsidered. This may include whether someone is offered antibiotics or treatment with NIV. What is challenging is that these patients may live a further six to twelve weeks with frequent admissions. Their mobility may deteriorate further and they are not considered for PR, exercise or physiotherapy as this may be considered to be too aggressive. Patients with severe end-stage COPD may benefit from increasing their activity levels through supported exercise on NIV and possibly gain QOL benefit from increased activity within this later stage of disease.

1.21 Motivations for undertaking the study

1.21.1 Personal Perspective

In recent years I have witnessed a change in clinical practice towards patients with COPD. Previously it was not common for palliative care to be offered to patients with severe COPD until they were considered to be dying. However in the last five years patients are frequently referred and considered to be palliative if they have had multiple admissions. Previously each patient with COPD had an exacerbation treated as an isolated acute event up until their death, often in hospital. They were unable to access the support of palliative care, Macmillan nurses and hospice care. Over time, thanks to well publicised recommendations, this approach has changed to an almost over-zealous approach to referral to
palliative care. Now on frequent admission patients are advised that there is little else to be done, and they are referred to palliative care, given Oramorph medication for breathlessness and advised on advanced planning related to end of life care. COPD is a disease with a difficult to predict prognosis, therefore early referral does ensure that a dying patient receives appropriate palliative support, however I couldn’t help but feel palliative care should not be the only treatment option for this group.

In the past, whilst working within respiratory, health care professionals have often expressed a helplessness to treat patients who are frequently admitted with exacerbations of COPD. Occasionally terms like “repeat admission”, “social admission”, “panicker” and, more recently “palliative” have been used to describe these patients. Occasionally it seemed that reasons for hospital admission were even associated with the patient with suggestions such as “still smoking”, “declined social services”, “never attended the clinic appointments”, “declined PR” and “turned their O₂ up”. This possibly meant that these patients may not be considered suitable for early discharge schemes, PR or smoking cessation, as it may have been assumed they would decline to attend or fail the intervention.

As a more junior physiotherapist I remember feeling a sense of responsibility and a sense of personal failure if a patient was readmitted soon after discharge. I felt I must have missed a new infection or failed to meet all their rehabilitation needs. Then later I became hardened to this and maybe shared the frustration of my colleagues. More recently the sense of failure returned and I felt I wanted to address more than palliative care in these patients. I wanted to help them access other treatment options. I think this probably came to the forefront when I witnessed a new junior physiotherapist happily completing a smoking cessation referral and PR referral for a regular attender after the patient consented. I probably would not have even offered those things to this patient knowing that they had declined previously.

The patients with very severe COPD were frequently bed bound on admittance into hospital in an unresponsive state. They were previously deconditioned and often housebound. They repeatedly became dependent on the NIV used to treat their acute respiratory failure and became breathless with removal. Using my clinical knowledge of balancing wean and rehabilitation it made sense to me to
continue rehabilitation on the ventilator. The practicalities of this were very individual to each patient. I increased the pressures in response to breathlessness and desaturation. It seemed to be an effective way to rehabilitate this very breathless group, however I had no clear idea of the physiology behind it, whether it did really clinically benefit the patient or if there was a preferred method for delivery. Therefore I was keen to create a study that investigated whether exercising on NIV was feasible out of hospital and if it had any clinical benefit. I also wanted to give the patients with severe COPD another chance at treatment.

1.21.2 Clarification of the role of the PhD student

To enhance understanding it is important to clarify my role throughout the thesis. I thought out the research question and developed the design and protocol. I sought out commercial funding and applied for ethical approval. I am the researcher who undertook recruitment and consented participants into the study. I am the physiotherapist who treated the participants with the intervention and I am the researcher who assessed the outcome measures. I completed the quantitative data analysis. I undertook the interviews, transcribed and coded the content. I evaluated the intervention and research design.
1.22 Aims of the Research and Thesis

1. To evaluate the acceptability of applying non-invasive ventilation (NIV) during exercise in both the hospital environment and at home to patients with severe COPD who have been hospitalised for an acute exacerbation with acidotic respiratory failure.

2. To gather qualitative data to aid understanding of the patient experience of participation in the intervention arm of the research trial to enhance quantitative acceptability data.

3. To evaluate the feasibility of a randomised controlled trial design including:
   - Ability to complete the design in clinical environment with available resources
   - Availability of the participant sample pool
   - Recruitment numbers and recruitment time period
   - Randomisation process and acceptability
   - Participant retention in the trial, drop-out rate and reasons

4. To evaluate the feasibility of collation and completion of the quantitative outcome measures to inform a future trial of the potential primary outcome and secondary outcomes. These measures include:
   - Six minute walk test (6MWT)
   - St George’s Respiratory Questionnaire (SGRQ)
   - European Quality of Life - 5 Dimensions - 5 Levels (EQ-5D-5L): Utility score and visual analogue score
   - The Activity of Daily Living Questionnaire (LCADL)
   - Activity levels
   - Medication use, access to healthcare and hospital admissions

1.23 Objectives

1. To review and critically evaluate the existing literature regarding exercising patients with severe COPD on NIV. To inform the development of the feasibility study design. Focusing on the reasoning behind the study question, sample
characteristics, recruitment and retention of participants, trial design and hypothesis, outcome measure choice, SAEs and duration of follow up.

2. To review and critically evaluate the existing literature regarding the planned intervention of the practicalities of exercising patients with severe COPD on NIV. To understand which modes, pressures, circuitry of ventilation and type, duration, intensity of exercise to use.

3. To review and critically evaluate the existing literature regarding exercising patients with severe COPD on NIV. The research question was shaped in clinical practice but the researcher wanted to be certain that the research was novel.

4. To design and carry out a research protocol for patients with severe COPD to exercise on NIV documenting clearly the methodology to inform future studies. To develop an outline of the future research protocol justified by the feasibility trial.

5. To evaluate the feasibility of the research design, research method, process and intervention as a whole to inform the outline of a protocol for the future trial. The scope of this evaluation includes recruitment and retention of participants, and implementation of an individualised exercise programme on patients who have been seriously ill and are deconditioned. Evaluation of the intervention arm of applying NIV during exercise at a high PS. Evaluation of the outcome measures and sample size calculation for statistical significance of the chosen primary outcome.

6. To evaluate whether it is feasible to deliver the intervention in everyday practice. The feasibility of recruiting participants who have been acutely unwell from the hospital environment and exercising them on NIV for a three month period in both the acute care and community environment with the available resources.

7. To evaluate the acceptability of the research to participants.

8. To explain the experience of the participants of the research and intervention.

9. To evaluate the process and timing of collating the outcome measures and their completion, including the description of any trends in changes in the
outcome measures recorded between treatment groups, to inform primary and secondary outcome measures in a future trial.

10. To fully integrate both the quantitative results and qualitative results to ensure a complete evaluation of feasibility.

1.24 Structure of thesis

To assist the reader with navigation of this thesis the following paragraphs provide a brief description of each chapter’s content.

Chapter 2 provides a critical analysis of the literature on exercise on NIV in patients with COPD. The literature review informs the planned feasibility study design and intervention.

Chapter 3 outlines the chosen mixed methods methodology and the justification for this. It chronicles the development of key methodological decisions including the change in research study aim to feasibility. It goes on to discuss the strengths and weaknesses of the chosen methodology.

Chapter 4 reports the quantitative method from initial design, gaining funding, ethical approval and intellectual property rights. It goes on to discuss the choice of outcome measures and briefly discusses why alternatives were not considered.

Chapter 5 describes the qualitative method of semi-structured interviews used and how analysis was carried out using a step by step approach using thematic analysis (TA).

Chapter 6 presents the quantitative results. In particular it seeks to answer the aim of feasibility focusing on recruitment retention, outcome measure completion and presentation of any trends in the data.

Chapter 7 portrays the findings and analysis from the qualitative semi-structured interviews. It seeks to offer an insight into the patient experience by presenting as many of the participants’ voices as possible. Themes are presented under concepts based on the research aims and objectives.

Chapter 8 explains how the researcher saw herself as influencing and interacting with the research. The chapter describes how this was present and how it evolved at each stage of the research process. It goes on to demonstrate the researcher’s
learning journey. By presenting this information in an open and honest way the researcher hopes to improve rigour and offer further insight into the qualitative findings.

Chapter 9 is the discussion integrating both the quantitative and qualitative data to answer the original question of feasibility. It discusses the feasibility of all aspects of the research trial from recruitment to undertaking the outcome measures. It also discusses the acceptability of the research and intervention to participants, a valuable component of feasibility. It discusses the strengths and limitations of the research and alternative methods that could have been used. It goes on to outline how a definitive RCT may look based on the findings of this feasibility study.

Chapter 10 concludes the thesis. It reviews the research aims and objectives, evaluating the extent to which they have been achieved.

1.25 Conclusion

This chapter has laid the foundation and set the scene for the research project and thesis by reviewing the historical background, definitions, pathophysiology and personal perspectives that have inspired the research and provided motivation for this thesis. It included a detailed account of COPD including prevalence, cause and pathology. It discussed the symptoms and impact of COPD on patients’ lives. It discussed how the pathophysiology of COPD limits exercising. It then focused on available treatment, in particular PR. Unfortunately PR is not accessible to all patients with COPD, especially those with severe disease, thus this required further investigation. One possible intervention available was exercising on NIV. In clinical practice the researcher had witnessed patient reported benefits of exercising on NIV. The next chapter of the literature review sought to evaluate the quality of the research available on exercise on NIV in patients with COPD and highlight missing research in the literature to inform the development of the planned feasibility study.
Chapter 2 Literature Review

2.1 Introduction

This thesis differs from some traditional theses because the research question has been directly derived from clinical practice, thus the literature review has been carried out following the initial research development. The purpose of the literature review was to inform and develop the design of the feasibility study and intervention. A further extended review of studies that were not included in the SRs was also included to further inform the study and intervention.

The literature review was composed of two parts:

Part A: Reviewed the high quality evidence from SRs regarding exercise on NIV in patients with COPD (to inform the design of the research study and intervention).

Part B: Reviewed any literature not included within Part A (to inform the design of the research study and intervention).

2.2 Aims: Part A

The literature review for Part A sought to meet the following aims:

1. To carry out a literature search for SRs on exercise on NIV in COPD.

2. To evaluate the quality of the evidence reviewed.

3. To inform the development of the feasibility study. Focusing on the reasoning behind the study question, sample characteristics, recruitment and retention of participants, trial design and hypothesis, outcome measure choice, SAEs and duration of follow up.

4. To inform the design of the complete intervention. Focusing on type and mode of ventilation, ventilation settings and interface, location of intervention, type of exercise, duration and timing of intervention.

5. To establish whether the research question formed in clinical practice was novel.
2.3 Methods: Part A

2.3.1 Search strategy

The initial search began in 2012 and it was continually updated. Updated searches were based on the Menadue et al., (2014) SR search strategy. A literature search was performed using the following electronic databases: Cochrane central register of controlled trials (CENTRAL), the Allied and Complimentary Medicine database (AMED), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica database (Embase) (1974-2001), Medical Literature and Analysis and Retrieval System Online (MEDLINE), Physiotherapy Evidence Database (PEDro), Psychological Information Database (PsycINFO) and PubMed. This was searched between the dates of 2000 to 2015. This was because the literature pre-dating this had been discussed during Chapter 1 (Introduction) and because of advances in ventilator technology. Articles were screened for inclusion criteria based on their titles; duplicates were removed; and the abstracts and finally the full articles were reviewed and analysed. The reference lists of each reviewed article were screened to identify any other relevant articles. Careful notice was taken at key conferences (ERS 2013, ERS 2014, ERS 2015, BTS 2013, BTS 2014, BTS 2015 and European Respiratory Care Association Congress (ERCA) 2015) for any unpublished data by key authors. Boolean operators of AND/OR were used to combine the search terms as Exercis* OR pulmonary rehabilitation AND COPD AND BIPAP OR NIV OR CPAP OR non-invasive ventilation OR PAV OR proportional assist ventilation OR NIPPV. Table 2.1 shows the key words used in the search.
Table 2.1 Key search terms

<table>
<thead>
<tr>
<th>COPD</th>
<th>NIV</th>
<th>Exercise</th>
<th>Review</th>
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<tr>
<td>Chronic Obstructive Pulmonary disease</td>
<td>Non-invasive ventilation</td>
<td>Rehabilitation</td>
<td>Meta-analysis</td>
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<td>CAL</td>
<td>NIPPV</td>
<td>Pulmonary rehabilitation</td>
<td>Systematic</td>
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<td>Chronic airflow limitation</td>
<td>Ventilation</td>
<td>PR</td>
<td>Review</td>
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<td></td>
<td>Pressure support</td>
<td>Exercise*</td>
<td>Overview</td>
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<td></td>
<td>Positive pressure</td>
<td>Exercise therap*</td>
<td>Literature</td>
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<td></td>
<td>PAV</td>
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<tr>
<td></td>
<td>Proportional Assist ventilation</td>
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2.3.2 Inclusion/exclusion criteria

Only SRs and meta-analyses were considered. This was because SRs and meta-analyses are considered to be the most reliable source of evidence when evaluating the effectiveness of interventions in healthcare (Scottish Intercollegiate Guidelines Network (SIGN), 2010). SRs from the year 2000 were included because ventilator technology had advanced significantly over recent years and thus newer data were more likely to be relevant and applicable to the intended study. SRs not written or translated in to English were excluded because of the potential difficulty of obtaining correct translation. This may have introduced language bias into the review, however bias may be reduced as some of the reviews themselves included non-English studies. Only SRs on adults were included as COPD is only diagnosed in adults (see Chapter 1 Introduction, section 1.2). The final inclusion criteria were:

1. Full SRs and meta-analyses of exercise on NIV
2. Dates from 2000 to present
3. Treatment was positive pressure on exercise
4. Included patients > 18 years old
5. The full review was published in English

There was a limited number of articles relating to NIV on exercise therefore specific exclusion criteria were deliberately limited. The only exclusion criterion was not including paediatric studies.
2.3.3 Methodological quality assessment

The SRs are presented using the 27-item checklist for Preferred Reporting Items for SRs and Meta-Analyses (PRISMA) tool (Moher et al., 2009). The PRISMA tool was considered useful to present the content of the SRs but an additional critical evaluation of the quality of the reviews was presented using the Critical Appraisal skills programme (CASP) tool (CASP, 2014). Initially both the CASP and Scottish intercollegiate guidelines network (SIGN) (Scottish Intercollegiate Guidelines Network, 2012) tools were considered as these were both familiar to the researcher from evidence evaluation in clinical practice. The use of an appraisal tool is important for maintaining a consistent approach. The tools were useful because they were aimed at reviewing a particular type of research for example, SRs (Aveyard, 2010). There is no gold standard critical appraisal tool developed for allied health research (Katrak et al., 2004). The researcher chose the CASP tool because it was more relevant to clinical practice and demonstrated the researcher’s thought processes more effectively. The CASP tool was concise, encompassed a wide range of appraisal questions, had pragmatic content and was useful for investigating the rigour of methods and reporting of the research evaluated (Nadelson and Nadelson, 2014). The CASP tool consists of three parts: Assessing whether the results are valid; what the results are and if it will help locally. There are ten questions within the tool answerable with yes, no, or can’t tell. Within each question there are prompts to help the evaluation. The quality assessment will be further discussed in the Discussion.

2.4 Results: Part A

2.4.1 Introduction

This section will present the results of the literature search, tabular data detailing the included SRs and the results of the assessment of their methodological quality. The quality of the SRs will be further discussed in the Discussion: Part A, section 2.5.1

2.4.1 Included SR results

There were three SRs that met the inclusion criteria and were analysed for methodological quality. Of the ten studies that did not meet the inclusion criteria two full studies were not documented in English (Gravier et al., 2015; Vargas et
al., 2011). One SR was not included because it was just an abstract (Correia, Tomas and Carolino, 2014). Five were excluded because they were narrative reviews (Ambrosino and Cigni, 2015; Corner and Garrod, 2010; De Backer et al., 2010; Dreher, Kenn and Windish, 2008; Araujo et al., 2005). Two reviews were excluded because the intervention was not exercising with NIV (Dretzke et al., 2015; Struick et al., 2013). The results of the literature search are presented in figure 2.1

![Figure 2.1 Literature search flow diagram](image)

2.4.2 Methodological quality assessment.

The detail of the three SRs included from the literature search are presented in Table 2.2 using the PRISMA checklist followed by Table 2.3 using the CASP tool for further methodological quality evaluation of the SRs.
**Table 2.2 Review of SRs using the PRISMA checklist for the reporting of SRs**

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<tr>
<td><strong>3. Introduction:</strong></td>
<td>a) 1. Benefits of high intensity PR training and why COPD inhibits this. 2. NIV and use in exercise. b) Variability of NIV protocol.</td>
<td>a) 1. Benefits of high intensity PR training and why COPD inhibits this. 2. NIV and use in exercise. b) Methodological quality of studies.</td>
<td>a) 1. Benefits of high intensity PR training and why COPD inhibits this. 2. NIV and use in exercise. b) NIV use during multiple exercise sessions.</td>
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<tr>
<td><strong>4. Objectives</strong></td>
<td>Evaluate the effectiveness of different modes of NIV during exercise to reduce exertional dyspnoea and improve exercise endurance acutely, in patients' with COPD.</td>
<td>1. Evaluate the physiological effects of exercise training with NIV after PR in patients with COPD: 2. Investigate dose response relationship of benefit and total training time with NIV.</td>
<td>Does NIV during exercise training (as part of PR) affect exercise capacity, HRQOL and physical activity in COPD compared with exercise training alone or exercise training with sham NIV?</td>
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<tr>
<td><strong>5. Methods:</strong></td>
<td>Protocol not documented or located.</td>
<td>Protocol not documented or located.</td>
<td>Cochrane number.CD007714. Published protocol &amp; amendment</td>
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| **6. Eligibility criteria:** (PICO-Patient, intervention, comparison and objective measure) | **Patient:** COPD: ERS definition (Siafakas, et al.1995)  
**Intervention:** NIV  
**Comparison:** Cross over trial (control). Randomisation of intervention order (NIV versus placebo).  
**Objective measure:** Borg-scale during cycling or walking exercise test at 50% or 80% VO<sub>2peak</sub> or 50% of W<sub>max</sub>. Endurance time at 50% VO<sub>2peak</sub> test), 50–60% W<sub>max</sub>, 60–70% W<sub>max</sub>. On 80% W<sub>max</sub>, on 75% W<sub>max</sub>, 80% VO<sub>2peak</sub>. Walking distance at a comfortable speed.  
Other: Published in the English, Dutch, or German language. | **Patient:** Stable COPD (received PR)  
**Intervention/comparison:** Comparative: effect of NIV and exercise training  
**Outcomes:** Lactate production, heart rate (HR), walking or physical exercise performance, respiratory outcomes, and training characteristics (number of and duration per session of sessions, and rehabilitation schedule)  
Other: Published in the English language. | **Patient:** 1. Stable diagnosed COPD, no exacerbation in past month. 2. FEV<sub>i</sub>/FVC < 70% and FEV<sub>i</sub> < 80% predicted GOLD stage II to IV (GOLD 2013). 3. Excluded: non-COPD, NMS, restrictive/thoracic or cardiac disease.  
**Intervention and Comparison:** NIV (bi-level, PS and PAV) via mask/mouthpiece during supervised exercise. Control: exercise training with/without sham NIV. O<sub>2</sub> provision (both groups). Nocturnal NIV included (in both groups). Training: arm and/or leg endurance and > 4 (no < 2) supervised sessions/week.  
**Objective:** Exercise capacity (peak capacity, constant work rate, endurance, functional capacity) post exercise training, without NIV). HRQOL (disease specific/generic instrument). Physical activity measure. |
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<td><strong>8. Search</strong></td>
<td>Following thesaurus (MeSH) terms were used: pulmonary rehabilitation, noninvasive ventilatory support, inspiratory PS, CPAP, PAV, COPD.</td>
<td>“noninvasive ventilation,” “training exercise,” and “chronic obstructive pulmonary disease” as key words.</td>
<td>(exercis* or physical* or train* or rehabilitat* or conditioning or ergometry or treadmill or endurance or “upper limb”) AND (non-invasive* or noninvasive* or “non invasive*” or NIV or “positive pressure” or NIPPV or “pressure support” or IPS or “assist* ventilation” or PAV or “ventilatory support” or bilevel or BVS or “mechanical ventilation” or “artificial ventilation” or “artificial respiration” or mask* or BiPAP or IPAP or EPAP or nasal* or NIV during exercise training for people with chronic obstructive pulmonary disease or “positive airway*” 1/1/1987, NIV delivered via mask 1987.</td>
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<tr>
<td><strong>9. Study selection</strong></td>
<td>Abstracts were included if reported detailed method and results.</td>
<td>Controlled trials included.</td>
<td>RCTs compared NIV during exercise training versus exercise training alone or with sham NIV in people with COPD.</td>
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<td><strong>10. Data collection process</strong></td>
<td>After consensus meetings: studies evaluated quality independently by two reviewers (a third if required).</td>
<td>Conducted independently, copied by two reviewers. Independently selected studies for inclusion. Disagreements resolved by consensus or third senior author. Data extract sheet: piloted on three randomly selected articles. Extracted author, study year, participants, country, outcomes, training schedule characteristics, and dropouts. Second reviewer checked accuracy.</td>
<td>Two reviewers independently included studies. Titles/abstracts were reviewed; kept or discarded. Kept papers were evaluated. Kappa coefficient calculated: Agreement between authors on inclusion from initial and second selection. Two reviewers independently extracted data: Pre-set form: Methods; sample; intervention; outcomes; and results. Post training data: extracted if participants were evaluated off NIV. Discrepancies resolved by consensus. If no numerical data: (Engauge Digitizer, <a href="http://digitizer.sourceforge.net/">http://digitizer.sourceforge.net/</a>) converted graphical images. Two reviewers independently manually extracted data from graphs. Authors contacted for missing data.</td>
</tr>
<tr>
<td><strong>11. Data items:</strong> <strong>Outcome</strong></td>
<td>Exertional dyspnoea &amp; exercise endurance</td>
<td>Post training physiological effects.</td>
<td>1. Exercise capacity, HRQOL and physical activity. 2. Training intensity, physiological changes, dyspnoea, dropouts, AE, cost.</td>
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<td><strong>12. Risk of bias in individual studies</strong></td>
<td>Quality screening: Delphi) (Verhagen et al., 1998): Patient characteristics, randomization procedure, blinding procedure, control for co-intervention(s), reliability and validity of the assessment procedures, description of the intervention &amp; description of withdrawal/dropout.</td>
<td>Two reviewers: PEDro scale (Physiotherapy Evidence Database, 1999): study design, statistical analysis and intention to treat. Age, gender, and FEV1 random effects comparison, and comparisons between NIV and placebo at isotime were reported.</td>
<td>Two reviewers: Cochrane Handbook for SRs of Interventions (Higgins, 2011): randomisation sequence generation; allocation concealment; blinding; completeness of outcome assessment; selective reporting; and other bias. Included: Un-blinded studies. Graded: high, low or unclear risk of bias.</td>
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<td><strong>13. Summary measures</strong></td>
<td>For effect size of each study: calculated the difference between the means of the experimental and control phases, divided by SD of control phase.</td>
<td>Baseline age, gender, and FEV1 compared by means of random effects comparison, and comparisons between NIV and placebo at isotime</td>
<td>Mean post-intervention values, changes from baseline values and SDs for continuous variables from both groups within each study. MD and 95% CI were used when combining continuous data measured on the same scale. SMD used when studies reported data measured on different scales that could not be converted to a common scale. When possible, estimates of treatment effect NIV during training for people with COPD (and confidence limits were related to the MID for each outcome.</td>
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<td><strong>14. Synthesis of results</strong></td>
<td>Results: Pooled and combined after each study was weighted to estimate variance of the summary effect size. Z statistics &amp; <em>P</em> values: Calculated from totals of the added values in experimental and control groups and the estimated variances for the total group. Summary effect sizes: Calculated Borg and cycling time or walking distance/time. For different modes summary effect sizes (best-case, worst-case scenario, greatest and lowest effects reported, were pooled separately). Post hoc analysis and summary effect sizes calculated: Effects of different modes on endurance. For each summary effect size, the homogeneity (or heterogeneity) test (<em>Q</em> statistics) was examined to see if studies shared a common effect size to explain if variance was from sampling error alone, justifying the fixed effects model. For any statistically significant heterogeneity found: random-effects model was used to decide significance. The value for rejecting H0 was 0.05.</td>
<td>Analysis: compared results between PAV and PS ventilation; variable modification at isotime after training in the NIV arm using a meta-analytical approach. If the heterogeneity evaluated by <em>I</em>^2^ was &gt; 50%, the random effects model was selected over the fixed effects model.</td>
<td>Dichotomous data combined, treatment effect was defined as odds ratio (OR) with 95% CI. Unit of analysis = participant. Missing data: If dropouts (&gt; 15%), and results from ITT and per-protocol analyses were reported, data extracted from ITT analyses: if not reported, data from the per-protocol analyses were used for meta-analysis. If incomplete statistical results reported in an included study for a given outcome the missing data was requested. If still unavailable then not used for that outcome. Effect of heterogeneity: Using <em>I</em>^2^ statistic, indicated the percentage of the total variation in observed intervention effects across studies caused by heterogeneity not chance alone. If included studies were clinically homogeneous, data were combined using software: Forest plots created. A fixed-effect model for all analyses unless a moderate or greater degree of heterogeneity was detected (<em>I</em>^2^ &gt; 30%): a random-effects model used.</td>
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<td><strong>15. Risk of bias across studies</strong></td>
<td>Bias: Scoring totals provided.</td>
<td>Bias: Small study &amp; publication bias effect: funnel plot. Harbord &amp; Egger tests applied if $&gt;5$ studies included</td>
<td>Small number of included trials meant no funnel plots to assess publication bias.</td>
</tr>
<tr>
<td><strong>16. Additional analysis</strong></td>
<td>No additional analysis</td>
<td>If training duration influenced changes in outcome in the NIV arm, used random effects meta-regression approach and evaluated training duration as explanatory covariate. Study weight from meta-analysis was used in the regression analysis as a weight variable. $p&lt;.05$ was significant, and all statistical were two-tailed. Performed Meta-analysis, meta-regressions, and Harbord &amp; Egger asymmetry tests.</td>
<td>No subgroup analysis.</td>
</tr>
<tr>
<td><strong>17. Results: Study selection</strong></td>
<td>10 articles &amp; 5 abstracts evaluated 1 article &amp; 2 abstracts not included: No exercise endurance or dyspnoea. 3 articles excluded: No BORG. 2 studies excluded: No randomisation of order of exercise with NIV and then control. 5 articles &amp; 2 abstracts included.</td>
<td>107 results selected. 53 excluded: Duplicates or not comparative studies. 33 excluded: not stable COPD. 21 papers remaining: only 8 detailed training.</td>
<td>12,392 studies, excluded 12,299 by title/abstract (substantial agreement: Kappa 0.78), 1 from a reference list, 6/94 studies included (perfect agreement Kappa 1.0). Exclusions: 38 not RCT, 37 not exercise training, 6 not COPD. 4 NIV not used during exercise, 1 not stable COPD.</td>
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<td><strong>18. Study characteristics</strong></td>
<td>65 patients with COPD, mean age of 64 years and FEV&lt;sub&gt;1&lt;/sub&gt; of 35% predicted. 6 studies: exercise endurance: Measured endurance time (cycle), 1: exercise endurance: maximal walking distance (treadmill). 5 studies: the effects of 2 or more modes. 4 studies: Exertional dyspnoea (BORG). One mode of NIV reported.</td>
<td>174 patients with stable COPD, mean age 67 years. FEV&lt;sub&gt;1&lt;/sub&gt; 26-48% predicted. 8 Studies: 12-36 training sessions and 6-12 weeks duration. Studies: 6 NIV v control, 1 NIV v O&lt;sub&gt;2&lt;/sub&gt;, 1 NIV v heliox. Training: cycle ergometer, treadmill and endurance walking. Different NIV protocols. Measures: HR at Isotime, lactate post exercise and VO&lt;sub&gt;2&lt;/sub&gt;.</td>
<td>126 patients with COPD (control n = 63 v NIV n = 63) FEV&lt;sub&gt;1&lt;/sub&gt; range 26-48% predicted. Individual study size n = 18-29. Mean age = 63-71 years. Training in outpatients; 2 hospital based. Training 6-8 weeks duration, 2-3 sessions/week of 45 minutes exercise at moderate intensity. Different NIV protocols.</td>
</tr>
<tr>
<td><strong>19. Risk of bias within the studies</strong></td>
<td>All studies: lung function, randomization and co-interventions were applied equally and NIV protocol described well. All studies: No description of: randomization, or blinded observer or of the reliability &amp; validity of the outcome measure, withdrawals and dropouts.</td>
<td>All studies: satisfactory score on PEDro % predicted FEV&lt;sub&gt;1&lt;/sub&gt;: heterogeneous (not statistically significant) Duration of training: homogenous Session duration: heterogeneous</td>
<td>Quality of evidence low for exercise capacity and moderate for QOL, training intensity and isoload blood lactate. Randomisation sequence: adequate in 50% of studies (not reported in 3). Blinding: trainers &amp; participants not blinded: High risk of performance bias 5/6 studies. 50% studies blinded assessor to evaluate clinical outcomes. 5/6 studies reported drop outs. 2 studies did not report full results.</td>
</tr>
<tr>
<td><strong>20. Results of individual studies.</strong></td>
<td>Reported 7 studies: Analysed FEV&lt;sub&gt;1&lt;/sub&gt;, outcome, effect size and SD and p value.</td>
<td>Reported 8 studies: Analysed mean age, FEV&lt;sub&gt;1&lt;/sub&gt;, training protocol. NIV v placebo: trend for differences in HR or VO&lt;sub&gt;2&lt;/sub&gt; but not statistical.</td>
<td>Reported 6 studies: Analysed 6MWT, SGRQ, endurance, lactate levels, work capacity and respiratory muscle strength.</td>
</tr>
</tbody>
</table>
21. **Synthesis of results**

- **van’t Hul, Kwakkel and Gosselink (2002)**
  - Statistically significant summary effect size: Dyspnoea (0.57; CI 0.04-1.07; \( p = 0.03 \)).
  - Heterogeneity statistic: Not significant (\( \chi^2 = 0.28; \ p = \text{NS} \)).
  - Average (weighted) improvement in Borg on exercise with NIV was < 2 units during isotime control phase.
  - Best-case: Effect of NIV on endurance, a statistically significant summary effect size was found (0.58; CI 0.29-0.87; \( P < 0.001 \)).
  - Overall heterogeneity: Not significant (\( \chi^2 = 3.95; \ p = \text{NS} \)).
  - Summary effect size: Mean (weighted) improvement in endurance of 3.3 min.
  - Worst-case: Summary effect size on exercise endurance was still statistically significant (0.33; CI 0.05-0.62; \( p = 0.02 \)), an average (weighted) increase in exercise endurance: 1.7 min.

- **Ricci *et al.* (2014)**
  - Sub-analysis by ventilation protocol did not show statistical significance in the pooled analysis.
  - After training NIV arm: HR at isotime improved by 6 beats/minute (95% CI 0.98-11.01, \( p = 0.02 \)).
  - Work load (fixed effect mean change 242.11(95% CI 154.93-329.9), \( p = 0.001 \)).
  - Lactate: not statistically significant but trend for improvement (fixed effect mean change 0.21 (95% CI -0.1 to 0.54), \( p = 0.205 \)).
  - Effect of training intensity on patient performance: Meta-regressions reported: positive relationship between variable modification and training time for all outcomes considered.

- **Menadue, Piper, van’t Hul and Wong (2014)**
  - NIV on exercise arm: Comparative risk (95% CI) and relative effect size (95% CI) of the intervention: Exercise capacity (% change in peak work rate incremental cycle/treadmill test) \( n = 48 \) (3 studies): 17% higher (95% CI 7-27%).
  - Exercise capacity (% change constant work cycle endurance test cycle endurance test) \( n = 48 \) (2 studies): 59% higher (95% CI 4-114% higher). Exceeds 34% the minimally important difference. Endurance time (minutes) (constant work rate cycle exercise test): \( n = 48 \) (2 studies): 3.62 minutes higher (0.17 minutes lower to 7.41 minutes higher).
  - HRQOL: SGRQ mean score: \( n = 48 \) (2 studies) 2.45 points higher (2.3-7.2 points higher).
  - Physical Activity: not measured.

22. **Risk of bias across studies**

- **van’t Hul, Kwakkel and Gosselink (2002)**
  - Agreement between reviewers on 78/91 criteria scored (Cohen’s kappa = 0.86).
  - The methodological quality score was 31% to 54%.

- **Ricci *et al.* (2014)**
  - Agreement between reviewers satisfactory > 95%. Funnel plots & Harbord & Egger test did not exclude small study or publication bias effect.

- **Menadue, Piper, van’t Hul and Wong (2014)**
  - Small number of included trials meant no funnel plots to assess publication bias.
### PRISMA Checklist

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<tbody>
<tr>
<td><strong>23. Additional analysis</strong></td>
<td>Heterogeneity statistic: not significant ($\chi^2 = 2.3; p=NS$) when CPAP, PS, and PAV on endurance pooled separately. Significant, homogeneous ($\chi^2 = 0.02; p=NS$) summary effect size only for PS (0.41; CI 0.06-0.77; $p = 0.03$): Average (weighted) improvement: Time 2.2min.</td>
<td>A statistically significant effect on slope found when considering HR, work load as response variables: random effects estimates of these slopes were: 0.015 (95% CI 0.008-0.22) for HR 0.01 (95% CI 0.0002-0.0215) for work load.</td>
<td>Isoload blood lactate (mmol/L) $n = 37$ (2 studies) -0.97 mmol/L lower (1.58 to 0.36 lower).</td>
</tr>
<tr>
<td><strong>24. Discussion: Summary of evidence</strong></td>
<td>Caution acknowledged: Small significant effect size: use of PS over other modes. Further research: NIV during training is required.</td>
<td>Similarities (training) between studies and differences (Ventilator protocol) Further large numbered, based on power calculations, RCTs needed.</td>
<td>Effect on exercise capacity is unclear. NIV in training may improve the % change in peak and endurance capacity. Further good quality, large numbered RCT are needed, with assessment of outcome measures with known MID &amp; economic evaluation and long term impact.</td>
</tr>
<tr>
<td><strong>25. Limitations</strong></td>
<td>Differences in PS and outcome measure (BORG) unclear on MCID.</td>
<td>Drop out heterogeneity and small sample sizes.</td>
<td>No assessment of publication bias: small numbers, could not contact all authors.</td>
</tr>
<tr>
<td><strong>26. Conclusions</strong></td>
<td>NIV during exercise in COPD results in acute improvements of exertional dyspnoea and exercise endurance</td>
<td>The Meta-analysis: no evidence of superiority of using NIV to train. The trend for improvements in HR and VO$_2$ post training with NIV suggest benefit. Longer training duration in PR leads to improved physiological outcomes</td>
<td>No clear conclusions made. NIV in COPD during leg training may allow patients to exercise at higher training intensities and achieve greater physiological training effect compared with training alone or with sham NIV.</td>
</tr>
<tr>
<td><strong>27. Funding</strong></td>
<td>The Dutch Asthma Foundation (grant 3.2.99.28)</td>
<td>Not disclosed: no conflict of interest reported.</td>
<td>Royal Prince Alfred Hospital, Australia. Commercial funding: author declaration.</td>
</tr>
<tr>
<td>Abbreviation key:</td>
<td>ANZCTR Australian New Zealand Clinical Trials Register, CI Confidence interval, CINAHL Cumulative Index to Nursing and Allied Health Literature, EMBASE Excerpta Medica Database, FEV1/FVC Forced Expiratory Volume in 1 second/Functional Residual Capacity, H0 Null Hypothesis, HRQOL Health Related Quality of Life, ITT Intention-to-treat, LILACS Latin American and Caribbean Health Science, MD Mean Difference, MID Minimal Important Difference, Min Minute, NMS Neuromuscular, NS Non Significant, PAV Proportional Assist Ventilation, PEDro Physiotherapy Evidence Database, PS Pressure Support, SD Standard Deviation, SMD Standardised mean difference UMIN University Hospital Medical Information Network, VO2peak Peak oxygen uptake, Wmax Maximum Workload.</td>
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Table 2.3 Evaluation of the quality of the SRs using the Critical Appraisal Skills Programme (CASP) tool for SRs

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<tbody>
<tr>
<td>2. Did the authors look at correct papers?</td>
<td>Yes: RCTs and crossover studies.</td>
<td>Yes: RCTs but included one other, focused on aims of SR with intervention appropriate.</td>
<td>Yes: RCTs focused on aims of SR and intervention.</td>
</tr>
<tr>
<td>3. Were all the important, relevant studies included?</td>
<td>Yes: Good search strategy: Cochrane Airways group for RCT (2002). Detailed search terms. References were scanned and abstracts were included. Problem: 1) No authors contacted for extra studies. 2) No unpublished data.</td>
<td>No: No clear protocol, used electronic databases and manual search of reference lists. Problem: 1. No authors contacted for extra studies. 2. No unpublished data. 3. Excluded 11 papers: no detail on training regime but no clarification sought. 4. Only included English studies</td>
<td>Yes: Good strategy, clear search criteria and all search terms documented, used a wide range of electronic databases, including hand searching reference lists, personally contacting experts, and also screened conference abstracts. There were no language restrictions on studies.</td>
</tr>
<tr>
<td>4. Did the review's authors do enough to assess the quality of the included studies?</td>
<td>Yes: Scoring system based on Delphi list, a criteria for quality assessment of RCTs (Verhagen et al., 1998). Independently assessed by 2 reviewers and 3rd if disagreement.</td>
<td>Yes: PEDro scale. Independently assessed: 2 authors. Problem: Details of bias described but not tabulated.</td>
<td>Yes: 2 authors assessed internal validity and rigour of the studies. Strategy from Cochrane (Higgins, 2011), authors contacted. Problem: Did include unblinded studies.</td>
</tr>
<tr>
<td>Question</td>
<td>van’t Hul, Kwakkel and Gosselink (2002)</td>
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<td>5. If the results combined was it reasonable to do so?</td>
<td>Yes: Pooled and calculated best and worst case scenario. Calculated summary effect size for different modes of ventilation. Problem: Did not consider differences in PS used.</td>
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<td></td>
<td>Yes: For HR, workload, lactate and VO$_2$. Sub-analysis of pooled data for differences in mode of ventilation used. Problem: Not the same NIV, mode and settings. Did consider mode but not level of PS used.</td>
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<tr>
<td></td>
<td>Yes: Same objective measures, same intervention. Results displayed and discussed. Tested combined results with/without a study of mild COPD severity. Problem: Not the same NIV, mode or settings.</td>
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<tr>
<td>6. Are the overall results of the review clear and precise?</td>
<td>Yes: Results are clear</td>
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<td></td>
<td>Yes: Majority of results clear. Problem: Clearer figure needed to demonstrate the random effects meta-regression and paired comparison effect estimation in the NIV arm.</td>
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<tr>
<td></td>
<td>Yes: Results are clear.</td>
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<tr>
<td>7. How precise are the results?</td>
<td>Not sure. Problem: CI % is: not documented.</td>
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<td></td>
<td>Yes: Expressed as 95% CI.</td>
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<td></td>
<td>Yes: Expressed as 95% CI.</td>
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<tr>
<td><strong>Not sure:</strong> COPD, FEV$_1$ 25-39% predicted. Age range 59-69 years. <strong>Problem:</strong> 1. Recruitment location not documented to decide if any patients were missed. Stability of patients not classified. 2. Not elderly so may exclude sicker group.</td>
<td><strong>Not sure:</strong> Moderate-severe COPD with FEV$_1$ 26-48% predicted, only Bianchi, <em>et al.</em> (2002) study is moderate severity. Age range 64-72 years would fit with some of population of COPD seen in the UK. <strong>Problem:</strong> 1. Did not consider very elderly patients, therefore sicker patients with more co-morbidities not represented. 2. Did not consider unstable patients. 3. No recruitment location detail</td>
<td><strong>Not sure:</strong> Severe COPD (mean FEV$_1$ 26%-41% predicted + 1 moderate severity study FEV$_1$ 48%) and an age range 63-71 years. <strong>Problem:</strong> 1. Studies selected participants from outpatient clinics or PR referrals. This may miss non-attendees. 2. Stable patients, co-morbidities, elderly not included so may have excluded sickest population. 3. Drop outs included patients having an exacerbation therefore excluding sickest population.</td>
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<tr>
<th>9. Were all important outcomes considered?</th>
<th>No: Only considered exercise endurance and dyspnoea. <strong>Problem:</strong> 1. Did not consider common clinical measures e.g. 6MWT. 2. Did not consider QOL. 3. Did not consider activity levels. 4. Did not consider economic evaluation 5. Did not consider hospital admission or exacerbation rate.</th>
<th>No: Only considered physiological measures. <strong>Problem:</strong> 1. Did not consider common clinical measures e.g. 6MWT. 2. Did not consider QOL. 3. Did not consider activity levels. 4. Did not consider economic evaluation. 5. Did not consider hospital admission or exacerbation rate.</th>
<th>Yes: Considered both physical and QOL measures. <strong>Problem:</strong> 1. Did not consider common clinical measures e.g. 6MWT. 2. Did not consider admission or exacerbation rate. 3. Did not consider economic benefit outcome.</th>
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<tbody>
<tr>
<td></td>
<td>There is benefit detected, but not enough evidence to offset harm or cost.</td>
<td>Not enough evidence to detect harm, cost or benefit of using NIV during exercise. Further research is required.</td>
<td>Not enough evidence to detect harm, cost or benefit to use NIV during PR. Further research is required.</td>
</tr>
</tbody>
</table>

**Abbreviation Key:** CI Confidence interval, COPD Chronic Obstructive Pulmonary Disease, CPAP Continuous positive airways pressure, ERS European Respiratory Society, FEV$_1$ Forced expiratory volume in one second, HR Heart rate, HRQOL Health related quality of life, RCT Randomised controlled trial, PEDro Physiotherapy evidence database, PS Pressure support, QOL Quality of life, SR systematic review, UK United Kingdom, VO$_2$ Measure of oxygen consumption, 6MWT Six minute walk test.
2.4.3 How did the SRs inform the proposed research study design

The information as to how the SRs informed the proposed research study design is presented in Table 2.4

**Table 2.4 How the SRs may inform the proposed research study design.**

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<tbody>
<tr>
<td><strong>Sample Characteristics</strong></td>
<td>Stable COPD. Mean age 64 years. Mean FEV$_1$ of 35% predicted. 1 trial: less disease severity and no statistical or perceived effect. Sample size range $n = 6$-$39$.</td>
<td>Stable COPD recently carried out PR. Mean age 67 years. Mean FEV$_1$ of 34% predicted. Sample size $n = 7$-$15$ patients.</td>
<td>Stable COPD, no exacerbation in the past month. FEV$_1$ 26-48% predicted. Sample size range $n = 19$-$33$.</td>
</tr>
<tr>
<td><strong>Recruitment location/method</strong></td>
<td>Not recorded.</td>
<td>Not recorded.</td>
<td>2 trials from referrals to outpatient PR. 1 from Respiratory clinic. 1 trial referral to respiratory physical therapy. 2 trials not recorded.</td>
</tr>
<tr>
<td><strong>Number screened/ % recruitment</strong></td>
<td>Not recorded.</td>
<td>Not recorded.</td>
<td>Number of patients screened: 34-$89$. Not recorded in 3 trials. Recruitment %: 35-$85%$.</td>
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<tr>
<td>None of the studies described withdrawals or drop outs.</td>
<td>Drop outs 0-50% (difference between arms not discussed).</td>
<td>No details about participants who declined trial. Drop outs in NIV arm range from 21-44%. Drop outs in control arm range from 15-40%. 1 trial not recorded.</td>
<td></td>
</tr>
<tr>
<td>Reason for drop out (n = number of patients)</td>
<td>Not recorded.</td>
<td>Not recorded.</td>
<td>Intolerant of NIV n = 8, Acute exacerbation COPD = 15, Exercise Hypertension = 2, Unexplained coronary = 2, Non-pulmonary hospital Admissions = 2, Exertion of angina = 1, Non-concordance = 1, Liver disease = 1, Tibial fracture = 1, Conflict of schedule = 1, CCF = 1, Back pain = 1, Transplant = 2, CVA = 1, Fatigue = 1.</td>
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<tr>
<td></td>
<td>Not reported.</td>
<td>Not reported.</td>
<td>2 baseline assessments the week before training and 2 assessments in the week training completed. 1 baseline the week before and within 1 week of ending training. Baseline 2 weeks before start and final within 2 weeks of completion.</td>
</tr>
</tbody>
</table>

| Outcome measure that reflected change? | Exertional dyspnoea (BORG) decreased by 2 units (p = 0.3) and exercise endurance increased by 1.7(best case) - 3.3 minutes (worse case) (p < 0.001 to < 0.02). PS increased exercise endurance by 2.2 minutes (p = 0.03). | No clear benefit. The trend for improvements in HR and VO₂ post training with NIV suggest NIV may be of benefit. | Increase in percentage change peak and endurance exercise capacity with NIV during training. HRQOL: SGRQ possible effect. Physical activity was not assessed. Increase in training intensity with NIV and isoload lactate was lower with NIV. Effect of NIV on dyspnoea uncertain. |

| Outcome measure complications | Not described | Not described | Not described |

| AEs (other problem) | Not described | Not described | No AEs and no cost information. |

**Abbreviation key:** AE Adverse Event, CCF Congestive Cardiac Failure, COPD Chronic obstructive pulmonary disease, CVA Cerebral vascular accident, FEV₁ Forced expiratory volume in one second, NIV Non-Invasive ventilation, PS Pressure support.
2.4.4 How did the SRs inform the proposed intervention

Table 2.5 demonstrates how the reviewed SRs informed the proposed intervention.

**Table 2.5 How did the SRs inform the proposed intervention**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Mode:</strong></td>
<td>1 study: CPAP.</td>
<td>Mode: PAV: 2 studies.</td>
<td>Mode: PAV: 2 studies.</td>
</tr>
<tr>
<td></td>
<td>1 study: PAV versus CPAP versus CPAP and PAV.</td>
<td>PS: 6 studies.</td>
<td>PS: 1 study.</td>
</tr>
<tr>
<td></td>
<td>1 study: PS versus CPAP.</td>
<td></td>
<td>Bi-Level: 3 studies.</td>
</tr>
<tr>
<td></td>
<td>1 study: PS versus CPAP versus PAV.</td>
<td></td>
<td>Two studies also entrained O₂.</td>
</tr>
<tr>
<td></td>
<td>1 study: CPAP versus CPAP and PAV.</td>
<td></td>
<td>To keep SpO₂ at 90% in one study and SpO₂ at 92% in the other study.</td>
</tr>
<tr>
<td><strong>Ventilator Settings</strong></td>
<td>Treatment pressure CPAP 4 - 10cmH₂O.</td>
<td>PAV (FA 3.6, 0.7cmH₂O</td>
<td>FA 3.5 (1.6) cmH₂O/L/s, VA 6, EPAP 2cmH₂O.</td>
</tr>
<tr>
<td></td>
<td>PAV 2/1, 8/3, 6/3, 10/3.</td>
<td>VA 12.7, 1.5cmH₂O)</td>
<td>FA 3.6 (0.7) cmH₂O/L/s, VA 12.9.</td>
</tr>
<tr>
<td></td>
<td>PS 10-16cmH₂O.</td>
<td>(FA 3.5, 1.6cm H₂O</td>
<td>7 (1.5) cmH₂O/L during exercise training.</td>
</tr>
<tr>
<td></td>
<td>Small significant effect size for PS over other modes in improving exercise endurance.</td>
<td>VA 6.6, 2.2cm H₂O)</td>
<td>PS range 5-10cmH₂O.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PS range: 4-11cmH₂O</td>
<td>EPAP range 0-6cmH₂O.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EPAP range: 0-8cmH₂O</td>
<td></td>
</tr>
<tr>
<td><strong>Research setting</strong></td>
<td>Not reported</td>
<td>Not documented</td>
<td>1 study: Hospital outpatient</td>
</tr>
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<td>4 studies: Outpatient centre.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1 study: No information.</td>
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</tr>
<tr>
<td><strong>Exercise type</strong></td>
<td>6 studies: Cycle ergometer. 1 study: Treadmill.</td>
<td>Tread mill training, cycle ergometry and endurance walking/cycling.</td>
<td>Cycle ergometry.</td>
</tr>
<tr>
<td><strong>Intensity, duration, number of sessions</strong></td>
<td>One off exercise test.</td>
<td>Intensity not documented. 12-36 sessions. 20-60 minutes. 6-12 weeks duration.</td>
<td>Cycle ergometry: 3 studies: 50-70% of peak work capacity, 65% peak work capacity. Treadmill training: 50-60% maximum METS, 65-70% initial walking speed, Or 70% maximum baseline speed, Training session of 12 weeks led to greater training effect size.</td>
</tr>
<tr>
<td><strong>Intervention participation/training session attended</strong></td>
<td>One off test.</td>
<td>Not documented.</td>
<td>3 studies: Not documented. 1 study: all attended 1 study: 10/12 sessions attended. 1 study: Extended weeks if patient missed session.</td>
</tr>
<tr>
<td><strong>Reported problems/changes to intervention</strong></td>
<td>Not documented.</td>
<td>Not documented.</td>
<td>Mask intolerance led to drop outs.</td>
</tr>
</tbody>
</table>

**Abbreviation Key:** CPAP Continuous positive airways pressure, EPAP End positive airways pressure, FA Flow assist, METS Metabolic equivalents, PAV Proportional assist ventilation, PS Pressure support, SpO₂ Saturation of arterial blood with oxygen, VA Volume assist.
2.5 Discussion: Part A

2.5.1 Introduction

This discussion focused on the results of the SRs including the quality of the research methods used. It combined the results of the SRs and informed the planned feasibility.

2.5.2 Aims and outcome measures of the SRs

The SRs all had clear questions, aims and population group that they intended to review. The outcome measures of exercise endurance (van’t Hul et al., 2002), exercise capacity (Menadue et al., 2014) and physiological measures (Ricci et al., 2014) may not be that relevant to patients because it may be hard for them to translate the benefits into their everyday lives. The outcome measures that may be considered more relevant to patients are exertional dyspnoea on exercise (van’t Hul, Kwakkel and Gosselink, 2002), as breathlessness is a common symptom experienced by patients with COPD, and the HRQOL measures evaluated (Menadue et al., 2014).

2.5.3 Quality of the search methods

Ricci et al. (2014) was the only review that did not have a documented search protocol which may have biased the search resulting in missed studies. Menadue et al. (2014) carried out the most rigorous search of the literature that included unpublished data and approaching key authors for access to unpublished data. This may have resulted in the variation for the initial list of studies to search with 12,392 in Menadue et al.’s (2014) review compared to 107 in Ricci et al.’s (2014) review and only 15 in van’t Hul, Kwakkel and Gosselink (2002) review. Ricci et al. (2014) was the only review that did not consider English papers but the reasons for this were not recorded. All three studies used a third author to resolve any differences between the initial reviewers regarding inclusion and exclusion of studies. Menadue et al. (2014) demonstrated good methodology for searching as they also assessed for statistical agreement with the Kappa coefficient, achieving a substantial agreement score (Kappa = 0.78) for the initial selection and perfect agreement score (Kappa = 1.0) for the final selection. This is a robust method for reviewing inter-rater agreement for categorical points (Gwet, 2014).
2.5.4 The SRs' quality assessment

All three reviews used a research evidenced scoring system to assess quality. Menadue et al. (2014) presented the most detailed quality review in the SR, Ricci et al. (2014) presented the least complete quality review with no details of the quality scoring for each study.

2.5.5 Quality of the results

All of the SRs combined the results but this may have been inappropriate because all of the studies used different NIV models, modes and PS, therefore the intervention could have been quite different. Whilst van’t Hul, Kwakkel and Gosselink (2002) and Ricci et al. (2014) considered different modes they did not consider different models or PS.

2.5.6 How do the SRs reviewed inform the current study design and intervention?

Although the reviewed studies’ involved patients diagnosed with severe COPD, the samples may not be reflective of patients usually treated in acute clinical practice. This is because the studies reviewed recruited stable patients from the outpatient setting who had not experienced recent exacerbations and who did not suffer from extensive co-morbidities. Both Menadue et al. (2014) van’t Hul, Kwakkel and Gosselink (2002) commented on the observation that there were three studies who recruited patients with less severe lung disease. These studies did not demonstrate statistical or perceived benefit.

Only one SR recorded the number of participants screened and recruitment location. No time duration was recorded for screening. There was a variation in the percentage of participants recruited from the samples, from 35-85%. No details were given regarding inclusion/exclusion numbers or reasons given for declining to participate (Menadue et al., 2014). Drop-out rates were sought by two SR’s, van’t Hul, Kwakkel and Gosselink (2002) reported that this was not documented in the reviewed included studies. It was difficult to predict time of recruitment and screening numbers required from the reviewed SR’s. The lack of detailed documentation informed the planned feasibility study and it was noted that good documentation of recruitment and retention was an important consideration.
Menadue et al. (2014) reported that eight participants dropped out because of being intolerant to NIV and three of the eight were because of mask discomfort. In the planned feasibility study consideration was required for the time allocated to allow tolerance of NIV and mask comfort. An alternative consideration was recruiting participants that had already tolerated NIV acutely in hospital because this may have led to less drop outs. The other main reason for dropping out (n = 15 participants), in both the treatment and control arms, was an acute exacerbation of COPD. Whilst not unexpected this was concerning because the sample was a stable group of patients. Therefore if the planned feasibility study involved a less stable group then they could experience more exacerbations.

Two of the SRs supported the use of exercise endurance as an effective outcome measure to show change (Menadue et al., 2014; van’t Hul, Kwakkel and Gosselink, 2002). van’t Hul, Kwakkel and Gosselink (2002) demonstrated that BORG dyspnoea score may evidence change when evaluating studies of exercise on NIV. Therefore these were considered as potential outcomes for the feasibility trial. The discussion resulting from the SRs contemplated using outcome measures which are commonly used in clinical practice to measure the effects of exercise on NIV (for example the 6MWT) so the results are clinically meaningful. The results for HRQOL were inconclusive (Menadue et al., 2014). Thus it was valuable to consider HRQOL measures to review whether exercising on NIV is perceived by patients as being beneficial. The validity of each outcome measure should be documented in the research methods of the planned trial to ensure it measured what it intended to measure.

The SR’s informed the future intervention by detailing the mode and PS used. There was limited information about circuitry and mask used. van’t Hul, Kwakkel and Gosselink (2002) demonstrated a small significant effect size for the use of PS over other modes. When reviewing the exercise content cycle ergometry and treadmill were used as the intervention. The exercise sessions varied in length, intensity and number. These aspects were not evaluated in relation to exercise on NIV but one SR reported a greater training effect size in the 12 week programme (Menadue et al., 2014). Therefore the planned feasibility study may have benefited from undertaking a 12 week programme.
The overall reported quality of the studies varied. Menadue et al. (2014) reported the evidence to be of low quality for exercise capacity, moderate quality for HRQOL, training intensity and post training blood lactate levels (Menadue et al., 2014). For the proposed feasibility study consideration was undertaken to ensure clear documented methods would be used including recruitment, randomisation procedure and calculation of a prospective sample size for the selected primary outcome.

2.6 Conclusion: Part A

This literature review has demonstrated that a further RCT was necessary on the effects of exercising with NIV on patients with COPD. The review demonstrated that there was a gap in the literature considering exercising with unstable patients with COPD on NIV who have recently experienced an exacerbation.

The literature findings are inconclusive on using NIV to exercise patients with COPD. There were a number of methodological limitations identified that need to be addressed in future research to improve the available evidence. Therefore the intention of this doctoral research is to address these. Further evaluation was required to develop the research design and intervention, reviewed in Part B.

2.7 Aims: Part B

The literature review for part B sought to meet the following aims:

1. To carry out a literature search for studies on exercise on NIV in COPD that were not included in the SRs (reviewed in Part A).
2. To evaluate the quality of the evidence reviewed.
3. To inform the development of the feasibility study. Focusing on the reasoning behind the study questions, sample characteristics, recruitment and retention of participants, trial design, hypothesis, outcome measure choice, possible AEs and duration of follow up.
4. To inform the design of the complete intervention. Focusing on the type of ventilation, mode, settings, mask, location of intervention, type of exercise, duration and timing of intervention.
2.8 Methods: Part B

2.8.1 The search criteria

The initial search began in 2012 and it was continually updated. The search was completed using the same methods used for Part A, see section 2.3.1, Search strategy. Individual studies were sought rather than reviews. Table 2.6 shows the key words used in the search.

*Table 2.6 Search terms for literature review Part B*

<table>
<thead>
<tr>
<th>COPD</th>
<th>NIV</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Chronic Obstructive Pulmonary disease</td>
<td>Non-invasive ventilation</td>
<td>Rehabilitation</td>
</tr>
<tr>
<td>2. CAL</td>
<td>NIPPV</td>
<td>Pulmonary rehabilitation</td>
</tr>
<tr>
<td>3. Chronic airflow limitation</td>
<td>ventilation</td>
<td>PR</td>
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<td></td>
<td>Positive pressure</td>
<td>Exercise*</td>
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<td></td>
<td>Pressure support</td>
<td>Exercise therap*</td>
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<td></td>
<td>PAV</td>
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<td></td>
<td>Proportional Assist ventilation</td>
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</tbody>
</table>

2.8.2 The search inclusion criteria

The search inclusion criteria were:

1. Full studies of exercise on NIV
2. Published between 2000 to January 2016
3. Treatment was positive pressure on exercise
4. Included patients > 18 years old
5. The study was published in English
6. Not included in the SRs by van’t Hul, Kwakkel and Gosselink (2002), Ricci et al. (2014) and Menadue et al. (2014)

2.8.3 The search exclusion criteria

The search exclusion criteria were:

1. Paediatric studies
2. Not published in English
3. Not positive pressure use during the actual exercise
4. Included in the SRs by van’t Hul, Kwakkel and Gosselink (2002), Ricci et al. (2014) and Menadue et al. (2014)

2.8.4 Methodological quality assessment

The quality of each of the studies were critically evaluated using the CASP tool (CASP, 2014). The CASP was chosen because it is relevant to clinical practice and demonstrated the researcher’s thought processes more effectively.

2.9 Results: Part B

2.9.1 The results of the literature review

The results of the literature search are presented in figure 2.2. A list of the excluded studies can be found in Appendix 1.

![Flow diagram of the results of the literature search of part B](image)

*Figure 2.2 Flow diagram of the results of the literature search of part B*
2.9.2 Summary of the studies within the results of literature search B

There were 21 studies included in the results. The publication dates ranged from 2000 to 2014. The investigations were predominantly crossover designs and three were feasibility studies. The sample size of the studies ranged from \( n = 4 \) to \( n = 45 \), with a mean sample size of \( n = 14 \). In 19 of the studies one-off exercise tests were performed, two of the studies considered exercising with positive pressure during more than one exercise session. In nine of the studies cycle ergometry was the chosen exercise test. The other tests used included 6MWT, 12MWT, treadmill walking, endurance shuttle walk test (ESWT), UAE’s and knee extensor exercises. The two studies that attempted to undertake a longer programme of exercise both used cycling. The primary outcome measures used included endurance time, workload and limit of tolerance for cycle ergometry, E SWT and UAE. A few of the studies chose distance walked measured 6MWT. It included physiological values of respiratory including \( \text{PaO}_2 \) and muscle’s including IL-6 plasma levels. There were 13 studies that demonstrated statistical improvement of their primary outcome. Summaries of the included studies are presented in Table 2.7.
Table 2.7 The description of the included studies including reporting any statistical improvement

<table>
<thead>
<tr>
<th>Author/Date published</th>
<th>Sample size, age and lung function</th>
<th>Design</th>
<th>Outcome measure</th>
<th>Clinical or statistical improvement</th>
</tr>
</thead>
</table>
| Allan et al. (2009)   | n = 12. Mean age 70 ± (Standard deviation) 3 years Mean FEV₁ 42 ±10% predicted Mean FEV₁/FVC 41 ±7% predicted | Feasibility sequential randomised, placebo-controlled crossover. Cycle exercise test at (80% of maximal workload) with: 1. Air via mask 2. Sham NIV: PS 3cmH₂O 3. NIV 4. 60:40 (Helium: O₂ ratio) heliox with sham NIV 5. 60:40 heliox with NIV. | **Primary:** Total exercise time.  
**Secondary:** HR, SpO₂, RR. | **Primary:** Partial: NIV and Heliox (13.53 ±11.57 mins) duration was significantly more (p = 0.01) than heliox alone (10.10 ±10.04 mins) or NIV alone (p = 0.007) (0.95 ±10.14) but not significantly greater (p = 0.009) than sham treatment (05.57 ±05.50 mins).  
**Secondary:** Partial: With Heliox and NIV SpO₂ was significantly greater than just NIV (p < 0.001) or sham (p < 0.001). Authors reported the RR for sham was significantly greater than all of the treatment arms at peak exercise, but p-value was not reported. |
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<tr>
<th>Author/Date published</th>
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| Barakat et al. (2007)  | N = 12  
Mean age 64 ±8 years  
Mean FEV$_1$ 0.8 ±0.42L  
Mean FEV$_1$/FVC 0.31 ±0.07L | Crossover trial of:  
1. 10 sessions x 25min of static cycling at 25-50% of their maximum power without NIV.  
2. Followed by 10 sessions with NIV.  
PS 14-17cmH$_2$O, EPAP 3-4cmH$_2$O. | **Primary:** Work load and exercise time.  
6MWT.  
**Secondary:** Dyspnoea: BORG, SGRQ, Cardiovascular variables, CRQ. | **Primary:** Yes. Maximal mean workload was 50 $W_{\text{max}}$ ($p < 0.05$) with NIV and 27 $W_{\text{max}}$ without NIV.  
**Primary:** Yes. Mean exercise time 33.75 ±3.4min with NIV ($p < 0.05$) and 19.37 ±3.4min without NIV.  
**Primary:** Yes. 6MWT increased by mean 38m ($p < 0.01$) with NIV (245 ±87 to 282±111) verses 14m unsupported (231 ±97 to 245 ±87).  
**Secondary:** Yes. Mean BORG score improved from 4.7 ±1.81 to 1.3 ±0.6 ($p < 0.01$) with NIV and from 6 ±2.6 to 4.7 ±1.81 without NIV.  
NIV group showed SGRQ clinical improvement (< 4 units) in total scores: 63.71 ±12 to 58.39 ±17 with NIV verses 60.69 ±10 to 63.71 ±12 in unsupported group ($p$-value not documented).  
No change: Impact scores, cardiovascular variables and CRQ. |
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<tr>
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<th>Outcome measure</th>
<th>Clinical or statistical improvement</th>
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| Borghi-Silva et al. (2008) | n = 16
Mean age 59 ±6 years
Mean FEV₁ 42 ±14% predicted
FEV₁/FVC 43 ±15% predicted | Blinded crossover. Constant work rate (70-80% peak) cycle ergometry tests with: 1. PAV 2. Sham NIV: PS 5cmH₂O and PEEP of 2cmH₂O. | **Primary:** Exercise tolerance: Time. **Secondary:** Deoxyhaemoglobin levels, Dyspnoea (BORG), Leg discomfort. Cardiovascular & SpO₂. | **Primary:** Yes. PAV significantly increased time: mean 337±189 seconds versus sham NIV 273 ±142 seconds (s) (p = 0.01). **Secondary:** Yes. PAV lowered deoxyhaemoglobin concentration and significantly lessened the decrease in oxyhaemoglobin concentrations at 75% isotime and cessation. (PAV -85.4 ±19.4 to -70.4 ±18.8 versus sham -87.7 ±18.7 to -69.3 ±19.4. (p < 0.05). **Secondary:** No. No significant difference in dyspnoea; leg discomfort; cardiovascular or SpO₂ response. |
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<tr>
<th>Author/ Date published</th>
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<th>Outcome measure</th>
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<tr>
<td>Borghi-Silva et al. (2009)</td>
<td>n = 24 Mean age 68 ±8 years. Mean FEV$_1$ 33 ±10% predicted FEV$_1$/FVC 56 ±9%. Predicted n=18 healthy (added control)</td>
<td>Prospective cross over double blinded RCT. Maximum isokinetic dynamometer testing of concentric knee-extensor strength and 1min endurance test on: 1. Bi-level: (PS 8cmH$_2$O) 2. Sham Bi-level: IPAP 3cmH$_2$O and EPAP 2cmH$_2$O (PS of 1cmH$_2$O)</td>
<td><strong>Primary:</strong> Fatigue Index of the Quadriceps muscle. <strong>Secondary:</strong> SpO$_2$.</td>
<td><strong>Primary:</strong> Yes. Group 1. Bi-level had significantly less muscle fatigue 36.3 ±11.7 (mean % fatigue index score) than with 2. Sham 29.9 ±11.5% (p = 0.003). <strong>Secondary:</strong> Yes. Group 1. Bi-level significantly improved SpO$_2$ to 89 ±5% compared to using sham at 84 ±4% during isokinetic exercise (p &lt; 0.0001).</td>
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<td>Carrascossa et al. (2010)</td>
<td>n = 20 Mean age 62 ±7 years Mean FEV$_1$ 39 ±10% predicted FEV$_1$/FVC 0.46 ±0.14L</td>
<td>Randomised crossover. Constant load (75-80% peak work rate) cycle ergometry to the limit of tolerance whilst: 1. Mask only 2. Using PAV</td>
<td><strong>Primary:</strong> Tlim <strong>Secondary:</strong> SV, HR, CO.</td>
<td><strong>Primary:</strong> Partial. PAV had a statistical improvement in Tlim median 252s (range 163-645) compared to 219s (range 144-1200) p=0.05 (seen in n = 8/20 patients but n=12/20 Tlim decreased -20.5 (range -4 to -9). <strong>Secondary:</strong> Partial. SV slowed with PAV in n = 13 participants at the onset of exercise (p &lt; 0.05). <strong>Secondary:</strong> Partial. HR remained unaltered in 9/20 (p &gt; 0.05) with PAV. <strong>Secondary:</strong> Partial. CO reduced in n = 9/20 (p = 0.01).</td>
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<tr>
<td>Author/Date published</td>
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| Dreher, Storre and Windisch, (2007) | n = 20  
Mean age 65 ±9 years  
Mean FEV$_1$ 27 ±8% predicted | Feasibility randomised cross-over 6MWT test with rollator with NIV and O$_2$ versus just O$_2$. Mean IPAP 29 ±4cmH$_2$O and mean EPAP 4 ±0.4cmH$_2$O. | **Primary:** PaO$_2$  
Secondary: BORG, 6MWT | **Primary:** Yes. With NIV PaO$_2$ increased by 10.5 ±10.8mmHg (95% CI 5.4 to 15.6mmHg; p < 0.001) but decreased without NIV by 10.8 ±8.0mmHg (95% CI -14.5 to -7.1mmHg; p < 0.001).  
Secondary: Yes. BORG significantly (p < 0.001) decreased after walking with NIV from 6 (IQR 4.5-10) to 4 (IQR 1.5-4.5).  
Secondary: Yes. 6MWT distance significantly (p = 0.027) increased from 209m (IQR 178-279) to 252m (IQR 203-314) in favour of NIV assisted walking. |
| Dreher et al. (2009) | n = 19  
Mean age 63 ±10 years  
Mean FEV$_1$ 26 ±19% predicted  
FEV$_1$/FVC 39 ±7% predicted | Randomised cross over, three x 12MWTs. 1. Walk with usual O$_2$. 2. Walk with double the dose of O$_2$. 3. Walk with NIV and usual O$_2$. Mean IPAP 29 ±4cmH$_2$O and mean EPAP 2 ±1cmH$_2$O. | **Primary:** PaO$_2$  
Secondary:12MWT, BORG | **Primary:** Yes. PaO$_2$ decreased with O$_2$ by 8.2 ±10.9 and with the double O$_2$ by 4.2 ±10.9mmHg. PaO$_2$ increased by 14.0±16.66 mm Hg with NIV and O$_2$ compared to O$_2$ alone (p < 0.003).  
Secondary: No. Distance was less with NIV and O$_2$ (555 ±227 m) compared with usual O$_2$ (619 ±210 m) and double dose O$_2$ (622 ±215) (p < 0.024).  
Secondary: No. The median change of Dyspnoea (BORG) for O$_2$ was 4 (2.25-6.375), for Double O$_2$ was 3 (2-5.875) and for NIV was 4 (2.375-5.75). There was no significant difference p = 0.266. |
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<tr>
<th>Author/Date published</th>
<th>Sample size, age and lung function</th>
<th>Design</th>
<th>Outcome measure</th>
<th>Clinical or statistical improvement</th>
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<tr>
<td>Dyer et al. (2011)</td>
<td>Part A: n = 12. (No COPD). Part B: n=4 Mean age 72 ±12 years Mean FEV₁ not recorded</td>
<td>Cycle 20 min on static bike at 20 watts at 40-60 revolutions per min. NIV Mode ST IPAP 15cmH₂O EPAP 5cmH₂O +/- O₂ if desaturation.</td>
<td>Primary: Part A: effect of NIV on a single exercise test of exercise time and work done.</td>
<td>Primary: Part A: Not relevant: as no COPD. On NIV (n=5) median increase in exercise time of 854.4 seconds, median total work done significantly increased (p = 0.016) from 1560 (600-9720) J – 8336 (1200-21960) J. Primary: Part B: No. Not feasible to recruit to trial.</td>
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<td>Hannink et al. (2014)</td>
<td>n = 8 Mean age 62 ±2 years Mean FEV₁ 42 ±17% predicted FEV₁/FVC 33 ±12% predicted</td>
<td>Pilot cross over of 40W constant work-rate cycle exercise until symptom limitation or 20 min: 1. Unaided. 2. NIV aided. IPAP 12.0 ±0.8cmH₂O (range 10-14cmH₂O) and mean EPAP 5.0 ±0.4cmH₂O (range 4-6 cmH₂O).</td>
<td>Primary: IL-6 plasma levels, oxidative stress response to ROS, PaO₂. Secondary: Mean duration of exercise. HR, PCO₂, blood lactate. Leukocyte plasma concentrations, neutrophil plasma levels, dyspnoea (BORG) and leg pain.</td>
<td>Primary: Yes. IL-6 plasma levels increased significantly on control exercise, pre exercise 2.7 ±2.1pg/mL and response to exercise was +0.4 ±0.3pg/mL. IL6 plasma levels did not rise significantly upon exercise on NIV, pre-exercise 2.8 ±2.3pg/mL and response to exercise was +0.0±0.6pg/mL (p&lt;0.05). Primary: Yes. The oxidative stress response of ROS increased significantly in the NIV on exercise group by a response of +22.6 ±14.8 relative light units/second (RLu/s) compared to the unsupported group response of -6.6 ±40.5 RLu/s (p &lt; 0.05). Primary: Yes. PaO₂ decreased significantly more with NIV by -1.2 ±1.0kPa than unaided exercise by -0.5 ±1.0kPa (p &lt; 0.05). Secondary: No. Mean duration of exercise was similar in both tests 12.9 ±2min. Both tests caused increased HR, PCO₂, blood lactate levels, leukocyte plasma concentrations, neutrophil plasma levels, dyspnoea and leg pain but there were no significant difference.</td>
</tr>
<tr>
<td>Author/Date published</td>
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| Highcock, Shneerson and Smith (2003) | n = 8  
Mean age 66 ±8 years  
Mean FEV₁ 36 ±15% predicted  
FEV₁/FVC 34 ±13% predicted | Crossover.  
Compared three NIV devices (Nippy2 (B=D Electrical Ltd., UK), BIPAP ST 30 (Respironics Inc., USA), Vpap II ST (Resmed Ltd., UK)) during submaximal treadmill verses an unaided walk and mouthpiece walk.  
NIV: Mean IPAP 12.2 ±2.2cmH₂O. | **Primary:** Mean distance walked.  
**Secondary:** Vᵢ, Vₑ. | **Primary:** No. No significant difference between the unsupported walks (mean distance walked 259 ±123m). Mouthpiece walk mean distance was 211 ±96 m. NIV walk mean distance was 145 ±76m. There was a significant difference between the groups (p = 0.02). Post hoc analysis: only significant difference was between the unencumbered walks and the ventilator walks (p < 0.01). There was a significant difference (p < 0.05) in the last 20s of exercise between mean Ti: Bipap 0.85 ±0.14, Nippy2 1.0 ±0.13 and Vpap 0.89 ±0.14 s. There was a significant difference (p < 0.05) in the last 20 s of the test between mean IPAP: Bipap 12 ±2cmH₂O, Nippy2 15 ±3 cmH₂O and Vpap 13 ±2 cmH₂O. No difference between ventilators pre-exercise.  
**Secondary:** Yes. Vᵢ was significantly higher (p < 0.04) in all NIV walks (119 ±371mL) compared to mouthpiece walk (1035±284). Vₑ was significantly higher (p < 0.03) during the NIV walks (32.7 ±13.8mL) than mouthpiece walk (27.4 ±10.3mL). |
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<tr>
<th>Author/Date published</th>
<th>Sample size, age and lung function</th>
<th>Design</th>
<th>Outcome measure</th>
<th>Clinical or statistical improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hussain et al. (2011)</td>
<td>n = 13  Mean age 65 ±10 years  Mean FEV$_1$ 28 ±10% predicted  FEV$_1$/FVC 39 ±13% predicted</td>
<td>Three submaximal constant-load cycle-ergometry test equal to 80% of the highest work rate (Watts) achieved were selected on: 1. 30% O$_2$ 2. 30% O$_2$ and 70% He 3. 30% O$_2$ with PS. Mean PS 9 ±2cmH$_2$O (start) – 19 ±2cmH$_2$O (end). EPAP 0cmH$_2$O.</td>
<td><strong>Primary: IC</strong> (measure of DLH)  <strong>Secondary: RR, V$_E$, Ti, T$_E$, PTPdi/min and index of drive to breathe, dyspnoea (BORG), exercise duration.</strong></td>
<td><strong>Primary: Yes.</strong> IC was significantly less (p ≤ 0.03) with He-O$_2$ or PS than O$_2$ after 1 min. At end-exercise decrease in IC was significantly greater (p &lt; 0.03) with PS and O$_2$ than with He-O$_2$. V$_T$ was significantly greater (p &lt; 0.04) with PS than O$_2$.  <strong>Secondary: Yes.</strong> At isotime RR and V$_E$ were significantly less with PS (p ≤ 0.003) than with He-O$_2$ or O$_2$. At end-exercise PS V$_E$ was significantly less (p = 0.008) than with He-O$_2$. At isotime T$_i$ and T$_E$ were significantly (p ≤ 0.007) longer duration with PS ergometry than with He-O$_2$ or O$_2$ alone. At end exercise only T$_i$ was significantly (p = 0.001) longer duration with PS than with He-O$_2$.  <strong>Secondary: Yes.</strong> Dyspnoea median (IQR) (BORG) at isotime decreased from 9 (4.5-10.0) with O$_2$ to 4 (2.5-5.0) with He-O$_2$ and reduced to 3 (2.5-5.0) with PS (significance p = 0.01).  <strong>Secondary: Yes: At PTPoes/min and index of drive to breathe was significantly less (P ≤ 0.02) with Helium-O$_2$ or with PS than O$_2$.</strong>  <strong>Secondary: No.</strong> At end-exercise inspiratory effort/breath and inspiratory effort/litre were significantly less (p ≤ 0.03) with Helium-O$_2$ than PS.  <strong>Secondary: Yes.</strong> Helium-O$_2$ and PS ergometry had significantly (p = 0.003) longer duration than O$_2$ alone (O$_2$ 6.9 ±0.8min; helium-O$_2$ 10.7 ±1.4min and PS 11.2 ±1.6min).</td>
</tr>
<tr>
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<tr>
<td>Kyroussis et al. (2000)</td>
<td>n = 12 Mean age 64 ±7 years Mean FEV₁ 27 ±11% predicted</td>
<td>Constant speed exhaustive treadmill walks: 1. Free walks 2. Free walk with PS. 3. PS assisted exhaustion walks.</td>
<td><strong>Primary Outcome:</strong> Respiratory muscle use by PTPₐᵱ, PTPₙₑ₂, PTPₖₙ.</td>
<td><strong>Primary: No just trend.</strong> PS caused a decrease on PTPₙᵱ and PTPₙₑ₂ of n = 6 compared to free walk and prevented the increase in PTPₖₙ. In PS exhaustive walk PTPₙᵱ and PTPₙₑ₂ did not reach the same levels as free walk.</td>
</tr>
<tr>
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<tr>
<td>Menadue et al. (2009)</td>
<td><strong>UAE</strong>: Mixed n = 17 (mixed n = 9 COPD n = 8 other) Mean age 62 ±12 years FEV₁ 20 ±5% predicted FEV₁/FVC 55 ±19% predicted <strong>ESWT</strong>: n = 15 (n = 10 COPD, n = 5 other) Mean age 62 ±7 years FEV₁ 28 ±12% predicted FEV₁/FVC 55 ±19% predicted</td>
<td>Randomised cross over study. Part A: Two UAE tests. 1. UAE unsupported 2. UAE on NIV. Part B: ESWT at 85% of the maximum walking speed stopped by fatigue, dyspnoea or time: 1: ESWT with NIV. 2. ESWT unsupported. Settings: EPAP 3-5cmH₂O, IPAP 13-15cmH₂O (set 10cmH₂O above EPAP) PS 10-13cmH₂O. (O₂ to maintain SpO₂ at 93% at rest).</td>
<td><strong>Primary</strong>: Exercise endurance time in UAE and ESWT. <strong>Secondary</strong>: Isotime and end time dyspnoea (BORG). Isotime and end time SpO₂ in UAE and ESWT.</td>
<td><strong>Primary</strong>: <strong>UAE</strong>: Yes. UAE on NIV significantly increased endurance time by a mean 91 s (95% CI: 10-172, p = 0.031) compared with unsupported. <strong>Primary</strong>: <strong>ESWT</strong>: No. Just trend: For increased endurance time on NIV compared with unsupported (119s, 95% CI: -17 to 254, p = 0.081). <strong>Secondary</strong>: <strong>Yes.</strong> UAE on NIV led to less dyspnoea (-2.3 Borg, 95% CI: -3.7 to -1.0, p = 0.002). End exercise dyspnoea was statistically lower after UAE on NIV (1.9 Borg, 95% CI: -3.3 to -0.5, p = 0.010) compared with unsupported UAE. <strong>Secondary</strong>: <strong>Yes.</strong> Isotime SpO₂ was greater (1.7%, 95% CI: 0.2-3.3, p = 0.033) with UAE on NIV compared to unsupported. End exercise SpO₂ remained higher (1.8%, 95% CI: 0.3-3.4, p = 0.023). <strong>Secondary</strong>: No. No difference in isotime dyspnoea between exercise with NIV or unsupported (-1.0, 95% CI: -3.0 to 1.0, p = 0.29). End time dyspnoea was not reported. <strong>Secondary</strong>: <strong>Yes.</strong> Significant improvement in SpO₂ at isotime with NIV (3.6%, 95% CI: 0.3 to 6.9, p = 0.033) was maintained at end exercise (3.8%, 95% CI: 0.1-7.5, p = 0.045).</td>
</tr>
</tbody>
</table>
Menadue *et al.* (2010) | **6MWT:** n = 18 (n = 12 COPD)  
Median age 65 years  
Interquartile range (IQR) 61-68  
Median FEV₁ 21 (IQR 16-27) % predicted  
FEV₁/FVC 46 ±17% predicted  
**UAE:** n = 16 (n = 12 COPD)  
Median age 64 years  
(IQR 56-66)  
Median FEV₁ 21 (IQR 16-24) % predicted.  
FEV₁/FVC 43 ±13% predicted.  
Randomised cross over study. Two 6MWT's and two UAE’s with:  
1. NIV: EPAP 4-5cmH₂O  
IPAP 14cmH₂O (PS = 10cmH₂O and O₂).  
2. O₂ alone.  
**Primary:** 6MWT: Distance walked.  
**Secondary:** 6MWT: Distance and time to first rest.  
**Primary:** UAE: Endurance time.  
**Secondary:** UAE: Isotime SpO₂ and dyspnoea (BORG).  
---

**Primary:** 6MWT: Yes. NIV and O₂ significantly increased total distance walked by mean 43.4m (95% CI 14.1 to 72.8, p = 0.006) compared to exercise with O₂.  
**Secondary:** 6MWT: Just Trend. For improvement with NIV for distance and time to first rest.  
**Primary:** UAE: Yes. Statistically significant improvement in UAE endurance time with NIV and O₂ compared to exercise with O₂ alone (median 201s (IQR 93-414) versus 157s (90-342), p = 0.033)  
**Secondary:** UAE: No. There was no difference demonstrated for isotime SpO₂ and dyspnoea (BORG).

Moga *et al.* (2014) | N = 10  
Mean age 68 ±6 years  
Randomised cross-over. Comparison of 3 symptom limited  
**Primary:** WLpeak.  
---

**Primary:** No. WLpeak significantly lower with PS 0cmH₂O EPAP 4cmH₂O (30.5 ±13.00 watts) and PS 10cmH₂O (33 ±16.70 watts) than no PS (43 ±19.50 watts) significance was p < 0.001.
<table>
<thead>
<tr>
<th>Author/ Date published</th>
<th>Sample size, age and lung function</th>
<th>Design</th>
<th>Outcome measure</th>
<th>Clinical or statistical improvement</th>
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<tbody>
<tr>
<td></td>
<td>FEV₁ 53 ±22% predicted FEV₁/FVC 46 ±13% predicted</td>
<td>cycle ergometry tests: 1: No PS 2: PS 0cmH₂O (IPAP 0cmH₂O EPAP 4cmH₂O) 3: PS 10cmH₂O (IPAP 14cmH₂O EPAP 4cmH₂O).</td>
<td>Secondary: Dyspnoea (BORG), $V_T$, $V_E$, $VO_2$, $VCO_2$.</td>
<td>Secondary: No. Dyspnoea (BORG) was similar between groups at peak exercise but lower with no PS compared with PS 0cmH₂O and PS 10cmH₂O $p &lt; 0.01$. Secondary: Unclear meaning. $V_T$ and $V_E$ were highest with PS 10cmH₂O (1.29 ±0.32L) and lowest with no PS (1.04 ±0.38L) both at peak exercise and isoload ($p &lt; 0.001$). Secondary: Unclear meaning. $VO_2$ and $VCO_2$ were significantly highest with PS 10cmH₂O compared with no PS EPAP 4cmH₂O ($p &lt; 0.001$) at both peak exercise and isoload.</td>
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<tr>
<td>Oliveira et al. (2010)</td>
<td>n = 21 Mean age 63 ±8 years FEV₁ 40 ±11% predicted FEV₁/FVC 50 ±15% predicted</td>
<td>Randomised to two high-intensity constant work rate cycle ergometry tests at 70-80% peak to tolerance limit with: 1. Assisted supported breath mode: PS 16cmH₂O and PEEP 5cmH₂O. 2. Unaided.</td>
<td>Primary: Exercise endurance Secondary: HR, SV, CO.</td>
<td>Primary: Partial. In n = 11 patients (Group A) exercise endurance significantly improved ($p &lt; 0.05$) with PS 115 seconds (-210 to 909) but not in n = 10 (Group B) when endurance was 51 seconds (-60 to 486). Secondary: Partial. PS reduced HR compared with non-assisted exercise. SV and CO was variable with PS. Group A. had stable or higher SV compared with group B. who were more hyperinflated had lower SV with PS.</td>
</tr>
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<tr>
<td>Pessoa et al. (2012)</td>
<td>n = 32&lt;br&gt; Mean age 69 ±7 years&lt;br&gt; FEV₁ 42 ±13% predicted&lt;br&gt; FEV₁/FVC 42 ±12% predicted</td>
<td>Randomised cross over trial of lifting containers (from 0.6-5 kg) repeated 5min:&lt;br&gt; 1. No NIV.&lt;br&gt; 2. NIV IPAP 10cmH₂O and EPAP 4cmH₂O.</td>
<td><strong>Primary:</strong> IC&lt;br&gt; <strong>Secondary:</strong> Dyspnoea (BORG)</td>
<td><strong>Primary:</strong> No. No significant difference in IC (indication of DLH) post exercise between intervention (1.69 ±0.60L) and control (1.73 ±0.57L) &lt;br&gt; <strong>p = 0.30</strong>.  &lt;br&gt; <strong>Secondary:</strong> No. No significant difference in dyspnoea intervention (BORG score 2.67) and control (BORG score 2.67) post exercise. No P value documented.</td>
</tr>
<tr>
<td>Poggi et al. (2006)</td>
<td>n = 8&lt;br&gt; Mean age 65 ±11 years&lt;br&gt; FEV₁ 0.72 ±0.23L</td>
<td>Randomised crossover of: 1. Spontaneous breathing.&lt;br&gt; 2. Spontaneous breathing with arm elevation.&lt;br&gt; 3. Arm elevation with PS.&lt;br&gt; 4. Arm elevation with PAV.&lt;br&gt; 5. PS only.&lt;br&gt; 6. PAV only.</td>
<td><strong>Primary:</strong> Vₑ&lt;br&gt; <strong>Secondary:</strong> V₉, RR, PEEPᵯᵩ, PTPᵯᵩ</td>
<td><strong>Primary:</strong> Yes. Arm elevation performed with PAV and PS mean Vₑ were 50% significantly greater (&lt;0.05) than unsupported. The rise in Vₑ with PAV (3.96 ±1.34L/min was significantly greater than both spontaneous breathing (1.11 ±1.34L/min) and PS (2.32 ±2.15L/min (&lt;0.05).&lt;br&gt; <strong>Secondary:</strong> Yes. PS increased Vₑ by mean 48% (&lt;0.05) (0.46 ±0.15L spontaneous breathing, PAV 0.72 ±0.72L and PSV 0.77 ±0.4L).&lt;br&gt; <strong>Secondary:</strong> No. Just trend. Arm elevation PEEPᵯᵩ decreased by 30% with PS (3.8 ±4.3cmH₂O) or PAV (1.3 ±0.9cmH₂O) compared to unsupported (3.8 ±4.3cmH₂O).&lt;br&gt; <strong>Secondary:</strong> Yes. PTPₑ decreased to -44% with PAV (268 ±170cmH₂O/min) and -54% with PS (219 ±75cmH₂O/min) compared to unsupported (478 ±27cmH₂O/min).</td>
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<tr>
<td>Polkey et al. (2000)</td>
<td>n = 8 Mean age 70 ±8 years FEV$_1$ 24 ±7% predicted</td>
<td>Cross-over of two treadmill walks until severe dyspnoea: 1. Free walk 2. PS provided</td>
<td>Primary: Walking time. Secondary: PaCO$_2$. Peak lactate level.</td>
<td>Primary: Yes. Mean (SD) free walking time was 5.5 (1.5) min and in PS walk 13.6 (6.0) min, increase of 149% (p = 0.01). Secondary: Yes. End mean PaCO$_2$ was higher in free walk 6.32kPa compared to 5.86kPa with PS (p &lt; 0.04). Secondary: Yes: Mean peak lactate level was significantly higher at the end of the free walk 2.96 than PS 2.42 (p = 0.01).</td>
</tr>
<tr>
<td>Revill, Singh and Morgan (2000)</td>
<td>n = 10 Median age 63 (IQR 58-81) years FEV$_1$ 0.60 L (IQR 0.35-0.45)</td>
<td>Performed four ESWT’s, following an ISWT to assess for speed of ESWT with: 1. PS 14cmH$_2$O (range 8-20cmH$_2$O) PEEP 3cmH$_2$O. 2. Sham PS &lt; 8cmH$_2$O. 3. O$_2$. 4. Sham O$_2$</td>
<td>Primary: ESWT duration. Secondary: SpO$_2$.</td>
<td>Primary: No. The mean ESWT walk distance was worse than baseline (172sec) with sham PS (84sec), PS (84 sec), sham O$_2$ (150sec). It improved with O$_2$ (242sec). Secondary: No. The mean SpO$_2$ 85% (standard error (SE 2.0) of the O$_2$ walk was significantly higher than the PS (80% (SE 2.0) and the baseline walk (80% (SE 2.0) (p &lt; 0.05).</td>
</tr>
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<tr>
<td>van’t Hul et al. (2004)</td>
<td>(n = 45) &lt;br&gt; Mean age 67 ±7 years &lt;br&gt; FEV(_1) 39 ±14% predicted</td>
<td>Three constant-load endurance tests were performed on a cycle ergometer at 75% of previously determined (W_{\text{max}}): &lt;br&gt; 1. PS 10cmH(_2)O. &lt;br&gt; 2. PS 5cmH(_2)O. &lt;br&gt; 3. PS 0cmH(_2)O.</td>
<td><strong>Primary:</strong> Exercise endurance: Time. &lt;br&gt; <strong>Secondary:</strong> (V_T), (V_E), (VCO_2), (VO_2), RR.</td>
<td><strong>Primary:</strong> Yes. PS 10cmH(_2)O compared with PS 5 cmH(_2)O led to a significant increase in duration (6.3 ±6.7 versus endurance was 2.2min, (p &lt; 0.01)). PS 10cmH(_2)O compared to PS 0cmH(_2)O was significantly longer (6.3 ±6.7 versus 4.3 ±2.6min, (p &lt; 0.01)). No statistical difference was found in endurance between PS 5cmH(_2)O and PS 0cmH(_2)O (4.4 ±2.9 versus 4.2 ±2.6min), (p = 0.70)). &lt;br&gt; <strong>Secondary:</strong> Yes. PS 10cmH(_2)O had a significantly higher (V_T) at isotime than PS 5cmH(_2)O at end-exercise (1.5 ±0.40 versus 1.38 ±0.36L, (p = &lt; 0.05)). &lt;br&gt; <strong>Secondary:</strong> Yes. PS 10cmH(_2)O had a significantly lower RR at isotime than PS 5cmH(_2)O at end–exercise (21 ±5 breaths min(^{-1}) versus 23 ±5 breaths min(^{-1})). &lt;br&gt; <strong>Secondary:</strong> No. (V_E) did not differ. &lt;br&gt; <strong>Secondary:</strong> Yes. (VO_2) and (VCO_2) were significantly lower at isotime for PS 10cmH(_2)O compared to PS 5cmH(_2)O ((VO_2) 0.76 ±0.25L min(^{-1}) versus 0.80 ±0.26L min(^{-1}), (p &lt; 0.05) and (VCO_2) was 0.74 ±0.29 L min(^{-1}) versus 0.77 ±0.30 L min(^{-1}). (V_E), (VO_2) and (VCO_2) were also significantly higher at end exercise with PS 10cmH(_2)O ((V_E) 34.0 ±10.0, (VO_2) 0.83 ±0.25 and (VCO_2) 0.81 ±0.29) compared with PS 5cmH(_2)O ((p &lt; 0.05)).</td>
</tr>
<tr>
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**Abbreviation key:** CO Cardiac output, CO₂ Carbon Dioxide, CRQ Chronic respiratory questionnaire, DLH Dynamic Lung Hyperinflation, ESWT Endurance shuttle walk test, He Helium, HR Heat rate, IC Inspiratory Capacity, IQR Interquartile range, IL6 Interleukin 6, ISWT Incremental shuttle walk test, O₂ Oxygen, PaCO₂ Partial pressure of arterial carbon dioxide, PaO₂ Partial pressure of arterial oxygen, PAV Proportional assisted ventilation, PEEPᵢ Intrinsic positive end expiratory pressure, PEEPᵢ,dyn Dynamic intrinsic positive end expiratory pressure, PS Pressure support, PTPᵢ Pressure/time products of transdiaphragmatic pressure, PTPᵢ,ga Pressure/time products of gastric pressure, PTPᵢ,oes Pressure/time products of oesophageal pressure, RR Respiratory rate, ROS Reactive oxygen species, SD Standard deviation, SpO₂ Peripheral capillary oxygen saturation, SV Stroke volume, TE Expiratory time, Ti Inspiratory time, Tlim Limit of tolerance, UAE Unsupported arm exercise, VCO₂ Volume of carbon dioxide breathed out, Vₑ Expired minute ventilation, VO₂ Oxygen uptake, Vₜ Tidal volume, WLₚₑａｋ Peak exercise workload, Wₘₐₓmaximal workload, 6MWT Six minute walk test, 12MWT Twelve minute walk test, IL-6 Interleukin-6.
2.9.3 Quality assessment of the individual studies

Table 2.8 presents the quality assessment of the individual studies. It represents the questions asked within the CASP tool. The majority of the studies had a crossover design. The CASP tool does not have a specific tool for crossover design. There is no known specific quality assessment for crossover design, therefore the studies were also evaluated for quality using the suggestions within the Cochrane handbook (Ding et al., 2015).
### Table 2.8 The quality assessment of the individual studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Clear design question</th>
<th>Good design and outcome</th>
<th>Randomised</th>
<th>Blinding</th>
<th>Similar groups at the start</th>
<th>Method equal for each group</th>
<th>Wash-out time</th>
<th>Similar groups finish</th>
<th>Treatment effect</th>
<th>Applicable to clinical context</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allan et al. (2009)</td>
<td>Yes: But 4 arms is a complex design.</td>
<td>Yes.</td>
<td>Yes: But coin toss could be biased.</td>
<td>Partial: Yes: Patient No: clinician No: Study team.</td>
<td>Yes: But small. Excluded n = 94/110.</td>
<td>No: Sham NIV: may have raised dead space affecting effort. Used 2 different makes of NIV thus not equal method.</td>
<td>Yes: Two days.</td>
<td>Yes.</td>
<td>Partial: Power calculation n = 12 (80% power) for primary outcome. No P value for RR. No P value of heliox HR verses placebo HR. Sample small needed n=38.</td>
<td>No: Stable group and post PR, no LTOT users) Outcome clinically relevant but may not be relevant to the patient.</td>
</tr>
<tr>
<td>Author</td>
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<td>Barakat <em>et al.</em> (2007)</td>
<td>Yes.</td>
<td>No: Crossover poor design choice because trial was 10 sessions that may cause long term change. Good detail in methods.</td>
<td>No: Not randomised to order of intervention. Lack of detail about how patient’s recruited unable to rule out selection bias</td>
<td>No.</td>
<td>Yes: small, only n = 2 female. n = 1 on home NIV could influence results.</td>
<td>No: Equal time but patients may be fitter from first training.</td>
<td>No: Effect could carry over.</td>
<td>Yes: n = 1 unable to use NIV.</td>
<td>No: No power calculation. No p value for SGRQ.</td>
<td>No: Stable, younger group with excluded co-morbidities but more severe as all on LTOT. Good programme length.</td>
</tr>
<tr>
<td>Author</td>
<td>Clear design question</td>
<td>Good design and outcome</td>
<td>Randomised</td>
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<td>Borghi-Silva et al. (2009)</td>
<td>Yes.</td>
<td>Yes: Good detailed method with SOPS, but 9cmH₂O may not be enough PS. Sham NIV may have increased work of breathing.</td>
<td>Yes: Intervention order with sealed envelopes.</td>
<td>Yes: Double. Sham used but no basis for sham settings.</td>
<td>Yes.</td>
<td>Yes.</td>
<td>No: Only 30min.</td>
<td>Yes.</td>
<td>Yes, power calculation for a sample size of n = 20.</td>
<td>No: Stable group, no co-morbidities although n = 6 on LTOT.</td>
</tr>
<tr>
<td>Carrascossa et al. (2010)</td>
<td>Yes.</td>
<td>Partial: Lack of detailed information. Outcome measure may be flawed for cardiac measure. Did use SOPS.</td>
<td>Yes: Envelopes</td>
<td>No.</td>
<td>Yes.</td>
<td>Yes.</td>
<td>No: 30min.</td>
<td>Yes, but unable to use data from n = 5 due to poor signal for SV.</td>
<td>No: No power calculation.</td>
<td>No: Stable group, no co-morbidities, no flare up of COPD in 3 months prior to study and no one on oral steroids.</td>
</tr>
<tr>
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<tr>
<td>Dreher, Storre and Windisch (2007)</td>
<td>Yes.</td>
<td>Yes: Lack of detail in method. Used high pressure that may only be tolerable because the patients were all patients with home NIV.</td>
<td>Partial: Lack of details to decide on any possible bias.</td>
<td>No.</td>
<td>Yes.</td>
<td>No: Did not use the same circuitry.</td>
<td>Yes: One day.</td>
<td>Yes.</td>
<td>Yes, power calculation collated.</td>
<td>Yes: Severe group with multiple pathology and on home NIV, but excluded bronchiectasis. Did not use a commonly used NIV device.</td>
</tr>
<tr>
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<tr>
<td>Dreher et al. (2009)</td>
<td>Yes.</td>
<td>Yes. Used very high pressures may only be tolerable because patients were all nocturnal NIV patients.</td>
<td>Yes.</td>
<td>No.</td>
<td>Yes: but n = 8 excluded as refused to walk with heavy kit. Drop outs had higher level of Hb.</td>
<td>No: patient carrying kit. Weight varied.</td>
<td>Yes: One day.</td>
<td>Yes.</td>
<td>Yes, power calculation.</td>
<td>Yes: Severe on home NIV, co-morbidities but no flare up’s. Did not include house bound. Pragmatic as patients usually have to carry their O₂ and NIV.</td>
</tr>
<tr>
<td>Dyer et al. (2011)</td>
<td>Yes.</td>
<td>No: different pathology, different sites conflicted design. Not RCT.</td>
<td>No.</td>
<td>No.</td>
<td>No: Selection bias possible as part A sample selected by staff.</td>
<td>No: Only some of the sample were NIV users.</td>
<td>N/A as study not feasible.</td>
<td>N/A.</td>
<td>No: For part B, no power calculation. No results.</td>
<td>Yes: Part B: acute group with hospital stay, better reflects clinical context.</td>
</tr>
<tr>
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<tr>
<td>Hannink et al. (2014)</td>
<td>Yes</td>
<td>Yes: But PS used may not have been enough to off-load muscles. No added $O_2$.</td>
<td>No.</td>
<td>No.</td>
<td>Partial: Baseline ROS not recorded.</td>
<td>Yes.</td>
<td>Yes: Two weeks.</td>
<td>Yes.</td>
<td>Yes, but no power calculation.</td>
<td>No: Stable group. No patients with normal or high fat-free mass.</td>
</tr>
<tr>
<td>Highcock, Shneerson and Smith (2003)</td>
<td>Yes</td>
<td>Yes: But circuits used may have led to $CO_2$ re-breathing.</td>
<td>Yes: Order of walks.</td>
<td>No.</td>
<td>Yes: Different circuitry.</td>
<td>No: 30min.</td>
<td>Yes.</td>
<td>No: No initial power calculation. Post-hoc power analysis (for 50%) on effect of order on walking difference in unaided walks.</td>
<td>No: stable, able to walk for 10min on the treadmill.</td>
<td></td>
</tr>
<tr>
<td>Hussain et al. (2011)</td>
<td>Yes</td>
<td>Yes, but added $O_2$ to all groups may be a confounder.</td>
<td>Yes: Order of test.</td>
<td>No.</td>
<td>Yes.</td>
<td>Yes: Four days.</td>
<td>Yes: $n = 3$ drop outs but still equal groups.</td>
<td>Yes, but no power calculation.</td>
<td>No: invasive testing.</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Clear design question</td>
<td>Good design and outcome</td>
<td>Randomised</td>
<td>Blinding</td>
<td>Similar groups at the start</td>
<td>Method equal for each group</td>
<td>Wash-out time</td>
<td>Similar groups finish</td>
<td>Treatment effect</td>
<td>Applicable to clinical context</td>
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<tr>
<td>Kyroussis <em>et al.</em> (2000)</td>
<td>Yes.</td>
<td>Yes, but PS used may not have been high enough to off-load muscles. Researcher bias in choosing who did the PS walk.</td>
<td>No.</td>
<td>No.</td>
<td>Yes.</td>
<td>Yes.</td>
<td>No: Same day.</td>
<td>No: n = 6 did PS walk, but only n = 5 did PS walk until unable as n = 1 dropped out.</td>
<td>No: No power calculation.</td>
<td>No: Sample had only one female.</td>
</tr>
<tr>
<td>Author</td>
<td>Clear design question</td>
<td>Good design and outcome</td>
<td>Randomised</td>
<td>Blinding</td>
<td>Similar groups at the start</td>
<td>Method equal for each group</td>
<td>Wash-out time</td>
<td>Similar groups finish</td>
<td>Treatment effect</td>
<td>Applicable to clinical context</td>
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</tr>
<tr>
<td>Moga (2014)</td>
<td>Yes</td>
<td>Yes, but PS used may not have been high enough to off-load muscles.</td>
<td>No. Exercise off NIV always before NIV exercise.</td>
<td>No.</td>
<td>Yes.</td>
<td>Yes.</td>
<td>Yes: 48 hours.</td>
<td>No.</td>
<td>No: No power calculation. Small sample size.</td>
<td>No: Not severe group.</td>
</tr>
<tr>
<td>Oliveira et al. (2010)</td>
<td>Yes</td>
<td>Yes, but lack of clarity in the results. Group A and B not clearly defined.</td>
<td>Yes, but no details.</td>
<td>No.</td>
<td>No: Not clear.</td>
<td>Yes.</td>
<td>Yes: 24 hours.</td>
<td>No: Not clear.</td>
<td>No: No power calculation. Not all results were reported.</td>
<td>No: No women and stable group.</td>
</tr>
<tr>
<td>Pessoa et al. (2012)</td>
<td>Yes</td>
<td>Yes, but PS used may not have been high enough to off-load muscles.</td>
<td>Yes, but occurred after baseline testing.</td>
<td>No.</td>
<td>Yes.</td>
<td>Yes.</td>
<td>No: 15-30min.</td>
<td>Yes.</td>
<td>No: Power calculation: For sample n = 22. No p value (BORG).</td>
<td>No: Stable patients, but good disease severity, included the elderly.</td>
</tr>
<tr>
<td>Author</td>
<td>Clear design question</td>
<td>Good design and outcome</td>
<td>Randomised groups at the start</td>
<td>Blinding</td>
<td>Similar groups equal for each group</td>
<td>Method equal for each group</td>
<td>Wash-out time</td>
<td>Similar groups finish</td>
<td>Treatment effect</td>
<td>Applicable to clinical context</td>
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</tr>
<tr>
<td>Poggi et al. (2006)</td>
<td>Yes</td>
<td>Yes, but balloon measure invasive, some patients may not tolerate this.</td>
<td>No</td>
<td>No: n = 2 not COPD.</td>
<td>Yes</td>
<td>No: Same time.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, but no power calculation.</td>
<td>No: stable, no women but all on LTOT thus more severe group.</td>
</tr>
<tr>
<td>Polkey et al. (2000)</td>
<td>Yes</td>
<td>Yes, but no details of settings used on NIV.</td>
<td>Partial: Previously chosen sample, but randomised to allocation of treatment.</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No: 30min.</td>
<td>Yes</td>
<td>Yes, but no power calculation.</td>
<td>No: Previous sample used so may not represent the normal COPD population. Only men.</td>
</tr>
<tr>
<td>Revill, Singh and Morgan (2000)</td>
<td>Yes</td>
<td>Yes, but NIV device had low flow rates.</td>
<td>Partial, possible selection bias as sample just done PR. Randomised to allocation of treatment.</td>
<td>Partial: Sample blinded to treatment</td>
<td>Yes</td>
<td>Yes</td>
<td>No: 30min.</td>
<td>Yes</td>
<td>No: No power calculation.</td>
<td>No: sample just completed PR, may be fitter than typical patient with COPD.</td>
</tr>
<tr>
<td>Author</td>
<td>Clear design question</td>
<td>Good design and outcome</td>
<td>Randomised</td>
<td>Blinding</td>
<td>Similar groups at the start</td>
<td>Method equal for each group</td>
<td>Wash-out time</td>
<td>Similar groups finish</td>
<td>Treatment effect</td>
<td>Applicable to clinical context</td>
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</tr>
<tr>
<td>van’t Hul et al. (2004)</td>
<td>Yes.</td>
<td>Yes: Outcome measures tested and ergometry tested for standards.</td>
<td>Partial: Only the two tests with PS.</td>
<td>Partial: Only the sample between the two PS tests. Not team.</td>
<td>Yes.</td>
<td>Yes.</td>
<td>Yes: One or two weeks.</td>
<td>Yes.</td>
<td>Yes, but no power calculation, but reviewed the effect of small sample.</td>
<td>No, Included no co-morbidities that can cause exercise limitation.</td>
</tr>
</tbody>
</table>

**Abbreviation Key:** CO₂ Carbon Dioxide, COPD Chronic Obstructive Pulmonary Disease, FiO₂ Fraction of inspired oxygen, LTOT Long term oxygen Therapy, min Minute, NIV Non-Invasive ventilation, O₂ Oxygen, PS Pressure Support, RCT Randomised controlled trial, ROS Reactive oxygen species Levels, SGRQ St George’s Respiratory Questionnaire, SOP Standard operating procedure, SpO₂ Oxygen saturations.
2.9.3 How did the individual studies inform the design of the planned feasibility study?

Table 2.9 Combined information that informed the design of the planned feasibility study from the reviewed individual studies.

<table>
<thead>
<tr>
<th>Sample characteristics</th>
<th>Studies combined information</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 4-45 (combined mean n = 14), Mean age range of 62-72 years (combined mean age of 65 years), FEV₁ (% predicted) mean range 20-56%, 4 not recorded (combined mean 32%).</td>
<td></td>
</tr>
</tbody>
</table>

| Recruitment method | Not recorded in 9 studies. From respiratory clinics in 6 studies, from PR cohort in 3 studies, home NIV clinic in 2 studies, and respiratory wards hospital in 2 studies. |

| Number/time period of screening | Not recorded in 19 of the studies. Allan et al. (2009) screened 122 patients in 12 months (n = 28 met inclusion, 16 of these excluded with less severe lung disease and additional lung disease) Dyer et al. (2011): n = 60 screened in 4 months. n = 42 excluded (56% MSK problems, 13 % dementia, 13 % neurology). n = 18 included but n = 10/18 declined n = 2/10 did not want to do research, n = 8/10 felt unable/did not want to exercise and then n = 4/8 excluded for logistical reasons. |

| Recruitment rate | Not recorded in 16 studies. Allan et al. (2009) Patients that met inclusion criteria was 23% of patients screened but recruitment rate (due to exclusions) was 10%. Dyer et al. (2011): Recruitment rate of patients that met the inclusion criteria was 30% but due to logistics, and refusals the final recruitment rate was 7%. |

| Retention rate | All participants completed the trial in 16 studies. Barakat et al. (2007) n = 9/12 completed (n = 1 could not tolerate NIV, n = 1 developed AF, n = 1 hospitalized exacerbation COPD). Dreher, Storre Windisch (2009) n = 11/19 completed (n = 8 withdrew as did not want to carry kit). Dyer et al. (2011) 2/4 (n = 1 frail, n = 1 breathless on exercise). Hussain et al. (2011) n = 10/13 (n = 1 new diagnosis of PVD, n = 1 new diagnosis of prostate cancer, 1 x knee pain). Kyroussis et al. (2000) n = 11/12 completed (n = 1 exacerbation COPD). |

| Outcome measure timing | Not recorded in 6 studies. Most of the studies did baseline tests on a separate day to the intervention. Timing ranged from every 30 seconds to once before training began and one measure the week after 8 week training. |
Studies combined information

<table>
<thead>
<tr>
<th>Outcome measure that reflected change</th>
<th>13 studies: Statistical improvement in their outcome measure:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Cycle ergometry: Exercise duration (Barakat et al. 2007; Borghi et al., 2008; Hussain et al., 2011; van’t Hul et al., 2004).</td>
</tr>
<tr>
<td></td>
<td>• BORG Dyspnoea score (Barakat et al. 2007; Borghi et al. 2008; Hussain et al., 2011; Menadue et al., (2009)).</td>
</tr>
<tr>
<td></td>
<td>• 6MW (Barakat et al., 2007; Dreher Storre and Windish 2007; Menadue et al., 2010).</td>
</tr>
<tr>
<td></td>
<td>• UAE endurance time (Menadue et al., 2009; Menadue et al., 2010).</td>
</tr>
<tr>
<td></td>
<td>• ESWT endurance time (Menadue et al., 2009).</td>
</tr>
<tr>
<td></td>
<td>• Treadmill walk time (Polkey et al., 2000).</td>
</tr>
<tr>
<td></td>
<td>• Cycle ergometry: increased work load (Barakat et al., 2007).</td>
</tr>
<tr>
<td></td>
<td>• Fatigue index of quadriceps: decreased score (Borghi et al., 2009).</td>
</tr>
<tr>
<td></td>
<td>• SpO₂ (Borghi et al., 2009; Menadue et al., 2009)</td>
</tr>
<tr>
<td></td>
<td>• PaO₂ (Dreher et al., 2007; Dreher et al., 2009; Hannink et al., 2014).</td>
</tr>
<tr>
<td></td>
<td>• IL6 (Hannink et al., 2014)</td>
</tr>
<tr>
<td></td>
<td>• Ve (Highcock, Shneerson and Smith, 2003; Hussain et al., 2011; Poggi et al., 2006)</td>
</tr>
<tr>
<td></td>
<td>• Vt (Highcock, Shneerson and Smith, 2003; Poggi et al. 2006; van’t Hul et al. 2004).</td>
</tr>
<tr>
<td></td>
<td>• IC (Hussain et al., (2011))</td>
</tr>
<tr>
<td></td>
<td>• De-Oxyhaemoglobin: decreased (Borghi et al., 2008).</td>
</tr>
<tr>
<td></td>
<td>• RR decreased (Hussain et al., 2011; Van’t Hul et al., 2004).</td>
</tr>
<tr>
<td></td>
<td>• Lactate decreased (Polkey et al., 2000).</td>
</tr>
<tr>
<td></td>
<td>• VCO₂ (van’t Hul et al., 2004).</td>
</tr>
<tr>
<td></td>
<td>• VO₂ (van’t Hul et al., 2004).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complications with outcome measures</th>
<th>None reported in 17 studies.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Borghi et al. (2008): May not measure what was intended.</td>
</tr>
<tr>
<td></td>
<td>Borghi et al. (2009): May not be sensitive enough.</td>
</tr>
<tr>
<td></td>
<td>Menadue et al. (2009) 3 tests stopped early due to SpO₂ &lt;75%.</td>
</tr>
<tr>
<td></td>
<td>Menadue et al. (2010) 3 tests stopped early due to SpO₂ &lt;75%.</td>
</tr>
</tbody>
</table>

| AEs | None reported in 20 studies. |
|     | Barakat et al. (2007) n = 1 could not tolerate NIV, n = 1 developed AF and n = 1 hospitalized COPD exacerbation. |

Abbreviation Key: AE Adverse Event, AF Atrial Fibrillation, COPD Chronic obstructive pulmonary disease, ESWT endurance shuttle walk test, IC Inspiratory Capacity, FEV₁ Forced expiratory volume in one second, IL6 Interleukin 6, MSK Musculoskeletal, NIV Non-invasive ventilation, O₂ Oxygen, PaO₂ Partial pressure of arterial oxygen, PR Pulmonary rehabilitation, PVD Peripheral vascular disease, RR Respiratory rate, SpO₂ Saturation of arterial blood with oxygen, UAE Unsupported arm exercise, VCO₂ Volume of carbon dioxide produced in a given time, VO₂ Volume of oxygen utilised by the body each minute, Ve Minute ventilation, Vt Tidal volume, 6MWT Six minute walk test.
2.9.4 How did the individual studies inform the intervention of the planned feasibility study?

Table 2.10 Combined information to inform the intervention of the planned feasibility study.

<table>
<thead>
<tr>
<th>Studies combined information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of ventilator/mode/circuit</strong></td>
</tr>
<tr>
<td>Ventilator: There were 13 different types of ventilator used. 4</td>
</tr>
<tr>
<td>studies used EVITA 4, 3 Studies used NIPPY S/T, and 2 studies</td>
</tr>
<tr>
<td>used VPAP III, Vision and BIPAP. 4 studies used a battery powered</td>
</tr>
<tr>
<td>device.</td>
</tr>
<tr>
<td>Circuit: 1 study used humidifier and 2 studies used double circuit.</td>
</tr>
<tr>
<td>Capabilities: Oliveira et al. (2010) detailed capabilities:</td>
</tr>
<tr>
<td>Evita 4: dual limb, rise fast 0.4 secs, trigger lowest, (V_E)</td>
</tr>
<tr>
<td>up to 99L/min, rise time 5ms, max inspiratory flow 180L/min.</td>
</tr>
<tr>
<td>van't Hul et al. (2004) detailed settings/capabilities:</td>
</tr>
<tr>
<td>Raphael: low trigger, (V_E) 50L/min, insp. Rate 180L/min,</td>
</tr>
<tr>
<td>dead space &lt; 15mls.</td>
</tr>
<tr>
<td>Interface: 11 studies used full face masks, 3 used mouthpiece</td>
</tr>
<tr>
<td>and nasal clips, 2 used nasal mask and 2 studies did not record</td>
</tr>
<tr>
<td>interface used.</td>
</tr>
<tr>
<td>Ventilator settings</td>
</tr>
<tr>
<td>PS range 6-27cmH_2O, 4 studies PS not recorded, 2 studies</td>
</tr>
<tr>
<td>used PAV and PS not calculated) (mean PS 13cmH_2O).</td>
</tr>
<tr>
<td>EPAP range 2-5cmH_2O, 4 studies EPAP not recorded, 5 studies</td>
</tr>
<tr>
<td>did not use EPAP (mean EPAP 4cmH_2O).</td>
</tr>
<tr>
<td>Entrained O_2</td>
</tr>
<tr>
<td>13 studies did not entrain O_2.</td>
</tr>
<tr>
<td>Barakat et al. (2007) entrained O_2 to achieve SpO_2 92%.</td>
</tr>
<tr>
<td>Dreher, Storre and Windish (2007) entrained O_2 to match home</td>
</tr>
<tr>
<td>prescription.</td>
</tr>
<tr>
<td>Dreher et al. (2009) O_2 entrained same as home prescription.</td>
</tr>
<tr>
<td>Hussain et al. (2011) entrained 0.3 FiO_2 to all.</td>
</tr>
<tr>
<td>Menadue et al. (2009) maintain 93% at rest.</td>
</tr>
<tr>
<td>Menadue et al. (2010)1-3L/min aim resting SpO_2 93%.</td>
</tr>
<tr>
<td>Poggi et al. (2006) entrained O_2 to keep SpO_2 at &gt; 92%.</td>
</tr>
<tr>
<td>Research setting</td>
</tr>
<tr>
<td>4 studies did not clearly document location.</td>
</tr>
<tr>
<td>9 study settings were physiology exercise laboratories.</td>
</tr>
<tr>
<td>4 studies were in lung function laboratories.</td>
</tr>
<tr>
<td>3 studies were in community PR centres.</td>
</tr>
<tr>
<td>1 study was in an acute hospital on the ambulatory respiratory</td>
</tr>
<tr>
<td>ward (Menadue et al. 2010).</td>
</tr>
<tr>
<td>Exercise type</td>
</tr>
<tr>
<td>Cycle ergometry used in 9 of the reviewed studies.</td>
</tr>
<tr>
<td>3 studies 6MWT and 1 study 12MWT.</td>
</tr>
<tr>
<td>2 studies used treadmill walking.</td>
</tr>
<tr>
<td>2 studies used ESWT.</td>
</tr>
<tr>
<td>4 studies UAE’s.</td>
</tr>
<tr>
<td>1 study knee extensor exercises (Borghi-Silva et al. 2009).</td>
</tr>
</tbody>
</table>
### Studies combined information

<table>
<thead>
<tr>
<th>Intensity, duration, number of sessions</th>
<th>Number of sessions: 1 study full training programme: Barakat et al. (2007) 10 sessions with NIV, 10 sessions no NIV. 25-30 min, more if patient able, 2-3 x week for 8 weeks. All of the studies were one off exercise tests.</th>
<th><strong>Intensity:</strong> 13 studies did pre-testing to determine peak work rate, peak of limit of tolerance and maximum speed. Ranged from 50%-80% maximum speed, 25-50% maximum power, to 80% work rate. 2 studies replicated a brisk walk. 4 studies exercised to extreme dyspnoea. 2 studies exercised until fatigue. 1 study exercised against a metronome timer. <strong>Duration:</strong> For tests that were not limited by symptoms the timing ranged from 6min to 40min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention participation/training session attended</td>
<td>19 studies had no non-attendees and all sessions were attended. Barakat et al. (2010) n = 3 drop outs. Dyer et al. (2011): due to discharge; n =1 only had 1 session and n = 1 only had 2 sessions. Kyroussis: n = 1 drop out.</td>
<td><strong>Problem:</strong> Allan et al. (2009) additional methodological variance could be traced to clinician inexperience with the use of the device, patient-ventilator asynchrony, inadequate inspiratory flow or flow-cycling times, unappreciated imposed work of breathing due to exhalation valve delays or resistance and poor mask fit. Barakat et al. (2010) Nasal mask problematic as they concluded most patients experienced oronasal breathing during exercise. Dreher et al. (2009) Problems with patients carrying ventilator (7Kg) led to drop outs. Dyer et al. (2011) not feasible to recruit to study. Highcock, Shneerson and Smith (2003) swivel valve in the circuit caused CO₂ rebreathe and there was resistance in the circuit with a mouthpiece. The researchers were unfamiliar with the NIV circuit. <strong>Benefit:</strong> Allan et al. (2009) individualised participant settings, increased by 2cmH₂O increased tolerance. Borghi et al. (2009) Participants benefitted from 30 min to get used to NIV pre-exercise. Dreher, Storre and Windish (2007) Dreher et al. (2009) All home NIV users so familiar with the device allowed for better tolerance.</td>
</tr>
<tr>
<td>Reported problems/changes to intervention</td>
<td>16 studies did not report any problems with intervention.</td>
<td><strong>Abbreviation Key:</strong> CO₂ Carbon Dioxide, EPAP End positive airways pressure, ESWT Endurance shuttle walk test, FiO₂ Fraction of inspired oxygen, NIV Non-Invasive ventilation, O₂ Oxygen, PS Pressure Support, UAE Unsupported arm exercise, Vₑ Minute ventilation, 6MWT Six minute walk test.</td>
</tr>
</tbody>
</table>
2.10 Discussion: Part B

2.10.1 What was the methodological quality of the individual studies?

The methodological quality of the studies included was reported in Table 2.7. The studies were small numbered. Only six studies carried out a power calculation to ensure their sample was big enough to detect statistical significance for the primary outcome measure (Pessoa et al., 2012; Menadue et al., 2010; Allan et al., 2009; Borghi-Silva et al., 2009; Dreher et al., 2009; Dreher et al., 2007). All of the studies had a clear research question, two of the studies design was overly complex as they were investigating the effects of two interventions (Allan et al., 2009; Hussain et al., 2011). Five studies did not have equal sample characteristics in each group or it was unclear if the groups were homogenous (Poggi et al., 2006; Menadue et al., 2009; Menadue et al., 2010; Oliveira et al., 2010; Dyer et al., 2011).

The sample selected often had exclusions including co-morbidities to avoid confounding factors and only one study had a sample with a mean age of > 70 years (Allan et al., 2009) In real world clinical practice a high proportion of the patients admitted to hospital are elderly and patients with severe COPD commonly experience exacerbations. This may mean that a successfully reported intervention may not work in clinical practice.

19 of the studies were cross-over trials. This was a good design for ensuring that the sample for each intervention had the same characteristics. It was important with cross over trials to ensure that there is an adequate wash out time of the intervention. The studies ranged from no wash out time (Poggi et al., 2006) to four days (Hussain et al., 2011). Baraket et al. (2007) used crossover design inappropriately because the training period was too long (ten sessions) and physiological changes may have carried over into the second arm of the trial. Randomisation was used in 15 of the studies, however the detail of randomisation was often omitted from the reported method, including randomisation protocol and timing.

There were only two studies that were double blindered, however not all of the researchers involved were blinded to the intervention (Borghi-Silva et al., 2009: Borghi-Silva et al., 2008). Three studies used a single blindered design and only

156
blinded participants to intervention arm (Allan et al., 2009; Vant Hul et al. 2004; Revill, Singh and Morgan, 2000). True blinding was challenging because there was no known piloted sham device for NIV and any change to circuitry or pressures may possibly influence breathing and thus results. This was observed by three studies who attempted to use invalidated sham comparisons (Allan et al., 2009; Borghi Silva et al., 2009; Revill, Singh and Morgan, 2000).

2.10.2 How did the individual studies inform the current study design?

The information that helped to inform the current study was reported in Table 2.8. The studies often lacked detail in regards to location, recruitment and methods. There was a need to carry out a feasibility study based on RCT design with detailed reporting and power calculation of the primary outcome measure.

The majority of the studies used stable patients without co-morbidities, only two studies recruited acutely unwell patients in hospital (Dyer et al., 2011; Menadue et al., 2010).

The interventions of the individual studies were performed in an exercise laboratory as one off exercise tests. There was only two studies that attempted to rehabilitate using the NIV as part of an exercise programme (Dyer et al., 2011; Barakat et al., 2007). However the trial by Barakat et al. (2007) may have been influenced by inefficient wash out and the trial by Dyer et al. (2011) was unable to recruit and retain participants as it was hospital-based and continued only until the point of the participant’s hospital discharge. This valuable study demonstrates the difficulties of recruiting and retaining within the NHS hospital environment. There is a gap of knowledge in the literature on exercising on NIV as a programme over time to see if any one-off benefits demonstrated during the exercise tests continue. Dyer et al. (2011) also informed the planned study by facilitating consideration of recruiting patients who had been more critically ill and were more likely to have a longer length of hospital stay, thus continuing to exercise the patients from hospital to home may have enabled them to be retained in the study. Familiarity with the device was used by the researchers to improve concordance. However using nocturnal users of NIV may have been a confounding factor. There
have been some improved outcomes from using nocturnal NIV during PR (Garrod et al., 2000).

The outcome measures chosen that demonstrated significant improvement assessed for a change in physiological variables for example SpO\textsubscript{2}, inflammatory markers and changes in lactate (Hanninck et al., 2014; Borghi et al., 2009; Polkey et al., 2000). Measuring physiological measures are important, but within clinical practice using outcome measures that can assess an observable change to both patient and clinical practice is important. A few of the studies had statistically significant results for endurance tests that may be more easily reproduced in clinical practice, are meaningful to both clinician and patient, and are able to measure changes associated with NIV on exercise. These included endurance time of cycle ergometry, UAE, ESWT and 6MWT (Menadue et al., 2010; Menadue et al., 2009; Dreher et al., 2009; Borghi et al., 2008; Dreher, Storre and Windish, 2007). Four of these studies assessed dyspnoea using the BORG score and demonstrated statistical improvement by decreasing dyspnoea with the use of NIV. This is an important objective measure because dyspnoea is a symptom that is meaningful to patients (Hussain et al., 2011; Menadue et al., 2009; Borghi et al., 2008; Barakat et al. 2007). Unfortunately none of the studies were able to demonstrate statistical improvement with a HRQOL measure. Barakat et al. (2007) used the SGRQ as an outcome measure and whilst not demonstrating statistical improvement there was clinically significant improvement in total scores. None of the reviewed studies considered the economic cost of NIV, or the effects on activity levels.

2.10.3 How did the individual studies inform the planned intervention in the future feasibility study?

There were 13 different makes of ventilator used making comparisons between studies difficult. Researcher experience of the ventilator was considered useful to ensure familiarity and standardise care. The other important factor was to choose a ventilator, circuit and mask that can support the V\textsubscript{E} of an exercising patient. Resistance in the circuit and mask may have increased the work of breathing reducing the ability to exercise (Allan et al., 2009; Highcock, Shneerson and Smith, 2003). The weight and portability of the ventilator was considered, too heavy and/or without a battery patients may not have been able to exercise with
it (Dreher et al., 2009). The use of PAV within three studies led to favourable outcomes, because it may have been able to respond to the rises in minute $V_E$ more efficiently. However, PAV is expensive, large, often driven by high flow gas, complex to set up and not suitable for clinical practice. The PS used ranged from 6cmH$_2$O to 29cmH$_2$O. The mean PS used in studies that demonstrated statistical significance when using NIV to exercise was 16cmH$_2$O. Four studies did not document the PS used, highlighting the importance of clear intervention documentation to allow analysis (Allan et al., 2009; Poggi et al., 2006; Kyroussis et al., 2000, Polkey et al., 2000). The amount of PS used could have influenced four of the studies that did not achieve statistical significance in their primary outcome the range of PS used was low including 6, 8, 10, 12cmH$_2$O (Moga et al., 2015; Pessoa et al., 2012; Highcock, Shneerson and Smith, 2003; Revill, Singh and Morgan, 2000). The majority of studies demonstrated that it was feasible for participants with stable COPD to exercise on NIV. Most studies reported no AEs, although in two studies participants desaturated and the test was stopped (Menadue et al., 2009; Menadue et al., 2010). Therefore it was important for the future study to consider when to entrain O$_2$. Fatigue may have contributed to a higher drop-out rate therefore individualised exercise was considered (Dreher et al., 2009).

2.11 Conclusion: Part B

The studies in literature review B informed the planned trial in regards to study population, mode, PS and feasibility of undertaking the research. The doctoral research planned to evaluate the effects of NIV on exercise following a hospital admission for an acidotic acute exacerbation of COPD requiring NIV compared to standard care. NIV was planned to be applied over a training period to confirm if the benefits of NIV observed on one-off exercise tests may possibly be improved upon with a training of a longer duration. The exercise on NIV was planned to continue from hospital to home to improve retention of participants into the study. Randomisation was to be applied before allocation. The outcome focused on both economic and QOL measures. Blinding of the participants and researcher was not considered possible because of the lack of credible sham-NIV.
2.12 How did the literature reviews in part A and B combined inform the decisions for the planned feasibility study?

2.12.1 Sample characteristics

The feasibility study was to include participants with a diagnosis of severe COPD. The participants were planned to be recruited following an admission with an acute exacerbation of COPD with uncompensated type II respiratory failure treated with NIV. The sample was planned to include co-morbidities except those that prevented the patient from walking and was inclusive of elderly patients. Research that involved a sample of patients who had been hospitalised for acidotic type II respiratory failure and who had been treated with NIV meant the patients had experienced NIV, with high pressure, but they may not be on home nocturnal NIV. For the study design to be novel and more clinically transferable it was necessary to study patients with more severe COPD who had been hospitalised following an acute exacerbation. The literature review informed the decision to use this group because of early hospital discharge affecting recruitment and retention. It was considered advantageous because they may have been hospitalised longer, may have been a sicker group (which the researcher had hoped to capture) and additionally the participants would have used NIV as treatment for acidosis in hospital so were familiar with the equipment.

2.12.2 Recruitment

The sample were to be recruited from acute respiratory hospital wards.

2.12.3 Design

The feasibility study was planned as a randomised controlled trial. The patients were randomised into three groups: A group of patients who have standard care, a group that use NIV on exercise during the length of their inpatient stay and a group that continue exercising for a further three months on NIV.

2.12.4 Outcome measure

The 6MWT was to be used as a measure of assessment. Dyspnoea was to be assessed using the modified BORG score (MBORG) and an additional dyspnoea measure. A measure of HRQOL was to be evaluated, this included SGRQ and an additional measure. A method for measuring of activity assessment was
considered. Additionally how to capture economic benefit was considered. The outcome measures were planned to be evaluated at baseline, hospital discharge, one month, two month and three months following discharge.

2.12.5 Exercise type, duration and intensity
The exercise plan was to be individualised in terms of duration and intensity because of the varying fitness levels of the patients. The aim was to exercise for 30min twice weekly supervised. The exercise was to consist of walking or cycling, weights and functional activities including sit to stands.

2.12.6 NIV intervention
NIV settings included IPAP and EPAP with S/T mode. The ventilator chosen needed to produce high inspiratory flow rates to meet the respiratory demands of exercise. A minimum PS of 10cmH₂O was considered to offload the respiratory muscles.

2.12.7 Quality and detail of reporting
The overall quality of reporting in the studies was variable, there was a lack of detail surrounding recruitment. The feasibility study attempted to provide a detailed report of the research process from recruitment to analysis to fully inform other researchers and the future study.

2.13 Overall conclusion
The literature reviews completed and documented in this chapter have successfully met the aims presented in section 2.2, Aims part A and 2.7, Aims part B. A logical system was used to search for both the SRs on exercise on NIV in COPD and studies not included in the part A SRs. The methodological quality of the SRs and individual studies was critically evaluated methodically using a recognised evaluation tool. The limitations of the reviews are that they excluded studies not published in English. There were two reviews and five individual studies not published in English. This may have meant some important studies were missing from the review. Nevertheless two of the SR’s reviewed included non-English studies and there were 11/21 individual studies from countries where the first language is not English. Another limitation is that there may have been publication bias, although the researcher attempted to reduce this by
searching abstracts from conferences but these were well known European based conferences that were familiar to the researcher, other less well known conferences were not searched. Additionally the review of the quality of the literature may have been biased because there was only a single researcher so no comparison of the quality of results could occur. However, the search was undertaken in a methodical way and clearly recorded to openly present the researcher's critical evaluation.

This literature review informed the research design and the intervention of the planned feasibility study. The following chapters focus on the study method from justification of the methodology (Chapter 3) to focusing on the separate quantitative (Chapter 4) and qualitative (Chapter 5) components.
Chapter 3 Methodology: Justification

3.1 Introduction

This chapter outlines the methodology and methods used for this research programme, justifies the choices made and examines the strengths and weaknesses of the approaches taken. Throughout the early phases of the research there have been significant changes to the design and these will be rationalised in this chapter.

The following two chapters (Chapters 4 and 5) chronicle the steps taken during both the quantitative and qualitative methodology. These chapters also describe the development of the methods used at the design, data collection and analysis stages of the research process.

3.2 Why mixed methods was chosen as a methodology

In the preliminary stages of the research project the researcher had chosen just quantitative methods for data collection. This may have been because the researcher had been working within the domain of medicine and possibly reflected the positivist influence of RCTs traditionally being seen as the gold standard of medical research. In comparison qualitative methods are sometimes viewed as less rigorous and unfamiliar (Mays, Pope and Popay, 2005).

However, following in-depth discussion with the PhD supervisors regarding the aims of the research and having gained a deeper understanding of the home intervention group, it was agreed that there was a need for additional qualitative methods to allow insight into the participants’ experience of the research.

3.3 Strengths and weaknesses of quantitative design

Quantitative methodology is objective and associated with a need to understand cause and effect. Quantitative methods have an advantage in that historically they are valued highly by health care professionals. This means that methods may be more easily disseminated and published (Pope and Mays, 1995). Quantitative
methods have been invaluable in contributing to the advancement of treating disease. The gold standard RCT means that quantitative research methods can be valid, reliable and repeatable (Robson, 2011). However quantitative methods will not capture the patient experience (Woolf, 2006), nor provide insight into how the treatment affects the patient’s life (Denzin and Lincoln, 2000). Quantitative methods are good at separating and recognising the cause and effect of differences observed at set moments in time, but quantitative researchers can only comment on the evidence observed (Borkan, 2004). However modern healthcare is now a very complex arena and quantitative research may no longer answer questions regarding organisation, culture and experience (Pope and Mays, 1995).

### 3.4 Strengths and weaknesses of qualitative design

Qualitative methods enable the researcher to ask the patient about their experience of the treatment. This may improve understanding of their emotions, perceptions and actions (Holloway, 2005). Qualitative skills allow insight into the processes building up to the witnessed differences. They add benefit because they can provide unforeseen understandings that had not been considered before (Borkan, 2004). NHS policy drivers have increased the use of qualitative research in healthcare. Traditionally medicine and healthcare researchers often only used and valued quantitative methods in their research design. The redefining of quality to incorporate lay perspectives (DH, 2000) means that there is a need to use good qualitative research to capture these views. It is important to not only understand if something works but also how and why it worked (Meyrick, 2006). The greater demand for qualitative research from the health field (Greenhalgh and Taylor, 1997) presents a challenge as this new audience comes from a predominantly positivist, biomedical standpoint (Meyrick, 2006). Qualitative methodology can provide information that is rich, exciting and challenging. It captures the complexity, mess and contradiction that makes up the real world and makes sense of it through patterns and meanings (Braun and Clarke, 2013).
3.5 The merits and challenges of combining both quantitative and qualitative design

The main purpose of this research was to evaluate feasibility of the research design and the feasibility of the intervention. Some of the main evaluations of feasibility include collating quantitative data regarding recruitment population numbers, numbers consented, randomisation process and retention of participants into the trial. It also includes evaluating the collation and completion of outcome measures (Bowen et al., 2009). Quantitative research methods are able to assess these aspects of feasibility. Additionally to these components of a feasibility trial it was considered important to evaluate whether the research design and intervention were acceptable to participants or not and gain understanding from the participants’ experience why this may or may not be. Therefore in October 2012 the decision was made to change the methodology to mixed methods. Mixed method design is when there is a significant component of quantitative data collection and a significant component of qualitative data collection in the same research programme (Robson, 2011). This involves combining the methods but using different research strategies.

There are critics who suggest that quantitative and qualitative methodologies do not study the same things and so cannot be combined (Guba, 1981; Sale, Lohfield and Brazil, 2002). There are theoretical hurdles to mixing both paradigms. Some researchers suggest that the two research methodologies are too separate in underlying assumptions, world view and epistemology that they cannot combine (Borkan, 2004). However a pragmatic view would suggest that the methods used should relate to the questions, rather than seeking to be purist in terms of method relating to a theological position (Bryman, 2006; Robson, 2011).

The potential disadvantages of mixed methods are that this is more time consuming, the researcher may not do either paradigm justice and it is complicated to combine the two methods (Creswell, Fetters and Ivankova, 2004). Another problem is that despite some researchers carrying out mixed methods studies they do not integrate the results well and often publish the two methods and results separately (Borkan, 2004).
Creswell and Clark (2007) focused on mixed methods as a research technique, which fitted in with the researcher’s aims for this study. The central premise is that the use of quantitative and qualitative approaches in combination provide a better understanding of the research problems than if either data set had been used alone (Creswell and Clark, 2007).

Mixed methods research has potentially more power in answering and testing the research question than just one research paradigm. It gives new insights on complex phenomena. Mixed methods let the researcher answer questions from the perspectives of both numbers and personal accounts therefore adding rigour to the research (Borkan, 2004).

The research programme underpinning this thesis was undertaken with participants with very severe COPD. The researcher felt it was important to understand the impact of living with COPD and how the intervention might influence their life, thus quantitative measures would not answer all of the research questions. There was a need to gain further understanding of the impact of living with COPD and how this research interacted with this. The choice of tool for the qualitative method was semi-structured interviews and the justification for this decision can be found in Chapter 5 (‘Qualitative Method’), section 5.2.3 Interviews.

The main aim of the in-depth interviews was to help contextualise the findings from the quantitative data, by providing insight into the lives of patients with severe COPD.

3.6 How to make mixed methods work

Mixed methods often work well when a researcher has knowledge of both. It can be challenging if the researcher is drawn more to one paradigm, leading to that paradigm being more represented (Bryman, 2006). However the supervision team for this research programme was made up of practitioners with experience in quantitative and qualitative research, thus providing clear input from both areas of research. The researcher had limited experience of either paradigm. Although her undergraduate dissertation was in qualitative methods most of her career had focused on reading and reviewing quantitative data. However mixed methods
must be more than simply collating the quantitative and qualitative data. The results and finding must be combined at some point during the research process (Creswell, Fetters and Ivankova, 2004). The researcher focused on 5 standards designed by Creswell, Fetters and Ivankova (2004) for designing and evaluating mixed methods studies.

3.6.1 Rationale for mixing the methods

The aim of this research study was feasibility therefore it was important to understand if the research had the potential to work but also why it might work and whether it was acceptable to patients.

3.6.2 Types of methods

The methods used were quantitative clinical measures and qualitative semi-structured interviews. These are discussed further (at length) in Chapter 5 and Chapter 6.

3.6.3 Priority given to qualitative or quantitative research

Often qualitative data is carried out as an exploratory research method prior to the initial quantitative research (Wilde et al., 1994; Eastbrooks, Field and Morse, 1994). The qualitative method in this study was used at the end of the intervention period. Whilst the initial phase was quantitative and there were more quantitative clinical outcomes evaluated, the research method for the qualitative component was time consuming and the findings from the qualitative research were deep and complex. The use of qualitative methods to complement the quantitative data is a common model for a mixed-method approach (Creswell, 2002), therefore whilst initially on the surface it may seem that priority was given to the quantitative methods, the researcher saw them both as having important but different values. It was equally important to understand if exercise on NIV might lead to clinical improvements and also if the intervention was acceptable to patients. Thus numbers can not be directly compared to the voice of the participants. Both are powerful in different ways, and to different audiences.
3.6.4 Implementation sequence

The quantitative data were initiated first but the personal reflective accounts collated by the researcher, which are an important component of reflexivity and qualitative methods began at the start of the study. Then followed the qualitative methods. However, the qualitative analysis began before the quantitative analysis. The details of the method of analysis can be found in Chapter 5 and Chapter 6.

3.6.5 Phase of study in which integration occurred

After completion of the data collection in May 2014 the researcher secured six weeks of funding explained in Chapter 4 (‘Quantitative methods’), section 4.7 Funding, enabled detailed analysis and integration of the two research paradigms. An explicit account of how the quantitative and qualitative data were collated will be explained within each method section separately to allow for a clear and coherent account that can be easily reproduced. However special importance will be given to ensuring that both quantitative and qualitative data are discussed together and related to each other where appropriate (Bryman, 2006).

3.7 Justification of change of primary outcome to feasibility

Another major change to the research project was to the primary outcome. Originally the primary outcome was to be economic evaluation. However on reflection the treatment in the study was complex and the researcher had many questions relating to the feasibility of the study and these should be reflected in the primary outcomes. The Medical Research Council (MRC) guidelines for developing and evaluating complex interventions (2008, pp. 6) defines complex interventions as

“… interventions with several interacting components”

This study was a complex intervention because it assessed two treatments in tandem, both ‘exercise’ and ‘non-invasive ventilation’, and is further complicated by using these interventions in both the acute and community environment.

The guidance suggests that due to the complexity of the intervention enough time should be allocated to testing the feasibility and piloting of the intervention to
ensure that the intervention works as intended (MRC, 2008). Figure 3.1 summarises the MRC’s guidance on the process for developing and evaluating the complex intervention.

![Figure 3.1 MRC Process for developing and evaluating complex interventions. Key elements of the development and evaluation process](image)

(Adapted from MRC, Developing and evaluating complex interventions: new guidance, 2008, p.9)

The NIV device was already CE marked and not contraindicated for use when exercising. Therefore the study was not testing the actual feasibility of the equipment.

It was a debatable issue for the researcher as to whether or not the study was classified as a pilot or a feasibility. Often previous studies have used the two terms interchangeably (Arrain et al., 2010). A pilot study is a complete version of the full study run on a smaller level to see if the parts of the research all work together (http://www.netscc.ac.uk/glossary/), however a feasibility study can be a complete model of a full study or it can be used to assess individual parts for example, adequacy of methods, assess participant recruitment strategies, identify potential retention problems, evaluate the protocol for realistic implementation, determine study resources and assess the preliminary evidence and its justification for a larger-scale study (Cope, 2015). Disadvantages of feasibility studies are that they may not be large enough to calculate sample size or response rates (van Teijlingen and Hundley, 2002). Another problem is that some peer reviewed journals could consider a feasibility study not worthy of being published (Cope, 2015), however the MRC (2008) suggested that it is essential to publish feasibility studies to inform other researchers and clinicians.
The change to a feasibility study was a challenging one as the researcher wanted to meet the needs of the sponsor company but also to fulfil the PhD requirements. However after considerable thought and follow up discussion with the supervision team in April 2013 the decision was made to make the primary objective feasibility. The secondary outcomes would still look to evaluate possible trends for changes in clinical outcome measures. The researchers aimed to publish the feasibility trial which should still meet the requirements from the sponsor, detailed in Chapter 4 Quantitative methods, section 4.3.

There was also a challenge in evaluating feasibility. There is limited published literature on standards to guide the design and evaluation of feasibility studies (Bowen et al., 2009). This study was in patients with a severe chronic disease who were near end of life and suffered frequent exacerbations and hospital admissions (BTS and Primary Care Respiratory Society-UK (PCRS-UK), 2011). It was important to investigate whether this research was acceptable to patients and whether recruitment was feasible. Hagen et al. (2011) reported a shortage of quality, powered clinical studies in palliative care. They reported that feasibility studies should be trialled and published to assess if the research is capable of being done.

Bowen et al. (2009) suggested that a design of a feasibility study should relate to three key questions:

1) Can it work?

2) Does it work?

3) Will it work?

Feeley et al. (2009) suggested that feasibility related to the ease of execution - how the research is planned, undertaken and completed. However, acceptability was described as how favourable the research is from the perspectives of the recipients, healthcare professionals and providers (Feeley et al., 2009). Therefore the descriptive analysis of the project sought to address both feasibility and acceptability.
3.8 Explanation of pragmatism: To be able to use the intervention in clinical practice

The researcher worked in a pressurised NHS environment, and patients were complex, often elderly and with multiple co-morbidities. The researcher did not work in a controlled laboratory with patients who only had one pathology. The MRC (2008) reported that a purpose of assessing feasibility of a complex intervention should be to evaluate whether the intervention works in every day practice. Often RCTs were so focused on eliminating bias that the inclusion criteria were so exclusive that they no longer mimicked patients in clinical practice (Zwarenstein et al., 2008). A pragmatic approach aspired to increase applicability of the trials results to usual care settings (Lee et al., 2001; Zarin, Young and West, 2005).

This way of thinking complemented the researcher’s background as a physiotherapist. The researcher had a desire to be able to be evidence based but realistically put findings into clinical practice. The researcher was keen for this research to be something other clinicians may be able to take into clinical practice, not just something laboratory-based that did not mimic NHS conditions or include participants that due to exclusions you would rarely have seen in clinical practice. Nor did the researcher want the research to be about solely producing a theory about a patient experience. Therefore the method needed to be pragmatic, real world research, using a mixed methods approach.

3.9 Conclusion

This chapter has justified the use of mixed methods research to allow for both clinical assessment of feasibility and allow a deeper understanding of the patient experience. The change of aim of the study to feasibility has been justified. The chapter also discussed the importance to the researcher that this was a pragmatic study that could be useful to clinicians in the real world. The following chapters (Chapter 4 and Chapter 5) will detail the quantitative and qualitative methods used to underpin the mixed method design.
Chapter 4 Quantitative Methods

4.1 Introduction

The literature review in Chapter 2 demonstrated that there was a clear need for a feasibility study investigating whether it was possible to use NIV during exercise on patients with severe COPD using high PS. This chapter outlines the quantitative methods used to answer this research question.

4.2 Type of study

A RCT using a mixed methods approach was chosen as the research method to assess the aim of feasibility. The reasoning behind this decision and justification for it can be found in Chapter 3, section 3.7. It was a pragmatic clinical study which randomised patients into three different limbs:

**Limb One: Standard Care:** Exercise and additional O$_2$ (if O$_2$ saturation (SpO$_2$) < 90% or the patient required long term O$_2$ therapy (LTOT) or AOT) for the duration of the hospital admission. This was based on the PR guidelines (BTS, 2014) and previous studies which had used AOT when the participants SpO$_2$ levels were < 90% (Dyer et al., 2012; Emtner et al., 2003; Wadell et al., 2001; Garrrod, Paul and Wedzicha, 2000; Rooyackers et al., 1997). The research was carried out prior to the publication of the home O$_2$ guidelines including advice regarding prescription of AOT (BTS, 2015).

**Limb Two: Exercise on NIV in hospital:** Exercise on NIV and additional O$_2$ (if SpO$_2$ < 90% or the patient required LTOT or ambulatory O$_2$) for the duration of the hospital admission. The reasoning for this second limb was that this currently matched what the researcher had been doing clinically within the critical care environment prior to the study. Clinically the researcher had seen patients respond well to getting out of bed on a ventilator, particularly in the early stages of recovery. Thus the researcher wanted to see if adding ventilation to rehabilitation in this group in the short term, acute hospital phase, changed outcome.

**Limb Three: Exercise on NIV in hospital and home:** As per limb two but patients would continue exercising on NIV supervised at home twice weekly for an additional three months following their discharge. The reasoning for this
research limb was that this would mirror an effective PR duration which is known to have long term health benefits in COPD (Lacasse et al., 2002).

The pathway for the study is shown in Figure 4.1.
Figure 4.1 Schematic of the research process
4.3 Commercial Funding

The researcher worked in a busy NHS department, therefore there were limited funding opportunities to be able to carry out the research. Consequently the researcher sought out a commercial company who sells respiratory ventilators, Philips-Respironics. She pitched the research proposal and protocol to them in a bid for the use of equipment and funding of research time. This involved preparing the proposal, preliminary interviews with key research personnel followed by an international telephone conference question and answer session with company representatives and engineers. The bid was successful and funding was secured for 18 months of part time (0.5 full-time equivalent) research time and use of their equipment.

The researcher was aware of the potential negative connotations of undertaking commercially funded research; however without this funding the research would not have been able to take place. To reduce the potential bias that the commercial sponsor might have had on the publishing of the results, the researcher was thorough to ensure that she owned the rights to the data. Therefore intellectual property contracts were negotiated between University of the West of England (UWE), University Hospitals Bristol NHS Foundation Trust (UHBristol) and the researcher, however there was an expectation from the company that the study would be published and all equipment used that was sourced and manufactured by Philips-Respironics would be recognised. This is discussed further in section 4.6.

4.4 Ethical Approval

The Central Bristol Regional NHS Ethics Committee (REC) reviewed the research and the committee gave a favourable ethical opinion following some clarification regarding the variation in care provided to patients in each limb of the study. Official ethical approval was received on 24/9/2012 (Appendix 2a). A favourable ethical opinion was also obtained from the Faculty of Health and Life Sciences Ethics Sub-Committee at the University of the West of England, Bristol (UWE) on 30/10/2012 (Appendix 2c).

An amendment was submitted on 18/3/2013 to The Central Bristol Regional NHS Ethics Committee and Health and Social Care Ethics Sub-Committee at the
University of the West of England, Bristol (UWE) requesting inclusion of the qualitative method of semi-structured interviews, and it was subsequently approved (Appendix 2b). The reasoning behind this decision was explained in Chapter 3 (Justification of the methodology), section 3.5.

4.5 Ethical considerations

All patients were given a comprehensive information sheet (Appendix 3) and approached in advance when considered to be medically stable by the researcher to allow adequate time for the patient to consider the study and ask questions. The patients who decided not to participate in the study still received standard care. Informed consent was received from all of the patients participating in the study (Appendix 4).

The researcher’s main ethical concern was that the group receiving standard care and hospital NIV only would not be referred to PR until the end of the 3 months following discharge. The hospital and home NIV on exercise group would be receiving supervised rehabilitation for the 3 months post discharge. However it is known from previous research that approximately 33% of patients offered PR decline and a further 33% fail to complete due to sickness, reduced motivation or logistical problems (BTS and PCRS-UK, 2011). Thus the researcher reasoned that many of these patients with severe disease, would not have been able to access or attend PR. Therefore the risk of this group not receiving PR was accepted. The ethics committee agreed with the researcher on this matter. Following discussion with PR providers the researcher decided to refer all participants at the point of discharge so that they could begin PR immediately on ending the trial, thus minimising any possible negative effects from having to wait longer for PR.

4.6. Research and Innovation (R & I)

There was a two month delay in receiving UHBristol R & I Department approval due to resolving an issue of Intellectual Property between the NHS Trust and UWE. This was eventually resolved with the exchange of contracts and approval granted on 24/1/2013 (Appendix 5). IP was an essential component of the contract between the researcher, UHBristol, UWE and Philips-Respironics. This established that the researcher owned the data and would be able to publish even
if the research produced negative data. It also established Philips-Respironics as the Sponsor of the study (Appendix 6).

4.7 NHS Funding

The Philips-Respironics funding only supported 18 months of research time for 0.5 full time equivalent therefore additional funding was sourced to provide back-fill into the researcher’s clinical post to release the researcher to be able to analyse the research data. A National Health Service (NHS) Clinical Academic Training Programme Internship was applied for and awarded in March 2014. This was an award of £10,000 to be spent supporting an application for higher level study as described in the accompanying document. This money can be used to support release from clinical practice if required. This allowed for 7 weeks of full time back-fill to allow for data analysis.

4.8 Choosing the ventilator

Before the research protocol was finalised the ventilator and settings were decided upon. It was important to use a ventilator that was familiar to the researcher, currently licenced and used within the clinical setting but also one that would be able to provide the inspiratory flow rates needed to support the participants increased breathing effort, both increased RR and increased depth of breathing (VT). It would also need to be portable with a battery. Therefore the NIV CE marked device used in the exercise on NIV in hospital group and the exercise on NIV in hospital and home group was the Trilogy 100 (Philips-Respironics). This was a domiciliary device currently used by UHB for overnight treatment; however, it was not contra-indicated for use during exercise (Figure 4.2).

Figure 4.2 The Trilogy 100 (Philips-Respironics)
The benefits of the Trilogy 100 were that it was able to record the date and time of use, breathing frequency and predicted $V_T$ and pressure settings. This was recorded on an integral SD card and was subsequently downloaded using software, Direct View (Philips-Respironics) and reports were generated, to assist with analysis. The specifications of the ventilator can be found in Appendix 7.

4.9 Preliminary Equipment Test

One of the concerns that the engineers from the commercial company raised during a telephone consultation was whether the Trilogy 100 would provide a high enough inspiratory flow rate to allow a participant to exercise. This question was really asking whether or not the ventilator would meet the increased demands of respiration as a response to exercise.

Therefore a cardiopulmonary exercise test on a treadmill was organised on a ‘normal’ male, over 50 years with no history of lung disease. The Trilogy ventilator and equipment was in situ, and average pressures of an inspiratory positive airway pressure (IPAP) of 20cmH$_2$O and an expiratory positive airway pressure (EPAP) of 6cmH$_2$O, (thus a pressure support (PS) of 14cmH$_2$O (PS = IPAP - EPAP)) were generated. The test was successfully undertaken with no problems in flow rate occurring. Therefore if the test was achieved in a normal person whilst using the Trilogy 100 then it would very likely meet the demands of the patients in the trial who had severely compromised lungs and would not reach the same exercise levels (Appendix 8). This is called VL and was previously discussed in Chapter 1 Introduction, section 1.16 the pathophysiology of COPD and exercise.

4.10 Ventilator Settings

During the actual study the settings were individualised for each patient, with the aim of providing a minimum PS of 10cmH$_2$O, titrating this to reach a maximum pressure support of 20cmH$_2$O during exercise. The mode used was spontaneous to allow for the patient to trigger all the breaths. If the patient did not breathe, no air or pressure were provided. If the ventilator detected a small inspiratory flow (flow trigger), this then activated the inspiratory pressure initiation (Kinnear, 2008).

EPAP was used to allow the patient to overcome the resistance of the mask and hose. This would also help overcome intrinsic positive end expiratory pressure
PEEPi, often experienced in patients with severe COPD. This is further explained in Chapter 1 Introduction, section 1.18 Non-invasive ventilation (NIV).

PS is the pressure achieved when EPAP is subtracted from the IPAP. The inspiratory time used was also individualised as this needed to be fast enough to meet the demands of an increased breathing frequency but not so fast that there was not adequate time to reach the desired PS. Clinical observations including RR, SpO\textsubscript{2}, HR and the MBORG scale sheet at two minute intervals was used to assess whether the participant work of breathing was offloaded by the ventilator and whether the pressure needed to be increased. Additionally the participants were asked if the pressure was enough or too strong at two minute intervals. If the settings needed to be increased this was carried out in 2cmH\textsubscript{2}O increments based on the findings in literature review B, section 2.9.4.

The mask used on the patient was individualised but the comfort gel full face mask was trialled in the first instance. This was a commonly used mask in the clinical setting and familiar to the researcher. Most people mouth breathe on exercise, therefore the full face mask was the primary choice (Figure 4.3A). A nasal mask was used in the patients unable to tolerate a full face mask (Figure 4.3B)

![Figure 4.3 A) The Comfort Gel full face mask (Philips-Respironics) and B) Swift Fx nasal pillows (ResMed)](image)

Further decision-making criteria behind the type of ventilator and settings are discussed within Chapter 2 (‘literature review’), section 2.10.2 How did the individual studies inform the current study.
4.11 Choosing the type of exercise

As discussed in Chapter 2 the patients selected for the study had severe lung disease. They were likely to be physically de-conditioned with very limited mobility. They may also have been afraid of exercising due to fearing the sensation of breathlessness. This causes further muscle wasting by the problematic cycle of inactivity. Therefore the exercise needed to be individualised. The BTS PR guidelines (2013) formed the basis for deciding on the content of the exercise plan. However, the exercise needed to be easily reproduced both within a busy hospital environment and small private accommodation in the community. The main focus of the exercise was on aerobic training through walking and cycling. However additional resistance exercises were included as they can lead to greater improvement in peripheral muscle strength than aerobic training in isolation (BTS, 2013). The exercise was made up of muscle strengthening exercises, with particular focus on the lower limbs, and also included walking and/or cycling, see Appendix 12. Portable leg weights, arm weights and cycling pedals were sourced to enable exercise within a confined space.

The frequency was decided as three exercise sessions per week with two of the three sessions supervised by the researcher. The duration of the session was built up to last for 30 minutes, however some of the patients were not able to achieve this. The exercise progression was modified according to MBORG score, patient verbal feedback and observation by the clinician of RR, HR, SpO₂ and overall work of breathing. When patients are exercising clinically on the wards and in PR a MBORG score of four to five is aimed for (somewhat severe to severe breathlessness) (European Lung Foundation and European Respiratory Society, 2000; Egan et al., 2012). The patients in this study were likely to have a resting MBORG score higher than this due to the severity of their lung disease. Therefore an individualised approach was taken and if MBORG score was greater than five at rest then exercise was completed at one unit higher than their resting score, if any greater the exercise intensity was reduced. If SpO₂ was < 85% exercise intensity was reduced based on safety instructions used during exercise testing (Zebathos and Weisman, 2002). The targeted intensity of the walking/cycling was at a minimum of 60% peak work rate as recommended by the BTS PR guidelines (2013), discussed in Chapter 1 (‘Background’), section 1.15.6 Training intensity,
also see Appendix 12. The study duration on discharge, for the patients exercising at home on NIV, was decided at three months. This is again based on PR guidelines and PR quality standards (BTS, 2013; BTS, 2014). RR was monitored, it is expected that RR can reach 50 breaths/minute during exercise in healthy individuals (Mcardle, Katch, and Katch, 2006). In combination with the other observations and participant feedback a RR of 40 was used by the clinician to determine if exercise intensity needed decreasing. If a participant suffered an exacerbation of COPD then the participant was reassessed and the intervention would be modified accordingly. The participant may have needed a higher PS or a lower exercise intensity, repetitions or duration of exercise. If a participant suffered an exacerbation requiring hospitalisation this was formally recorded as a SAE, SAEs are explained further in section 4.23.2. If a participant was admitted to hospital the intervention continued as planned but on the ward rather than at home. If a patient was unstable, for example acidotic or cardiovascularly unstable then the exercise would begin only when the patient was clinically stable, for example not acidotic and with stable cardiovascular measures. The participant did not get any extra time in the study and still completed the trial three months following the initial hospital discharge.

4.12 Researcher consideration to reduce bias

The researcher was a highly specialist respiratory physiotherapist with over 10 years of experience in both acute NIV and home NIV. Therefore the researcher was in a good position to be able to undertake this research. However, there were possible difficulties from the clinician being the only researcher conducting the study. From the initial design phase to the end analysis the researcher was aware of potential bias. Strategies were taken to reduce bias through the design of a RCT, the use of validated questionnaires and measures, the use of Standard Operating Procedures (SOPs) for objective measures and treatment, the use of a blinded additional coder for interviews and a blinded analyser of the quantitative data. Care was taken to give all three groups an equal amount of encouragement, for example during the 6MWT, to avoid bias during data collection. No quantitative data were analysed until the end of the research time period.
4.13 Recruitment preliminary data collection

Prior to designing the protocol an audit had been undertaken at UHBristol on one main respiratory ward. This collated data on the number of admissions requiring treatment with NIV. It identified 50 patients who had been treated with NIV over a 6 month period from October 2009 to March 2010 (this did not include other clinical speciality areas). It revealed that 33/50 patients who required NIV had a primary diagnosis of COPD. This information helped to determine the size of the potential recruitment pool.

4.14 Stakeholder involvement and preparation

The researcher met with the Bristol Breathe Easy group, a support group for patients with COPD, prior to and throughout the project time period. The researcher piloted equipment and questionnaires prior to the research project beginning to ensure acceptability to this patient group which included COPD patients and home ventilation users.

The researcher created a presentation detailing the specifics of the research and presented this to hospital consultants, nursing staff, physiotherapy teams, discharge teams and community teams to assist with recruitment and support for the study. Posters were put up in key clinical areas reminding staff of the study and reminder emails to key clinical staff were sent out prior to recruitment initiation.

4.15 Randomisation

Prior to any recruitment for the research the randomisation process was carried out. The study was randomised prior to recruitment. 30 participants was chosen as this was similar in size to other studies involving exercise on NIV, (this is detailed in chapter 2 literature review) and this seemed a realistic number to attempt to recruit based on the preliminary data, see section 4.13, and would be adequate to evaluate feasibility.

Randomisation software http://www.randomization.com, was used by a supervisor to generate the allocation of groups. Following feedback from examiners as part of the researcher’s PhD progression viva (which took place on 23rd October 2013), the randomisation process was adapted. The process was
changed to a blinded process using sealed envelopes to ensure that the researcher did not know which group the next participant would be randomised to. The exact process for this was one of the supervisors carried out the randomisation procedure and placed the allocated group into number ordered, sealed envelopes and stored securely. The researcher was not involved in that process and did not see or have access to the envelope until after a participant had been recruited into the trial. The supervisor would release each individual order numbered envelope after each successful participant recruitment.

4.16 Study Location

The study was carried out within the city of Bristol. The population of Bristol is 428,100 (Census Office for National Statistics, 2011), the largest city in the South West of England. The prevalence of COPD is 1.6%, similar to the national average of 1.5% (DH, 2010d). COPD is the second most common reason for a hospital admission via A&E at UHBristol, after chest and abdominal pain (NHS England, 2014)

The study was carried out at a single research centre, The Bristol Royal Infirmary, UHBristol. This was a 500 bedded acute teaching hospital with 10 medical wards. A sleep unit supplied home NIV to a caseload of 550 patients, of which 70 needed on-going follow up at home and 80 had a diagnosis of COPD. Respiratory patients were admitted via A&E, GP assessment unit or directly from respiratory consultants through a respiratory assessment clinic. They then transitioned through the hospital via the Medical Assessment Unit (MAU) to be treated on two respiratory wards. Recruitment was planned to include A&E, MAU, respiratory wards and acute medical wards. There were two high care beds in A&E that could provide NIV. There were two high care beds on MAU and nine high care beds on one respiratory ward (n = 13 total high care beds). There were 38 other respiratory beds, however during busy admission periods patients requiring NIV were managed on the main ward. The nursing to patient ratio for high care was one nurse to three high care patients. The other ward patients were managed by one nurse to eight patients. Physiotherapy to cover A&E, MAU, two respiratory wards and two general medical wards (52 beds) was provided by one 1.0 full-time equivalent (FTE) Band 7 (Senior) physiotherapist, two x 1.0 FTE Band 6 (Senior) physiotherapists, two x 1.0 FTE Band 5 (Junior) physiotherapists and two x 1.0

183
FTE Band 3 physiotherapy assistants. The home ventilation service (550 patients) was provided by one x 1.0 FTE Band 7 physiotherapist and one x 1.0 FTE clinical physiologist.

4.17 Recruitment screening

All patients admitted with an acute exacerbation of their COPD causing respiratory acidosis and type II respiratory failure treated with NIV in hospital were identified by the researcher. The researcher reviewed e-handover records from MAU and the two respiratory wards, attended medical rounds Monday to Friday and took referrals from nursing staff, physiotherapy staff and medical staff in person, by bleep, email or telephone. Weekend physiotherapy staff informed the researcher by telephone of any weekend admissions.

All of these patients were screened for the following inclusion and exclusion criteria prior to being approached to consider participating in the study (see Appendix 10 for the inclusion and exclusion form).

4.17.1 Inclusion criterion:

1. A diagnosis of a COPD exacerbation resulting in a hospital admission for respiratory acidosis and type II respiratory failure, requiring treatment with NIV during this hospital admission, for any length of time

4.17.2 Exclusion criteria:

1. Primary diagnosis not COPD
2. Not had a respiratory acidosis diagnosed through ABG analysis
3. Not had NIV treatment
4. Under 25 years of age
5. Unable to follow commands or unable to consent
6. Known contraindication to NIV (Royal College of Physicians, 2008)
7. Unable to tolerate acute hospital NIV
8. Unable to or refused to comply with physiotherapy
9. Had an additional pathology that limited ability to mobilise
10. Dying/receiving end of life care and not expected to survive hospital admission
The reasoning behind exclusion criteria one, two and three was to ensure that the correct patients were selected for recruitment. There are many reasons a patient can receive NIV, for example heart failure, and the researcher wanted to be clear that only COPD patients were to participate in the planned research.

Often patients with severe COPD can present to hospital with an ABG demonstrating chronic type II respiratory failure. This means that over time the body has compensated for a high CO\textsubscript{2} so that their cell pH has normalised. These patients do not have a respiratory acidosis on their ABG and do not meet the criteria for treatment with acute hospital NIV (BTS, 2002). Thus they were excluded from the study. It was important that the patient had been treated with NIV in hospital because this demonstrated the severity of their disease and also the researcher considered that this group of patients may be more concordant with the ventilator equipment because they had just been treated with a similar device.

Patients were screened for age because COPD is predominantly diagnosed in those over 35 years of age (NICE, 2015), however within Bristol some of the known COPD patients are younger because of increased cigarette smoking, known genetic disorders (for example alpha-1-antitripsin disorder), or inhalation of narcotics causing earlier non-reversible airway damage and a diagnosis of COPD.

Exclusion five was created because the researcher considered the intervention to be complex and a participant must be able to follow commands and understand potential side-effects of the equipment. Therefore those patients without mental capacity or an ability to follow commands were excluded from the study.

Exclusion six to nine were created to ensure all aspects of the intervention could be safely and consensually applied with a potential participant.

The final exclusion criterion aimed to preserve a patient's dignity and not cause any additional distress to a patient or relatives.

The sample size was initially planned to be 30 participants. Therefore 10 participants would be allocated to each study limb. The full details of the recruited sample size and consort diagram are presented within Chapter 5 (‘Quantitative
Results’), figure 7.1. The complexity of the recruitment will be discussed within Chapter 9 (‘Discussion’), section 9.2.1 Recruitment sample.

4.18 Recruitment

The recruitment period was from the end of January 2013 until the beginning of January 2014, over an eleven month period. Recruitment had been planned to begin in November 2012, but was delayed due to IP negotiations, discussed previously in section 4.6 R & I. The participant recruitment process was that each potential participant was issued with an initial verbal invitation by the researcher and if interested followed up by issuing a participant information sheet. The participant information sheet clearly described the equipment used, potential side effects and why participants were being invited to take part (Appendix 3). Potential participants were only approached when they were medically stable, and no longer had a respiratory acidosis detected by their ABG results. This was because the potential participant had to be alert and coherent enough to understand the information being offered. The potential participant was given time to think about their decision to participate and to discuss it further with friends, family or nursing staff. If a person decided to participate in the study they were reminded that they would be randomly allocated to one of three groups and that they would not be able to choose which group they were allocated to. All participants signed the consent form (Appendix 4), this was countersigned by the researcher and three copies of the form were taken, one for the medical notes, one for the research site folder and one for the participant to keep. A sticker detailing the NHS Trust Research & Innovation (R & I) Department number, REC number and key research information was put into the participant’s medical notes. The participant was issued with a participant identification (ID) number and the randomisation envelopes were accessed to reveal the participant group allocation. The participant was then informed of the allocation. The participant was allocated a case record file (CRF) labelled with their research ID. This was stored on a double encrypted Microsoft access file on a NHS Trust computer hard drive. The participant's details were kept in a separate paper file alongside their research ID number, locked in a separate filing cabinet. The participant’s recruitment details were then entered onto the R & I secure database of research information called “The Edge system”. A letter was sent to the participant’s GP informing them of
their registered patient’s inclusion into the study and revealing their group allocation (Appendix 9).

4.19 Baseline assessment
The baseline participant information was collated by the researcher immediately following consent. This assessment took place on the hospital ward. This was obtained from the participant directly and from their medical notes. This included basic information including age, ethnicity, address and contact details. It also included direct information regarding their medical history including those related to this hospital admission, BMI, smoking and alcohol consumption status, home environment and walking tolerance.

4.19.1 Outcome measures
The outcome measures were also recorded at baseline. They were as follows: 6MWT, SGRQ, LCADL, modified Medical Research Council (MMRC) dyspnoea score, MBORG and EQ-5D-5L. Further details of these measures are discussed and justified later in section 4.22

4.19.2 Self-reported symptom diaries
The participants were also issued with symptom diaries (Appendix 11). These were to be supplied on discharge for the patients to record their daily symptoms, medication use and access to health care services during the study.

4.20 Allocated treatment
Following consent the randomly allocated treatment was revealed to the participant. The justification for the three limbs was documented in section 4.2 Type of study.

4.20.1 Standard care
If the participant was allocated to standard care, this consisted of standard treatment according to the COPD Guidelines (NICE, 2015), tailored to the patient, on the basis of medical status and symptoms. From a physiotherapy perspective it consisted of a supervised exercise programme at least twice a week. This included walking or pedal cycling or lower limb and upper limb weights all on either air or O2 if the patient was on LTOT or O2 levels were less than 90% SpO2 at rest.
This was based on the ventilator SOP (Appendix 13). In addition any other routine physiotherapy was carried out e.g. chest clearance or stairs assessment by the ward physiotherapy team. At the point of discharge the patient was given a standard hospital discharge home exercise plan including basic chair exercises for lower limbs and upper limbs, sit to stand and marching on the spot. They were then followed up for outcome measure assessment and referred to PR to start at the end of the three month period following discharge.

4.20.2 Exercise on NIV in hospital

If the patient was allocated to exercise on NIV in hospital, they were set up on a Trilogy 100 ventilator as planned in the ventilator SOP (Appendix 13). They were seen twice weekly by the researcher for an individualised exercise programme on the ventilator based on the exercise SOP (Appendix 12). At the point of discharge the patient was given a home exercise plan (see section 4.20.1), followed up for outcome measures and referred to PR to start at the end of the three month period following discharge.

4.20.3 Exercise on NIV in hospital and home

If the patient was allocated to exercise on NIV in hospital and home, they were set up on a Trilogy 100 ventilator as in the SOP (Appendix 13). They were seen twice weekly by the researcher for an individualised exercise programme on the ventilator based on the exercise SOP (Appendix 12). However at the point of discharge they were also seen at home twice weekly by the researcher and continued with the supervised exercise programme on the ventilator. The exercise plan was individualised and progressed as able. If there were any hospital admissions required during the trial then the treatment continued within the hospital environment when the patient was medically stable and then continued at home on discharge. In such circumstances study participation was not extended beyond the original three months. They were also referred to PR to begin after the three month trial.

4.21 Follow up

All of the patients were followed up for three months following hospital discharge from hospital. At the point of hospital discharge outcome measures were reassessed. The time between baseline assessment and hospital discharge
assessment was different in each participant because of the varying severity of acute illness and length of hospital stay.

4.21.1 The BODE Index score

The BODE Index score was calculated at discharge for each of the participants. This scoring system is a prediction of all-cause mortality and respiratory-related mortality. The calculation is based on the Forced Expiratory volume in one second (FEV₁), Body Mass Index (BMI), 6MWT and MMRC dyspnoea score. The calculation for this was sourced from the work of Celli et al (2004). This was recorded because it was useful in assessing the severity of the participants’ health conditions in the study.

Additionally participants in all three groups had their lung function recorded in line with standard hospital care for this group. This assisted with determining the severity of participants’ COPD within the groups. All of the patients in the standard care group and exercise on NIV in hospital group were contacted weekly by phone to ensure symptom diaries were being completed. At the end of every month, for three months, a time and place convenient to the participants was organised and the researcher would visit. In cases where a patient could not be reached by telephone the patient was sent a letter confirming that the researcher would be visiting them at home at a chosen time or date unless otherwise indicated by the participant. The researcher collected diaries, checked the ActiCal activity monitors (discussed in detail in section 4.22.9 ActiCal Data) were being worn, measured 6MWT and collated the questionnaires. All the outcome measure data were placed within the participant’s CRF and locked away as per research governance requirement. No information was analysed until the end of the trial.

4.22 Outcome measures

This section outlines the different outcome measures that were used to assess the feasibility of the trial and the feasibility of the intervention. They were assessed at five time points (baseline: in hospital on the day of enrolment into the trial, discharge: in hospital on the day of hospital discharge, month one: one month following the hospital discharge date, month two: two months following the hospital discharge date and month three: three months following the hospital discharge date) within a busy acute hospital environment and within the home
environment over a considerable length of time. The time of baseline to discharge were individualised for each of the participants because severity of illness and length of hospital stay varied for each participant. However the month one, two and three measures were all taken after the same amount of time.

The justification for the timing of the outcome measures was that baseline assessment was required as an individual participant starting point following stabilisation in hospital (CVS stable, not acidotic and medical team in agreement), against which the potential benefit of the intervention could be assessed. This was because it would be difficult to predict hospital admission in a given sample and assess baseline pre-admission. It was also important to wait until the patient was medically stable to ensure that the participant was safe to exercise. The discharge time point was chosen to identify if participants would get any benefit from using NIV to exercise in hospital. The time points after one month, after two months and after three months post-discharge were chosen because of the participants' levels of disease severity. The researcher was unsure of their potential morbidity and mortality. Participants may die after the first or second month and potential outcome measure data would be lost. There is a 10% mortality risk for patients admitted with an acute exacerbation of COPD and a 40% risk of mortality in the year following discharge (Groenewegen et al., 2003; Connors et al., 1996; Seneff et al., 1995). As part of the analysis of feasibility of the trial identifying when to assess the outcome measures was an important finding for a future trial.

The primary outcome was feasibility evidenced by recruitment and retention (illustrated via the CONSORT diagram), completion of outcomes and trends of the measures.

The outcome measures consisted of activity (measured by ActiCal device), symptoms (recorded in a symptom diary), Dyspnoea assessment, QOL (assessed by questionnaires) and walking distance (6MWT). It was important that they were validated in COPD, routinely used in clinical practice and provided relevant information that was easily reproducible by other clinicians. They would be used to evaluate any potential trend in clinical outcomes from exercising on NIV compared to standard care. Figure 4.4 presents the timing of the outcome measures.
Baseline assessment (Within 24hrs of recruitment)

Outcome measures
1. 6MWT
2. SGRQ
3. LCADL
4. EQ5D-5L
5. MBORG
6. MMRC score
7. Spirometry

Discharge assessment (Morning of discharge)

Outcome measures
1. 6MWT
2. SGRQ
3. LCADL
4. EQ5D-5L
5. MBORG
6. MMRC score
7. ActiCal monitor issued
8. Patient self reported diary issued
9. BODE score

After 1, 2 and 3 months (Location: Participant’s home)

Outcome measures
1. 6MWT
2. SGRQ
3. LCADL
4. EQ5D-5L
5. MBORG
6. MMRC score
7. ActiCal monitor issued
8. Patient self reported diary issued
9. Ventilator data download

Completed study

Figure 4.4 Diagram of the timing of outcome measure assessment
4.22.1 Assessment of feasibility

Recruitment and retention was assessed from the recruitment data. This included the number of patients’ screened for inclusion and the time scale of recruitment. The number of patients excluded and who declined to participate was also captured. This enabled the calculation of the recruitment rate. Retention into the trial was recorded including drop outs and deaths. This helped to determine whether a larger RCT would be feasible in this group.

The specific reasons for patients declining to participate or dropping out of the study were also recorded to allow for evaluation of acceptability of the trial and/or intervention to the participant.

The ease of completion of outcome measures was evaluated by any missing/incomplete data and by the ease of completion reported by the researcher and also by the exercise on NIV in hospital and home group from their semi-structured interviews. Further acceptability of the design and intervention would be assessed by the qualitative data discussed in Chapter 5 Qualitative Method.

4.22.2 Clinical outcomes

The clinical outcomes used were the SGRQ for assessing HRQOL in COPD, the LCADL and the EQ-5D-5L.

Also used were the MBORG and MMRC Dyspnoea scores for evaluating breathlessness in this patient group.

The other important clinical outcome was the 6MWT to determine any trend for improvements in walking distance, which has been linked to mortality (Pinto-Plata et al., 2004). The order of the outcome measures was decided following the stakeholder feedback, section 4.14. The questionnaires that were the most time consuming were carried out first as the Breathe Easy group felt they required more concentration. Table 4.1 provides a brief summary of the outcome measures used. Following the table each of the outcome measures and the justification for their use is discussed.
<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Description</th>
<th>Minimum clinically important difference (MCID) (unless otherwise documented)</th>
<th>Range of Scores</th>
<th>Number, type of questions, and time to complete.</th>
</tr>
</thead>
<tbody>
<tr>
<td>St George’s Respiratory Questionnaire (SGRQ)</td>
<td>Questionnaire that measures impairment in patients with COPD (Jones, 2005).</td>
<td>4 (Jones, 2005).</td>
<td>0-100. Symptoms, Activity, Impact and a total score (Higher score = worse impairment), (See Appendix 14b for full questionnaire).</td>
<td>There are 19 questions split into two parts, the first part relates to symptoms and the second part to activities limited by dyspnoea and activities unable to complete. It takes 8-15 min to complete (Jones, 2005).</td>
</tr>
<tr>
<td>London Chest Activity of Daily Living Questionnaire (LCADL)</td>
<td>15 questions assessing the impact of breathlessness on daily activity (Garrod et al., 2000).</td>
<td>Minimal detectable change of 4 (Bisca et al., 2013; Garrod et al., 2000).</td>
<td>0-75. (Higher score = worse symptoms), (See Appendix 15 for full questionnaire).</td>
<td>There are 16 questions evaluating the ability to perform a daily activity. It takes 1-5 min to complete (From stakeholder feedback, section 4.22).</td>
</tr>
<tr>
<td>Outcome Measure</td>
<td>Description</td>
<td>Minimum clinically important difference (MCID) (unless otherwise documented)</td>
<td>Range of Scores</td>
<td>Number, type of questions, and time to complete.</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>European Quality of Life – 5 Dimensions – 5 Levels (EQ-5D-5L)</td>
<td>Patient questionnaire and visual analogue score (VAS) of QOL (NICE, 2008).</td>
<td>Utility score is not established in the literature for EQ-5D-5L (Obadovic, Lal and Liedgens, 2013). The minimally important difference for the predecessor EQ-5D is 0.03 (Brooks, 2003). VAS = 8 points (Zanini et al., 2015).</td>
<td>Utility score and VAS 0 = death/worst possible health to 100 = best possible health. EQ-5D-5L utility scores range between -0.594 and 1 (full health), (See EuroQual, 2015 for full questionnaire and VAS).</td>
<td>There are 25 questions and a VAS score on current health status. The questions relate to assessing the health state of their mobility, self-care, usual activities, pain/discomfort and anxiety/depression. It takes 2-5 min to complete (From stakeholder feedback, section 4.22).</td>
</tr>
<tr>
<td>Modified BORG Dyspnoea Score</td>
<td>VAS of breathlessness (Wilson and Jones, 1989).</td>
<td>Not established in the literature (Ries, 2005).</td>
<td>0 (no breathlessness) to 10 (maximal breathlessness), (See Appendix 16 for VAS).</td>
<td>One question assessing level of breathlessness. Takes a few seconds to complete (From stakeholder feedback, section 4.22).</td>
</tr>
<tr>
<td>Modified Medical Research Council (MMRC) Dyspnoea Score</td>
<td>Simple measure of breathlessness (Bausewein et al., 2007).</td>
<td>Not established in the literature (Ozalevli and Ucan, 2006).</td>
<td>0 (breathless only on strenuous exercise) to 4 (too breathless to leave the house/ too breathless to get dressed), (See Appendix 17 for full measure).</td>
<td>One question assessing level of breathlessness on activity with four possible choices. Takes a few seconds to complete (From stakeholder feedback, section 4.14).</td>
</tr>
<tr>
<td>6 minute walk test (6MWT)</td>
<td>Walking test on the flat to assess distance covered in 6 min (ATS, 2002).</td>
<td>30m (Justified in section 4.22.7) (Holland and Nici, 2013).</td>
<td>Distance (m) walked.</td>
<td>N/A</td>
</tr>
</tbody>
</table>

194
<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Description</th>
<th>Minimum clinically important difference (MCID) (unless otherwise documented)</th>
<th>Range of Scores</th>
<th>Number, type of questions, and time to complete.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ActiCal (Philips-Respironics)(Activity monitor)</td>
<td>Wrist monitor of step count (Pita et al., 2006).</td>
<td>Not established (Waschki et al., 2011).</td>
<td>Number of steps.</td>
<td>N/A</td>
</tr>
</tbody>
</table>
4.22.3 The St George’s Respiratory Questionnaire (SGRQ)

The SGRQ (Appendix 14b) measures impairment in patients with COPD, permission was sought to use the questionnaire and approval granted (Appendix 14a). There is a detailed manual that explains how to complete the SGRQ (Jones and Forde, 2009). The questionnaire is in two parts; part one has a symptoms score and part two has an activity and impacts score. Each questionnaire answer has an individual empirically calculated 'weight'. The lowest possible weight is zero and the highest is 100. The higher the score the worse the patient feels. The total score is derived from three separate domain scores of Symptoms, Activity and Impacts. For analysis there is a specially designed Microsoft Excel calculator which calculates the three component scores and the total score for each participant. The MCID for SGRQ is 4 units (Jones, 2005).

The SGRQ is a questionnaire responsive to change, particularly in the total and impact score (Ferrer et al., 1997; Jones, 2005). The SGRQ is more responsive than most generic questionnaires although some research suggests the Chronic Respiratory Questionnaire is more responsive to change than the SGRQ (Puhan et al., 2007). Nevertheless the SGRQ is widely used in clinical practice, particularly as an evaluation of PR intervention (Ferrer et al., 2002). The SGRQ is confirmed as a valid measure of impaired health in patients with COPD (Jones et al., 1992). This measure was carried out first following the 6MWT because this was the longest questionnaire.

4.22.4 London Chest Activity of Daily Living Questionnaire (LCADL)

The LCADL is a questionnaire that measures dyspnoea during routine daily activities. It comprises 15 questions which give a total score of 75 (Appendix 15). Questions focus on self-care (four questions), domestic (six questions), physical (two questions) and leisure activities (three questions) (Garrod et al., 2000). Each question is scored out of 5 ranging from 0 ('wouldn’t do task anyway’) to 5 ('I need someone else to do this’). The highest score represents maximum disability. The minimum detectable change (MDC) for total score is a change in 4 points (Bisca et al., 2013; Garrod et al., 2000). Within each section the MDC is 0.89 in self-care, 2.60 in domestic, 0.44 in physical and 0.58 in leisure (Bisca, et al., 2013). The MDC is the smallest change in a score used to measure a symptom that can be
seen that falls beyond the measurement error of the measuring tool (Crosby, Kolotkin and Williams, 2003).

The LCADL is intended for use in patients with severe COPD (Garrod et al., 2000). It is important that the impact of breathlessness on daily life is evaluated. It is validated in patients with severe COPD, reliable and responsive to change. The LCADL was validated in 60 patients with COPD and compared with other measures of health status (Garrod et al., 2000). The LCADL has been reliably used to measure the impact of a course of PR on dyspnoea however, it has not been tested in other interventions (Garrod, Paul and Wedzicha, 2002). Nevertheless it may be useful to evaluate the effect of exercising on NIV. It is easy to carry out and not time consuming. However the scoring for domestic tasks may not be as useful in patients with severe disease as they still may not be able to do most of these domestic tasks following rehabilitation (Garrod, Paul and Wedzicha, 2002). This questionnaire was completed after the SGRQ because it is more concise.

4.22.5 The modified BORG Dyspnoea scale (MBORG)

This is a score which patients use to rate the difficulty of their breathing. It is commonly used in clinical practice and quick to score. This measure gives a score of breathlessness from 0 (‘nothing at all’) to 10 (‘maximal breathlessness’) (Borg, 1998) (Appendix 16).

The MBORG is considered a useful tool for breathlessness (Wilson and Jones, 1989). It has previously been used in participants enduring a 6-minute treadmill walk and was validated as a reliable tool for measuring dyspnoea in this group (Belman et al., 1991). Subjects were able to distinguish between different sensations of breathlessness using the levels of breathlessness on the MBORG during induced breathlessness (Simon et al., 1989). The MCID is unknown (Ries, 2005). The MBORG has been rated as easy to use by patients (Kendrick, Baxi and Smith, 2000). However it has been suggested that it is of most benefit if used with other QOL tools (Bausewein et al., 2007). This will be measured at rest and then used during the intervention to assist with progression of the intervention and optimise the settings of NIV. This was completed after the HRQOL questionnaires and EQ-5D-5L because the breathlessness scores were the quickest to complete.
4.22.6 The Modified Medical Research Council Dyspnoea scale (MMRC Dyspnoea scale)

The MMRC Dyspnoea scale is a simple measure of breathlessness, used as a screening tool for PR, developed from the MRC dyspnoea scale (Bestall et al., 1999). It is a patient selected score from 0 (‘I only get breathless with strenuous exercise’) to 4 (‘I am too breathless to leave the house or I am breathless when dressing’). It can be used to assess disease severity in COPD (Nishimura et al., 2002) (Appendix 17).

A study comparing the MMRC with a Visual Analogue Score (VAS) of breathlessness, baseline dyspnoea index and $O_2$ cost diagram favoured the use of the MMRC (Ozalevli and Ucan, 2006). They compared the measures using 40 patients with COPD and compared them to lung function and symptoms. The MMRC correlated most with lung function test results and physical symptoms of COPD (Ozalevli and Ucan, 2006). It can assess whether PR will be beneficial and PR is recommended for patients who are graded between 3 and 4 (BTS, 2013). The MMRC dyspnoea scale has been championed as a valid, simple and useful tool (Bestall et al., 1999), but it has been argued that it should be used with other measures to identify suitable patients for rehabilitation (Spruit and Wouters, 2007). This was the final patient completed outcome measure assessed at each measure point.

4.22.7 The Six Minute Walk Test (6MWT)

This test measures the distance a patient can walk on the flat ground (30m) within 6 minutes (American Thoracic Society (ATS), 2002). The 6MWT needs few resources and it is easy to perform in clinical practice (ATS, 2002). Walking is a useful assessment because all but the most debilitated patients can mobilise a few steps. It was adapted from the 12MWT to include patients with respiratory disease who could not walk for that long (Butland et al., 1982). Other tests like the stair climb tests may be too difficult to perform in patients with very severe COPD (ATS, 2002). It was a useful measure for this study because it assesses both respiratory and other system effects of COPD (Spruit et al., 2010). The researcher used a research SOP to ensure the same methods were used each time and to try and reduce the bias of the researcher measuring the test (Appendix 18). This was a pragmatic measure as it was not possible to bring these patients back to
hospital for five assessments of 6MWT. Therefore the measures were carried out in the patients’ homes, gardens and public pavements to achieve the required measure. This was the first measure assessed, the reason for this was based on both the clinical experience of the researcher and feedback from stakeholders, (see section 4.14) that walking assessments may increase anxiety in patients because of the perceived fear of dyspnoea. Therefore by undertaking the 6MWT first may have meant the participants did not rush through the questionnaires facilitating careful completion.

This test is widely used in clinical practice to assess the effectiveness of treatments in the COPD population (ATS, 2002). The 6MWT has good reliability and validity (Garcia-Rio et al., 2009; Hernandes et al., 2011; Wijkstra et al., 1994). The 6MWT has been shown to respond to the treatment of PR. A meta-analysis of ten trials including 450 participants demonstrated a mean increase of 49m following a course of PR (Lacasse et al., 2002). The walk test does have a learning effect which plateaus after two walks (Guyatt et al., 1984), thus the researcher carried out a practice test when collating the measure at least one hour before the documented test.

There has been much debate surrounding the change in distance which is the threshold for MCID (Holland and Nici, 2013). Earlier studies cited 54m as required to show change (Redelmeier et al., 1997). Following further research which demonstrated poor clinical change, researchers questioned whether 54m was too high. Thus other MCID were proposed to range between 25-35m (Polkey et al., 2013; Puhan et al., 2008; Schunemann and Guyatt, 2005). The researcher thought that the lower score of 25-35m seemed a more reasonable figure particularly for patients with very severe COPD. There had been differing opinions regarding whether the MCID existed for the 6MWT. The 6MWT did not tally with other anchor based measures, for example QOL (QOL) measures (Holland and Nici, 2013), however a more recent large cohort study has reintroduced a figure for MCID which identifies an MCID for decline not just improvement, with an indication for an increased risk of mortality with a loss of > 30m in 6MWT (Polkey, et al., 2013). It has been suggested that to assess differences in individuals 40m should be used but 30m in clinical trials for between group analysis (Holland and Nici, 2013). Therefore this study will use 30m to define the MCID in the 6MWT.
The 6MWT was easy to carry out by the clinician and meaningful to both patients and clinicians; therefore it was highly likely to be retained for a future definitive trial.

4.22.8 EQ-5D-5L

There is a cost and resource implication of using NIV for exercise in the home, therefore it is important to justify the cost effectiveness of the intervention. For example the equipment cost is at least £3,500 per NIV device and additionally there are consumables, maintenance and professional supervision expenses. There are also societal costs and the impact on patients’ QOL that need to be considered. The EQ-5D-5L questionnaire is completed by the patient which results in a single index value for health status. It allows for cost-utility analyses by Quality Adjusted Life Years (EuroQol, 2015; Herdman et al., 2011; NICE, 2008).

The EQ-5D-5L measures self-reported health status at the time of completion. It consists of two pages; the descriptive page and the EQ visual analogue scale (EQ VAS). The descriptive page measures the dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is described by five answers of ‘no problems’, ‘slight problems’, ‘moderate problems’, ‘severe problems’, and ‘extreme problems’. The measure also incorporates the EQ VAS. The EQ VAS scores the respondent’s self-rated health on a 20cm vertical VAS with endpoints marked ‘the best health you can imagine’ and ‘the worst health you can imagine’. The participant’s answers are translated into a preference-based score, yielding an index score based on a scale from 0.000 (death) to 1.000 (excellent health). EQ-5D-5L is free to use in clinical practice but because this study had commercial funding there is a charge to use the measure. Therefore Philips-Respironics purchased the permission to use the EQ-5D-5L for the purpose of this and other research projects. The sample EQ-5D-5L and handbook for use can be found on the EuroQuol website (EuroQol, 2015).

It has previously been used with and is validated for patients with COPD in both stable disease and during exacerbations (Menn, Weber and Holle, 2010; Stahl et al., 2005). In a study comparing HR QOL measures 117 patients with COPD during a hospitalised exacerbation were assessed (Menn, Weber and Holle, 2010). They compared the Short Form Survey-12 (SF-12) and SGRQ with the
The EQ-5D was found to be the best measure in terms of completeness and ease of use. However, the authors reported a problem with the sensitivity of the score in relation to disease severity. At discharge, the scoring led to an abnormally high level of participants declaring themselves to have full health on discharge. The problem with using this type of measure is that perception of health is based on our personal normal, and in chronic disease people’s perception of normal might be stable health and ill health may be exacerbation from that resting state. However, as the preferred method of NICE it seemed beneficial to use it within this study (NICE, 2008). For the purpose of this feasibility study, the descriptive questionnaire and EQ VAS were collated. The quantitative utility score was calculated but the economic cost/savings was not calculated for the purpose of the feasibility study. This outcome measure was completed after the HRQOL measures but before the breathlessness scoring was carried out.

4.22.9 ActiCal Data

The CE marked ActiCal (Philips-Respironics) was worn on a wrist strap and used to monitor activity expenditure and step count over 24 hours for three months post discharge.

![ActiCal Device](image)

**Figure 4.5 ActiCal Device**

The ActiCal is a motion sensor used to detect body movement and step count. It can be used to objectively quantify physical activity in daily life over a predetermined time period (Pita *et al.*, 2006). It has been well validated, with clear information on the respective thresholds of activity in adults (Hooker *et al.*, 2011; Wong *et al.*, 2011). Hooker, *et al.* (2011) developed accelerometer thresholds to differentiate between light and moderate intensity physical activity in middle-aged and older adults. They evaluated non-obese participants aged between 45 to 64
years (n = 29), obese participants aged between 45 to 64 years (n = 21), and participants over 65 years (n = 23; of varying body composition). Participants completed laboratory-based sitting, household, and locomotive activities while wearing an ActiCal monitor. They concluded that for the ActiCal activity monitor, a point of 1065 (reflecting steps and motion activity) can be used to differentiate light and moderate intensity physical activity in people over 45 years of age. The ActiCal was put on the wrist rather than at the hip as many patients tend to wear hospital gowns as in-patients and loose clothing at home.

The ActiCal was set up with the patient’s research ID and basic measures of age, height and weight. The ActiCal was applied at the point of discharge and participants were advised to continuously wear it for three months until the study finished. It is important to look at activity monitoring additionally to the 6MWT because research has shown that there is a difference between predicted activity from the 6MWT and the intensity and amount of activity a patient actually undertakes at home (Walker et al., 2008). The ActiCal was removed from the patient when they had finished the study or in the case of two participants at the time of death. The data were downloaded and analysed using Philips-Respironics Actiwear software.

Basic pedometers have been suggested as a much cheaper device for recording step count and activity levels (Pita et al., 2005). Activity monitors are expensive, require technical knowledge and expensive software to interpret the data, however pedometers may not be useful in slow walkers (Hendelman et al., 2000; Pita et al., 2005). Therefore they were not used in this study involving relatively inactive patients with COPD. A known disadvantage of using any such device is that 20% of patients may not be concordant with wearing the device (Pita et al., 2006; Kochersberger et al., 1996), therefore at the weekly phone check-ins and at the outcome measure assessments each patient was asked if they were wearing their ActiCal monitors to discuss and encourage concordance.

4.22.10 Daily diary of symptoms and access to health care

This participant reported diary was adapted from one used at the time of the study at the UHBristol (Appendix 11). It recorded the participants’ symptoms, for example, sputum colour. It also recorded access to medical health care professionals, hospital admissions and additional medication use. The patient
was issued with four weeks of diary pages at discharge and then at each additional outcome measure point. The records for the previous month were collected by the researcher at each visit for collation of measures. Each week the patient was reminded by telephone to complete the diary. Symptom diary cards were analysed by hand to record symptoms, healthcare access and medication use (Vijayasaratha and Stockley, 2008).

4.22.11 Ventilator data

The ventilator data were downloaded from the SD card using Direct View software on a double-encrypted password protected UHBristol hard drive. The data were assessed for concordance, time used, $V_t$ achieved and pressure used. This was used to assess if any patients used the device when not supervised and to confirm the intended use of high pressures during use of the NIV. These were downloaded at the end of each patient’s participation in the trial.

4.22.12 Length of stay and therapy time

The time that the researcher spent with each participant was calculated from the medical notes and statistical data that records therapy contact time at UHBristol. The initial length of stay was calculated for each participant from the Medway hospital patient data, which has a record of admission length. These were calculated at the end of the trial. All follow-up exercise sessions with the exercise on NIV in hospital and home group were recorded by the researcher.

4.22.13 Mortality and morbidity data

The six months before and after the trial were evaluated post trial for each participant. This was captured from the Medway computerised system which captured admissions data within UHBristol. It recorded all hospital admissions and captured date of death (where relevant). This indicated any overall differences between groups and captured the severity of the participant’s condition.
4.23 Data Analysis

4.23.1 Feasibility analysis

This was evaluated by the numbers recruited and retained, presented using the CONSORT diagram. The completion of the outcome measures assessed feasibility of their use. The overall valid completion of an outcome measure was assessed. The number of items missed per measure was not specifically analysed. The concordance of participants using the ventilator equipment was evaluated using ventilator downloadable data and researcher observation. The ability of participants to tolerate high PS ventilation during exercise was also demonstrated by ventilator data.

4.23.2 SAEs

The National Institute for Health Research (NIHR) (2014) defines a SAE as any AE that:

1. Results in death.
2. Is life threatening, or places the participant at immediate risk of death.
3. Needs or lengthens hospitalisation.
4. Causes persistent or significant disability or incapacity.
5. Results in congenital anomalies or birth defects.
6. Is another condition which investigators judge to represent significant hazards.

SAEs were also evaluated to assess potential difficulties of exercising this cohort with very severe lung disease. SAEs were reported to the Sponsor and the Hospital Trust Research and Development department within 24 hours of occurring. No SAEs required further reporting to the ethics committee. These were then evaluated by a research trial committee at Philips-Respironics (Sponsor) and the outcome emailed to the researcher. The outcomes were documented in the research study portfolio. At no point was the trial discontinued in relation to SAEs. Any participant that experienced an SAE that did not result in death continued in the study. No extra time was given to their inclusion in the trial. The intervention and exercise was adapted as previously described in section 4.11.
4.23.3 Outcome analysis

The research evaluated three treatment limbs; Standard care; exercise on NIV in the hospital; and exercise on NIV in the hospital and home for a further three month period. The outcomes were measured at five time points; baseline (B); hospital discharge (DC); month one (M1); month two (M2) and month three (M3) following discharge.

Data were recorded in Microsoft Excel version 13, selected and exported into SPSS version 17, (IBM: Chicago, Illinois, USA) for statistical analysis. Descriptive statistics were calculated for the baseline data and outcome measures and the data assessed for normal distribution. When the data were normally distributed a one-way ANOVA was carried out to assess for differences in the data between groups at each time point.

When the data were not normally distributed non-parametric testing using Kruskall-Wallis was performed to assess for any differences between the groups. When the baseline data were not normally distributed median and interquartile range were calculated and non-parametric testing applied (Hazard, 2005). Any further statistical analysis was not possible because of the small sample size of each group.

Due to the volume of data collated only a selection of baseline severity raw data was included in the Appendices. All of the complete specific tool outcome measure raw data was included in the Appendices. This was to allow for inspection of the individual data. The SAE, admission and participant diary raw data information was not included in the Appendix because of the sheer volume of data.

4.24 Data Management

All medical and personal information was treated as confidential. Data were anonymised as far as possible and as early as possible in the process. Data were stored in a locked filling cabinet within a safe locked location. Any data held on the researchers NHS Trust personal computer was protected by double encrypted password protection. Data were collected and retained in accordance with the Data Protection Act 1998.
4.25 Conclusion

This chapter has described the quantitative research method used. It has discussed and justified the use of each outcome measure and explained how analysis was carried out. The next chapter describes the qualitative methods used to complete the mixed methods design.
Chapter 5 Qualitative Method

5.1 Introduction

The literature review demonstrated that the participants recruited to this study were likely to be a complex group of patients with severe lung disease. Quantitative clinical measures are useful to indicate an improvement in exercise capacity, dyspnoea and health status in line with PR guidelines (BTS, 2013), however there was a need to try to understand what impact, both positive and negative, the intervention had on the participants. The qualitative method used complemented the quantitative methods by providing the participant’s voice to add understanding and depth to the outcome measures used (Creswell and Clark, 2007).

5.2 Choosing the type of qualitative method

There are many different methods that can be used under the umbrella term of qualitative methodology including focus groups; ethnographic methods and interviews. These have been discussed below.

5.2.1 Focus group interviews

A method often used in health care is focus group interviews. This method means that data can be collected from multiple participants simultaneously (Braun and Clarke, 2013). However focus group research was not appropriate in this study because the participants were often house-bound, and may have been wary of mixing with others because of the risk of acquiring infections. Group discussions may have proved challenging with the participants involved experiencing breathlessness.

5.2.2 Ethnographic methods

Ethnographers aim to become embedded in the field (Hammersley and Atkinson, 1983), to understand the meanings people develop about their experiences (Bowling, 2009). Participation and observation are often used for data collection. The strengths of this approach are that it provides rich naturally occurring data, which is useful to study under-researched groups (Hammersley and Atkinson, 1983), although a criticism of this approach is that the presence of the researcher
may change the natural environment (Green and Thorogood, 2009). To use ethnography, the researcher would have to spend significant amounts of time with each patient to live the whole NIV experience with them which is unnatural, invasive and not achievable. Ethical approval may have been difficult to obtain as the participants may not be fully aware of the duration of time they would be observed and the implications of this. The material produced is large, hard to verify and difficult for the novice researcher to manage (Robson, 2011). Whilst ethnography may lead to understanding of the life experience of the participants, it can take time to capture. This research programme was time limited and this vulnerable patient group had a short life expectancy, meaning ethnographic methods were not appropriate.

5.2.3 Interviews

Individual semi-structured interviews were chosen as the method, with an interview guide using planned open-ended questions that the researcher built upon and which allowed for unplanned questions based on the participants’ responses (Robson, 2011). This method was chosen because an in-depth method was required to explore the participants’ views and experience of COPD and an understanding of what participating in this research meant for them as an individual. A semi-structured method allowed for each interview to be individualised and allowed for more open-ended questions based on the study’s focus. Alternatively a fully structured interview would ensure each participant was asked clear questions which while it would have met the aims of the study it may have led to a lack of detail of the participants’ experiences (Fontana and Frey, 2005). In comparison, although an unstructured interview may have yielded richer data it may have made achieving the aims of this study more challenging and comparisons across the entire data set may have been more difficult (DiCicco-Bloom and Crabtree, 2006).

Robson (2011) suggested that semi-structured interviews complement mixed methods studies well. They were useful in this study when the research was of a smaller scale and the researcher was also the interviewer. The researcher felt that often qualitative research is complex and needs years of experience to perfect. Although semi-structured interviews would prove challenging to the researcher,
the one-to-one nature of the interviews felt similar to the one to one consultations experienced when the researcher was in the role of physiotherapist.

Braun and Clarke (2013) suggested that a researcher must have a qualitative sensibility with a critical and questioning interest in the process and meaning, not just the cause of effect. As a physiotherapist the researcher had to tailor treatments to meet the expectations and demands of individual participants, requiring in-depth understanding of the patients. There was a need to have good interactional skills and to allow for trust to develop between the interviewer and participant (Braun and Clarke, 2013).

The researcher’s role as a physiotherapist often required trust and rapport between clinician and patient further enhancing the choice of interviews, however clinical interviews are arguably very different to research interviews. In a clinical interview the conversation is directed by the clinician to achieve the patient’s history to confirm or refute a diagnosis. The clinical interview is often concise and when patients deviate from specific physical health questions the clinician will guide the patient back to the topic. Clinical interviews are often time pressured and singularly directed by the clinician. The research interviews differed because they were focused on the participants enabling them to discuss their experiences and what was important to them. The interviewer, although guiding the interview in relation to aims of the research, was not dictating the course of the interview.

5.3 Choosing the sample: Why interview only the hospital and home exercise on non-invasive ventilation (NIV) group?

The interviews were only completed with those participants allocated to the exercise on NIV hospital and home group. This was because this group would provide the most information of the experience of being involved in the research and using the intervention. This was also partly because of the limited time and resources available to the researcher. Therefore the sample was purposive and suited the purpose of inquiry (Patton, 2002), which is quite common in qualitative research.
5.4 R & I Department approval

The R & I department at UHBristol was informed of the changes to the research design and subsequent ethical approval of the amendment. The ethical amendment was discussed previously in Chapter 4 (‘Quantitative Results’), section 4.4 Ethical approval)

Intellectual property was just as important an issue when undertaking the qualitative research as it was for the quantitative method. The participants could have expressed negative comments regarding the ventilator company’s equipment which meant that they may not want the data to be published. Thus the interview data were included in the intellectual property agreement between Philips-Respironics, UHBristol and UWE, (see Appendix 6, for the intellectual property contract).

5.5 Designing the interview guide

When designing the interview guide it was important to focus on the main aim of the research which was feasibility. The aim of the semi-structured interviews was to help contextualise the findings from the quantitative data, by providing insight into the lives of participants with severe COPD.

The open question interview guide was to facilitate the participants in revealing their personal experience of the treatment and involvement in the study. The guide had a list of key areas that the researcher would focus on, but importantly allowed scope for the participant to raise issues that the researcher had not anticipated (Braun and Clarke, 2013). The interview guide included an introduction focusing on the participants’ general health and hospital stay, to relax them and introduce the topic areas with ease. Further sections focussed on the specifics of using the equipment, experience of the intervention, advice to others undertaking the study and clinicians carrying out the study, and closing with time for the participant to disclose any other information. The iterative and flexible design of the qualitative component meant that analysis began after the first interview. This influenced the guide questions as key themes or further questions emerged (DiCicco-Bloom and Crabtree, 2006). The interview guide was reviewed and altered in conjunction with supervisors during March 2013 to include more probing and open questions. The open ended questions were important because they encouraged the participants
to provide more detail in their responses and enabled time for the participants to
discuss what was important to them not just the researcher agenda (Braun and
Clarke, 2013). The final interview guide can be found in Appendix 19.

5.6 Recording the interviews

Audio recording the interviews allowed the researcher to focus on communicating
with the participant rather than trying to write detailed notes (Legard, et al. 2003),
however all participants were asked if this was acceptable prior to interview. None
declined to be recorded. This produced a permanent record of the interview which
enabled repeated analysis (Robson, 2011). It also permitted for more thorough
analysis of what was said, as the researcher replayed excerpts repeatedly
(Silverman, 2001). The researcher then transcribed the interviews word for word.
The recording device used was a Sony ICD-PX312-digital voice recorder-flash
2GB-MP32. The batteries were checked at the beginning of each recording and
a test statement about the weather was asked of the participant, to ensure a good
quality recording was secured.

5.7 UWE interview workshops

The researcher attended a workshop provided by the graduate school at UWE on
developing interview skills. This allowed her to practice interview skills upon other
postgraduate students in October 2012 under the direction of an experienced
qualitative researcher. This was followed up with a further session as part of the
‘Qualitative research within clinical settings’ M-Level module undertaken by the
researcher at UWE, November 2012.

5.8 Pilot interviews

The researcher was keen to involve patients in the research process as user
involvement is important in qualitative research (Denzin and Lincoln, 2000). Pilot
interviews are recommended in order to inform the full interview (Mason, 2002).
The interview guide was piloted on three COPD patients who use NIV but were
not study participants. They identified terminology that may not be understood and
helped the researcher to improve interview skills (Robson, 2011). It also meant
that the interview guide could be further improved. The researcher was also able
to test the recording equipment and practice note taking during interview. Local
support groups were consulted for the preferred format of interview. The
suggestions were that the key questions should be shown to respondents prior to the interview to ease anxiety. It was decided that the interviews should be 30-60 minutes long to minimise potential for fatigue and breathlessness. All participants were offered a choice of telephone or face-to-face interviews, although no participant opted for a telephone interview. There is little data comparing telephone interviews with face-to-face interviews (Knox and Burkard, 2009), however the studies that have compared the two methods favoured face to face interviews because they were more advantageous in generating richer data (de Leeuw and Van der Zouwe, 1988; Jordan, Marcus and Reeder, 1980). Although telephone interviews are less inconvenient, safer for the researcher and less costly than a face-to-face visit, they may not last as long and contextual information would not be obtained (Shuy, 2003; Robson, 2011). It was recommended from the pilot interviews that the time and location should be the participant’s choice, however it was researcher preference to interview the patient in their home in keeping with the natural environment (Green and Thorogood, 2009). Face to face interviews also offered observation of both the verbal and non-verbal data, which could add valuable information to the findings (Hiller and Diluzio, 2004), thus field notes were collated to capture the context of the interviews and expressions of the participants.

5.9 Data storage

All personal and medical information was treated as confidential. Data were anonymised as far as possible and as early as possible in the process. All data were transcribed solely by the researcher so as to avoid any confidentiality issues of bringing in a third person. Data were stored in a locked filing cabinet within a locked office in accordance with the Data Protection Act 1998.

5.10 Personal safety

In advance of planning the interviews the researcher needed to think through the aspects of their personal safety if they were visiting areas alone (Robson, 2011). Researcher safety was considered and a lone worker device used. This device enabled the researcher to detail location and time to a mobile alarm device which informed a security helpdesk at UHBristol. If the alarm was activated by the
researcher the police would be informed. The researcher re-informed the device when leaving a location.

5.11 Qualitative analysis

Data analysis is referred to as the most complex and mysterious phase of qualitative research (Thorne, 2000). However it is really important that it is done in a systematic and repeatable way to ensure rigour. Rigour is discussed further in section 6.16. Although this was a mixed methods study the researcher wanted the qualitative data to do more than just supplement or illustrate the quantitative data (Robson, 2011). The researcher wanted the qualitative data to give a voice to the participants to understand their experience of the research and intervention. Therefore ensuring that a detailed and structured analysis occurred was very important.

5.12 Why Thematic Analysis (TA) was chosen?

This section discusses why TA was chosen as a process of analysis. It describes the reasoning for the method and how it was undertaken (Hansen, 2006; Darlington and Scott, 2002; Thorne, 2000). TA identifies, organises, analyses and reports patterns within the data to allow rich description (Braun and Clarke, 2006), however it may also allow deeper interpretation of the research area (Boyatzis, 1998). TA is not tied to any epistemological view so can be used for most philosophies, although it is often criticised as an anything goes approach (Antaki, et al. 2002), however if limited time and inexperience are an issue defenders of TA would argue it is better to use TA than use another method half-heartedly (Braun and Clarke, 2006). Critics of TA challenge flexibility as providing a lack of transparency (Mays, Pope and Popay, 2005). This is because TA can be commenced in many ways, for example inductive or deductive, led by theory and/or seek to be descriptive (Braun and Clarke, 2006).

There is no fixed formula for analysing qualitative data with some researchers referring to analysis as an art form (Robson, 2011). There are several other methods of qualitative research and analysis. An alternative qualitative methodology Interpretive Phenomenological Analysis (IPA) provides an in-depth analysis seeking verification and layered analysis. It is not seeking to present one overarching theory but instead to give detailed description and interpretation to
make sense of the participant’s experience (Chapman and Smith, 2002). IPA uses reflexivity to continually assess what experience the researcher has brought to the analysis. Whilst IPA seemed to reflect the aims of understanding the patient experience, the research was not seeking to underpin the findings with a philosophical approach. The main focus of the research was to understand the participant experience. This research required a systematic, repeatable method of analysis that organised and labelled the data in rich detail. TA provided such a method, enabling interpretation within the qualitative component (Braun and Clarke, 2006).

TA may give the insight needed to make sense of the subjective experience of this rare group, however, the researcher sought to address the criticisms of TA regarding transparency, which may discredit its findings, by following and documenting a detailed step by step approach (Braun and Clarke, 2006).

5.13 The Analysis Process

The researcher used the step by step guide of analysing with TA as described by Braun and Clarke (2006). Figure 5.1 illustrates the stages of analysis.
Figure 5.1 Phases of thematic analysis (TA) (Braun and Clarke, 2006)

The researcher undertook two workshops at UWE on coding data. The researcher practiced coding as part of the M-Level module of ‘Qualitative research in clinical settings’. Additionally as part of the postgraduate workshops in May 2013, the researcher was able to practice the phases of analysis as described by Braun and Clarke (2006). The researcher also attended a two day course in May 2013 on using NVivo 10 to offer an alternative tool for data organisation. The researcher’s reflection of her analysis can be found in Chapter 8 (‘Reflexivity’) section 8.6 Finding my role as an analyser.

5.13.1 Phase 1: Familiarisation

This phase was when the researcher became immersed in the data, Braun and Clarke (2013) describing this as the foundation of the analysis. The researcher had the advantage of collating the interview data herself therefore the
familiarisation of the data began at that point. The researcher also transcribed all of the interviews independently. The transcription occurred immediately after each of the interviews (see Appendix 20, for copies of all of the interview transcriptions). This was so the circumstances of each interview were recent in the mind of the researcher and so that they could inform the next interview. This was a time consuming process and took up to 6 hours for each interview.

The researcher typed up the transcriptions using Microsoft Word 2013 and a transcription pedal and software (Sony Digital Voice Editor 3.3.1). This allowed for hands free replaying of the interviews. This was all completed on a double-encrypted password-protected UHBristol computer. The transcription was typed 'verbatim' word for word. The researcher then re-listened to the audio recording and checked for any mistakes. The researcher repeatedly read the transcript but in an active way, searching for meanings and patterns (Braun and Clarke, 2006). The researcher highlighted the data and made notes against the text. This was carried out on paper and electronically on NVivo 10, see section 5.13.2 phase 2 for further discussion.

5.13.2 Phase 2: Generating the initial codes

The researcher at this point had created a list of ideas about the data. The next phase involved code creation. Codes have been described as evaluating the raw data using the simplest component (Boyatzis, 1998). Inductive “bottom up” approach and semantic “surface” coding were used because it was novel research, so there was limited pre-existing information (Braun and Clarke, 2006).

The researcher wanted to code both manually and using NVivo 10. This was to allow for all possible tools to be used to ensure the fullest analysis of the data. NVivo is a practical, safe and time efficient way of keeping all the information together (Johnston, 2006). It is also easy for another researcher to follow and leave an audit trail to increase credibility (Robson, 2011). Criticisms of the software are that it could distance the researcher from the data (Fielding, Lee and Lee, 1998). However, whilst the software manages the data, the analysis process must still be carried out by the researcher (Johnson, 2006).

Each interview was coded systematically initially soon after interview and then the whole data set was coded again when all the interviews were complete. When
preparing the data by hand the transcriptions were printed out several times and
the highlighted annotated sections cut out and pieced together with similar
themes. Care was taken to ensure all the data were coded. The copies of text
enabled multiple codes to be applied to the same text. The transcription was also
coded on NVivo where the transcriptions were saved and analysed on screen.
The transcripts were blind coded for themes by a member of the supervision team.
Multi-researcher analysis is important for ensuring findings are trustworthy
(Silverman, 2001).

5.13.3 Phase 3: Searching for themes
When the researcher had coded all of the interviews, themes were considered.
Themes house the meaning and content of the codes (Braun and Clarke 2006).
The researcher used hand drawn mind maps and spider drawings to collate the
codes into potential themes. When the researcher was unsure where to place a
code it went into a mind map entitled ‘unsure’.

Additionally the researcher used NVivo to move the codes (or ‘nodes’ as they are
called) into family trees and then applied themes. The researcher also trialled
Inspiration 8 software and Power Point 2013 to make mind maps. Ultimately the
researcher preferred to hand draw mind maps and then recreated them on Power
Point 2013. Some of the themes were made up from initial code names but other
theme names were unique to the analysis process. At the end of this process the
researcher had a group of potential themes and sub-themes in line with the
procedure suggested by Braun and Clarke (2006). Each theme was given a name
and a meaning by the researcher as some were similar in name but had
completely different meanings.

5.13.4 Phase 4: Reviewing themes
The next stage of the analysis was re-evaluating the themes. Each coded
transcript was evaluated to decide if some of the themes were part of the same
over-arching theme and whether other themes needed to be split into separate
themes. Then the researcher reviewed all the coded extracts of data to assess
whether they fitted in with each chosen theme. At this point the researcher moved
around some of the coded transcripts to new themes and some were put into a
discarded pile.
The researcher then considered the themes in relation to the whole data set. Braun and Clarke (2006) refer to this as ensuring an accurate reflection of the meaning of the whole data set. This took quite a few attempts by the researcher and lots of re-structuring of the themes until the researcher felt comfortable that the themes reflected the content of all of the interviews. It was at this point that the clean interview transcripts were shared with one of the supervisors who had experience of analysing qualitative data for a blind TA. Confidentiality was ensured and at this point all of the interviewees had alternative names. The purpose of this was to increase the trustworthiness of the analysis, see section 5.15, for further explanation.

5.13.5 Phase 5: Defining and naming themes

At this point the researcher had a thematic diagram of the data that was believed to be representative of the whole data set. Each theme was then reviewed for name and description of meaning. This stage was important because it encapsulated the substance of each theme and allowed for importance to be attached (Braun and Clarke, 2006). At this point the coding and themes that the supervisor produced were compared with those of the researcher. This was a positive experience because it strengthened existing themes. It also identified some additional themes and neglected some the researcher had identified. Therefore the researcher went back to Phase 4 to review the creation of themes.

5.13.6 Phase 6: Producing the synthesis

Once all the themes were identified they were sent to each of the interviewees to try to evaluate the extracted understanding of the patient experience. Originally the researcher had proposed to send each interviewee their transcript. However at the point of transcription it became evident that the way in which people talked inclusive of pauses and ‘erms’, may have been upsetting to see written down. Therefore a letter explaining the resulting themes was sent to each of the interviewees with the opportunity for them to feedback their comments.

No confidential information was made available to the interviewees. None of the interviewees offered any feedback at this stage. Subsequently talking to the participants revealed that the participants agreed with what was said or, in the case of two participants, they felt ill-equipped to give feedback. Therefore the final
analysis was completed and a synthesis produced (Chapter 8). It was important to link back to the research questions and aims whilst ensuring that anything unique was also captured. The synthesis needed to demonstrate clear analysis of the findings not just a description of the data (Braun and Clarke, 2013).

5.14 How rigour and trustworthiness were addressed

5.14.1 Introduction

There is much debate about if or how qualitative data should be assessed for quality (Meyrick, 2006; Lincoln and Guba, 1985). Some researchers believe that there are many truths and so there has to be more than one method for assessing quality (Meyrick, 2006). However the researcher felt that within the health care setting, where most research is quantitative, an explanation should be given as to how rigour and trustworthiness could be measured. It is important for the researcher to be aware of possible mistakes made within the methods used (Oakley, 2000). The researcher used the check list based on suggestions by Guba and Lincoln (1981) and Shenton (2004) to evaluate rigour within the method of this study.

5.14.2 Sampling

A random selection of participants may lessen researcher bias (Shenton, 2004; Preece, 1994). All the participants were randomised to groups. However in this study the sampling was purposive. Only participants in the treatment limb were interviewed due to time and the aim of the research which was to assess the feasibility of the project.

5.14.3 Triangulation

Triangulation involves the use of different methods to give strength to the findings (Shenton, 2004). The use of more than one method can compensate for their individual limitations and gain from their combined benefits (Brewer and Hunter, 1989; Lincoln and Guba, 1985). Whilst the researcher did not use triangulation by using more than one qualitative method, she used a mixed methods design. Therefore the complementing of the qualitative and quantitative methods should add credibility to the findings (Robson, 2011). The mixed research design can
make up for the limitations in each of the paradigms, whilst exploiting the benefits (Bryman, 2006).

5.14.4 Ensuring honesty

All participants were given the right to withdraw from the study at any time or to opt out of the interview component. Therefore the study only collated data from participants who wanted to participate. This was to ensure an honest response from participants (Shenton, 2004), however by not including everyone who participated one might miss some important information about the experience. It may be that those who had a negative experience were less likely to want to discuss it, which could have affected the analysis of feasibility. Of the six participants, it was possible to interview four. Unfortunately two participants died during the study so their viewpoints were not obtained, which may have contributed to the eventual analysis of the participant experience. They both had previously expressed very positive views regarding the research process and this may have added to understanding the acceptability of the intervention, however this was beyond the control of the researcher.

5.14.5 Frequent debriefing sessions

There were regular meetings between the researcher and the supervision team to discuss the outcome of each interview. There were additional debriefing and discussion sessions with the supervisor with the most experience of qualitative research. This developed the researcher’s ideas through the experience of self and others, whilst maintaining confidentiality of the participants (Shenton, 2004).

5.14.6 Researcher’s reflective commentary

It has been suggested that in addition to evaluation from supervisors, the researcher should continually evaluate throughout the research process (Shenton, 2004). These reflections captured the effectiveness of interviewing, the researcher’s thoughts during the data collection period and developing thought processes of patterns and themes during analysis. Guba and Lincoln (1981) refer to this as “progressive subjectivity”, the evaluating of the researcher’s own ideas in a transparent way that others can process. For the full details of how the researcher reflected upon the research process refer to Chapter 6 (‘Reflexivity’). The introduction Chapter 1 Background, section 1.20 Motivations for undertaking
the study, and Chapter 6 Reflexivity, section 6.2 Separating the self, addresses the background, qualifications and experience of the researcher which can be considered to affect credibility (Patton, 1990).

5.14.7 Credibility

Credibility is one of Lincoln Guba’s (1985) criteria for assessing whether the study measures what it set out to (Guba, 1981). One method for assessing this is whether the method used has been used with previous studies (Merriam, 1998; Lincoln and Guba, 1985). The researcher used semi-structured interviews which have been previously used successfully in patients with severe COPD and end of life patients (Hasson et al., 2008; Jonsdottir and Jondsdottir, 2007; Fraser, Kee and Minick, 2006), however as this was novel research there had been no previous studies that interviewed participants who had exercised on NIV.

The second method for assessing credibility is by developing an early familiarity with the culture of patients with COPD (Erlandson et al., 1993; Lincoln and Guba, 1985). As a respiratory physiotherapist the researcher had spent many years caring for people within this disease group. Therefore the researcher already had good clinical insight into this group of patients, although to allow for a deeper understanding the researcher went to local Breathe Easy patients with COPD support group meetings prior to beginning the research.

5.14.8 Member checks

The sharing of information with the participants has previously been discussed in Phase 6 (See Section 5.13.6 Phase 6: Producing the synthesis). Many researchers value this process for adding credibility to the findings (Miles and Huberman, 1994; Lincoln and Guba, 1981).

5.14.9 Examination of the research findings

The researcher ensured that the synthesis and discussion included a detailed description of the experience of the participants to ensure that the account was a true reflection of the participant’s experience and not just the researcher’s (Shenton, 2004). The discussion also compared the findings to previous literature to assess their potential relevance within previous research (Silverman, 2005).
5.14.10 Transferability

This method compares the study to other groups and assesses the ability to generalise (Merriam, 1998). However, to evaluate rigour in this way was not an appropriate method to use for this research because this research did not seek to generalise only to demonstrate feasibility and trends. In this qualitative research the researcher responsibility is transparency of the process of the study (Elman and Kapiszewski, 2014). Providing assistance to researchers for comparison regarding the process of research but simultaneously recognising that the researcher is the tool and no two studies will be identical.

5.14.11 Dependability

This again is a contentious issue as it could be argued that qualitative research values the individual, and if you performed the research in the same way you may not get the same results (Marshall and Rossman, 1999; Fidel, 1993). Guba and Lincoln (1981) suggested that “overlapping methods” can achieve dependability, however the researcher has used mixed methods research therefore any changes in QOL may be matched both in the interview data and also within the QOL questionnaires and walk test making the findings more dependable (Bryman, 2006). The researcher has also clearly documented the methods and reflections appraised to ensure that the research was repeatable. This includes Shenton’s (2004) checklist of research design and its implementation, operational detail of data collection, reflective appraisal of the process.

5.14.12 Confirmability

This is to ensure that as far as was achievable the findings presented were the experiences and concerns of the participants rather than the values of the researcher (Shenton, 2004). However it has been commented that the bias of the researcher is unavoidable (Patton, 1990). Triangulation of methods is offered by researchers as a method to confirm findings (Shenton, 2004). Again the use of mixed methods helped to consolidate the research findings and ensured they accurately reflected the true experience of the participants. The reflections that the researcher made during the research process addressed researcher tendencies and allowed other researchers to assess how analysis decisions were made (Miles and Huberman, 1994).
Additionally Braun and Clarke’s (2006) 15 point check list of criteria for good thematic analysis (TA) (Table 5.1) was used to evaluate the method of TA.
Table 5.1 Adapted 15 point checklist of criteria for good thematic analysis (TA) (Braun and Clarke, 2006)

<table>
<thead>
<tr>
<th>Process</th>
<th>No.</th>
<th>Criteria</th>
<th>How the criteria was achieved in this study.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcription</td>
<td>1</td>
<td>Detailed transcription checked against audio-recordings for accuracy.</td>
<td>The researcher transcribed all of the interviews independently.</td>
</tr>
<tr>
<td>Coding</td>
<td>2</td>
<td>All data has been given equal importance when coding.</td>
<td>The entire transcript was coded for each participant.</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Coding thorough and detailed to ensure themes are not generated from a few key examples.</td>
<td>Coding included entire interviews, repeated to ensure thoroughness.</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>All the extracts for each theme were collected.</td>
<td>Extracts were cut out and applied to each theme.</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Themes are checked against all the data and each other.</td>
<td>Themes checked for agreement within all the data set.</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Themes are internally coherent, consistent and distinctive.</td>
<td>Themes were repeatedly reviewed. Another reviewer from the supervision team ensured consistency.</td>
</tr>
<tr>
<td>Analysis</td>
<td>7</td>
<td>Data has not just been described but analysed and made sense of.</td>
<td>The data were made sense of through concepts discussed in Chapter 7.</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>The data must match up with the analysis.</td>
<td>Clear examples from transcriptions are given in the findings, Chapter 7.</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>The analysis must be an organized story of the data and topic.</td>
<td>The themes reflect the participants’ voice and relate to the objectives of this study, see Chapter 1.</td>
</tr>
<tr>
<td>Process</td>
<td>No.</td>
<td>Criteria</td>
<td>How the criteria was achieved in this study.</td>
</tr>
<tr>
<td>---------</td>
<td>-----</td>
<td>--------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Overall</td>
<td>10</td>
<td>A good balance between analysis and extracts.</td>
<td>The Qualitative findings chapter reflect the voice of the participants and analysis, see Chapter 7.</td>
</tr>
<tr>
<td>Written report</td>
<td>11</td>
<td>Enough time given to each stage of analysis.</td>
<td>External funding ensured analysis time, discussed in Chapter 4.</td>
</tr>
<tr>
<td>Written report</td>
<td>12</td>
<td>The assumptions and approach to TA are clearly explained.</td>
<td>Concepts regarding the aims of the thesis were used to synthesise the findings, see Chapter 7.</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>Described method and reported analysis are consistent.</td>
<td>The method of analysis was clearly followed and described.</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>The language and ideas are consistent with epistemological position of analysis.</td>
<td>A mixed methods approach met the aim of feasibility. Qualitative analysis completed the qualitative study component.</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>The researcher is active in the research process, themes do not just emerge.</td>
<td>The researcher discussed clearly her role in analysis.</td>
</tr>
</tbody>
</table>
5.15 Conclusion

This method chapter has demonstrated how the data collection and analysis for the qualitative component was carried out. Whilst providing a separate qualitative method in its own right, it also demonstrated how the qualitative methods complemented the quantitative methods to fulfil the mixed methods methodology. The next two chapters discuss the quantitative and qualitative results independently. The mixed methods will be combined and discussed together within the discussion chapter.
Chapter 6 Quantitative Results

6.1 Introduction

This chapter has 3 parts presenting the quantitative data:

Part 1 Feasibility and Acceptability (Aim 1 and Aim 2): This presents the data relating to feasibility and acceptability. This includes the recruitment data, presenting the CONSORT diagram and feasibility of recruitment and retention. It includes the acceptability of the trial including completion of outcome measures and adherence to intervention. Additionally the SAEs are presented that occurred during the trial, hospital admission data and access to health care from the participants’ diaries and hospital database.

Part 2 Presents the participant baseline information (Aim 1): Including the severity of disease and social circumstances.

Part 3 Outcome measure results (Aim 4): Including the 6MWT; breathlessness scores - MMRC and MBORG; and the HRQOL questionnaires – SGRQ, LCADL and EQ-5D-5L. It also includes the ventilator settings used during the trial and the activity data recorded from the ActiCal device worn by the participants.

6.2 Part 1 Feasibility and Acceptability

6.2.1 Introduction

The recruitment period of 11 months was from the end of January 2013 to the beginning of January 2014. The recruitment information is presented in the CONSORT diagram (Figure 6.1). 63 patients were screened for inclusion into the study. 30/63 patients met the exclusion criteria and were therefore not enrolled in the study.
Figure 6.1 The consort diagram
6.2.2 Exclusions

30 patients met the exclusion criteria (see CONSORT diagram in Figure 6.1 and the reasons for the exclusions in Table 6.1).

Table 6.1 Reasons for patient exclusions (n = 30)

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Primary Diagnosis not COPD.</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>2. Not had respiratory acidosis diagnosed through ABG analysis.</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>3. Not had NIV treatment.</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>4. Under 25 years of age.</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>5. Unable to follow commands or unable to consent.</td>
<td>6</td>
<td>3 severe dementia, 2 unknown cause, 1 head injury.</td>
</tr>
<tr>
<td>6. Known contraindication to NIV.</td>
<td>2</td>
<td>1 haemo-pneumothorax, 1 lung cancer: tumour main bronchus.</td>
</tr>
<tr>
<td>7. Unable to tolerate acute hospital NIV.</td>
<td>8</td>
<td>4 unable to tolerate, 4 refusing to continue with acute NIV.</td>
</tr>
<tr>
<td>8. Unable to or refused to comply with physiotherapy.</td>
<td>6</td>
<td>1 safeguarding issue regarding home, 1 self-harmer, 1 patient interested but the hospital was in a critical bed state and the patient was discharged prior to consenting, 1 initiating PR thus already in physio programme, 1 four weeks into PR course, 1 non-concordant with physiotherapy</td>
</tr>
<tr>
<td>9. Had an additional pathology that limited ability to mobilise.</td>
<td>1</td>
<td>Avascular necrosis of the hip.</td>
</tr>
<tr>
<td>10. Dying/receiving end of life care and not expected to survive hospital admission</td>
<td>7</td>
<td>1 ischaemic bowel, 1 bone metastases, 1 multiple MI, 4 Active treatment stopped</td>
</tr>
</tbody>
</table>

Abbreviation Key: ABG Arterial blood gas, COPD Chronic obstructive pulmonary disease, MI Myocardial infarction, NIV Non-invasive ventilation, PR Pulmonary rehabilitation
The most common reason for exclusion was that the participant could not tolerate acute NIV. The other two common reasons were that the patients were receiving end of life care or they were unwilling or unable to participate in the physiotherapy intervention.

6.2.3 Acceptability and follow up

Three patients declined to participate in the study, ten died and two lived out of area (see further details in table 6.2.)

Table 6.2 Other reasons patients were not included (n = 15)

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient declined.</td>
<td>3</td>
<td>1 worked fulltime.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 cared for grandchildren.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 disliked exercise.</td>
</tr>
<tr>
<td>Died during admission.</td>
<td>10</td>
<td>6 acute acidosis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 fractured neck of femurs led to pneumonia.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 gangrene sepsis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 hypovolaemic cardiac arrest.</td>
</tr>
<tr>
<td>Out of area.</td>
<td>2</td>
<td>1 lived in Wales.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 lived in Reading.</td>
</tr>
</tbody>
</table>

Two of the three participants who declined to take part in the study cited time commitments as reasons for not taking part. One participant still worked as a seamstress and felt this took all her time and energy and the other looked after her grandchildren after school and felt she could not commit to the time needed. There was only one participant who disclosed a dislike of exercise as the reason for not taking part in the study. There were two patients who lived out of area this had not previously been considered when planning the exclusions as it was expected that most of the participants would live within the local Bristol area. Due to the lone researcher and time limitations of the PhD they could not be included in the study. An area inclusion zone would need to be considered in the future RCT. No participants refused to be randomised or withdrew because of the possibility of not receiving the intervention.

During the study period three participants died. Their data were included in the evaluation of the results up to the last assessed outcome measure prior to the date of death. Of the participants who died one participant was in the standard care group and died during their initial hospital admission, thus only baseline data
were collated. The other two participants were both randomised to the group receiving exercise on NIV in hospital and home. Of those, one participant died one month following hospital discharge and one participant died two months after being discharged from hospital. The SAEs are explained within section 6.2.8 and the Chapter 9 Discussion chapter. There were no other participants who were lost to follow up, and all live participants completed the study (n = 15).

6.2.4 Feasibility of the intervention

It was feasible to exercise with NIV. Only one participant required nasal pillows to provide attachment to the NIV. All the others used a full face mask. There was no problem attaching the circuit and no disconnect occurred during supervised exercise. Some of the participants were able to carry the ventilator for the walking component of the exercise but some needed the clinician to carry the device during walking. There were no malfunctioning of equipment identified during the trial. Cycling, free weights, sit to stand, and step up’s were all able to be completed during the exercise. Seven NIV devices were required to be in use at the same time for this feasibility study.

6.2.5 Ventilator data

The mean EPAP used for all participants in both the exercise on NIV in hospital group and the exercise on NIV in hospital and home was 4cmH\(_2\)O. It was feasible to exercise with a PS >10cmH\(_2\)O. The mean PS end of study was 16cmH\(_2\)O for the exercise on NIV in hospital and home group compared to 12cmH\(_2\)O for the exercise on NIV in hospital group. Both groups received good PS, see table 6.3.

<table>
<thead>
<tr>
<th></th>
<th>Hospital exercise on NIV (n = 5)</th>
<th>Hospital &amp; home exercise on NIV (n = 6)</th>
<th>Total (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IPAP/cmH(_2)O start of trial ±SD</td>
<td>15.8 ±0.4</td>
<td>16.67 ±2.98</td>
<td>16.27 ±2.26</td>
</tr>
<tr>
<td>Mean IPAP/cmH(_2)O end of trial ±SD</td>
<td>16.4 ±0.8</td>
<td>19.67 ±4.85</td>
<td>18.18 ±3.97</td>
</tr>
<tr>
<td>Mean PS/cmH(_2)O start of trial ±SD</td>
<td>11.8 ±0.37</td>
<td>12.67 ±2.98</td>
<td>12.21 ±3.97</td>
</tr>
<tr>
<td>Mean PS/cmH(_2)O end of trial ±SD</td>
<td>12.4 ±0.8</td>
<td>15.67 ±4.49</td>
<td>14.18 ±3.97</td>
</tr>
</tbody>
</table>

Abbreviation Key: EPAP Expiratory positive airway pressure, IPAP Inspiratory positive airway pressure, PS Pressure support, SD Standard deviation.
6.2.6 Number of sessions prior to discharge

The median number hospital of physiotherapy contacts, amount of hospital therapy time spent with each group and intervention days initiated from when the participant was medically stable (normal ABGs) are shown in Table 6.4. There was a trend for both the NIV treatment groups to have used NIV acutely for longer (in both days and hours) than the standard care group. There was also a trend for the exercise on NIV in hospital group to have had more physiotherapy contact (in both number of sessions and hours) than the other two groups. There was no significant difference between hospital stay and therapy contact. Therefore it was feasible to set up NIV and begin training with no extra time needed.
Table 6.4 Table of acute hospital treatment received data

<table>
<thead>
<tr>
<th></th>
<th>Standard care (n = 7)</th>
<th>Exercise on NIV in hospital (n = 5)</th>
<th>Exercise on NIV in hospital and home (n = 6)</th>
<th>Total (n = 18)</th>
<th>P value ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital acute NIV use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median days any use (IQR)</td>
<td>1 (1-4)</td>
<td>5 (3-6)</td>
<td>4 (1-8)</td>
<td>4 (1-6)</td>
<td>0.8</td>
</tr>
<tr>
<td>Hospital acute NIV use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median hours used (IQR)</td>
<td>13 (5-60)</td>
<td>92 (69-98)</td>
<td>52 (31-95)</td>
<td>48 (11-103)</td>
<td>0.6</td>
</tr>
<tr>
<td>Median total number of</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>physiotherapy sessions (IQR)</td>
<td>7 (3-15)</td>
<td>13 (7-15)</td>
<td>7 (3-15)</td>
<td>9 (3-14)</td>
<td>0.9</td>
</tr>
<tr>
<td>Median hours of total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>physiotherapy treatment time</td>
<td>4 (2-8)</td>
<td>7 (4-7)</td>
<td>4(2-11)</td>
<td>6 (2-8)</td>
<td>0.9</td>
</tr>
<tr>
<td>Median intervention days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>available (IQR)</td>
<td>4 (3-12)</td>
<td>10 (5-18)</td>
<td>4 (3-9)</td>
<td>5 (3-13)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**Abbreviation Key:** IQR Interquartile range
Following discharge the exercise on NIV hospital and home group had between eight and 24 exercise sessions. The four live participants at the end of the study all received 24 sessions of exercise on NIV following hospital discharge. There were two participants who were hospitalised during their planned intervention period. They continued with their supervised exercise in hospital once stabilised (cardiovascular observations stable and acidosis corrected). For one participant this involved one session in hospital and for the other participant it involved seven sessions in hospital because of an extended length of stay. For this participant the exercise intervention needed to be re-evaluated as their MBORG score was considerably higher so exercise intensity and intervention was less. No live participant missed any supervised exercise session.

6.2.7 Feasibility of completion of outcome measures

All of the outcome measures for 6MWT, HRQOL and Breathlessness scores were 100% completed by all participants apart from in the three who died. There were no missing items. However, the ActiCal device was the only outcome measure that was incomplete not worn by 4 participants all of the time.

One participant in the standard care group died in hospital before discharge and so was not issued a device. One of the exercise on NIV in hospital and home group participants died during the trial therefore only had the first month’s data available. There were four further participants who had incomplete data, see figure 6.2. The reasons for lost data were two patients misplaced the device, one patient took the device off for her son’s wedding and forgot to put it back on and one patient submerged the device in water and the data were lost. This included two patients from the standard care group and one from both the exercise on NIV in hospital group and exercise on NIV in hospital and home exercise groups. Therefore these participants were excluded from the median total number of daily steps. However, where complete data were available for month one, two or three this was included when calculating the monthly medians for each group. The raw data for Actical was not included in the Appendices because it was incomplete and large in volume. Medians were calculated because the data were not normally distributed.
Figure 6.2 Bar chart of the number of concordance days with the ActiCal device across groups
The outcome measures were all completed at the planned time points in live participants. The participants took between 30 to 45 minutes to complete the outcome measures. The outcome measures were carried out on a different day to the intervention.

6.2.8 SAEs

There were 17 SAEs within the sample during the study, see table 6.5. All three groups had participants that experienced SAEs. The standard care group experienced the most, at nine and exercise on NIV in hospital the least, at three. There were three participant deaths during the study. One participant died within the standard care group and two died within the exercise on NIV in hospital and home group. The participant who died in the standard care group only had baseline assessment, their condition deteriorated in hospital and they died from a combination of respiratory infection and heart failure. The other two participants were from the exercise on NIV in hospital and home group. One of these participants died in hospital after one month in the trial. This participant died of an acute infective exacerbation of COPD causing uncompensated type two respiratory failure and respiratory arrest. The second participant died at home after completing two months of the trial. They died in their sleep in the afternoon following a GP visit that day for acute breathlessness treated with morphine-based medication. None of the participants who died had been exercising with the intervention during the three days before death.
### Table 6.5 SAEs for all three groups

<table>
<thead>
<tr>
<th>SAE: Total number (mean ±SD)</th>
<th>Standard care (n = 7)</th>
<th>Exercise on NIV in hospital (n = 5)</th>
<th>Exercise on NIV in hospital and home (n = 6)</th>
<th>Total (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 (1.29 ±0.88)</td>
<td>3 (0.60 ±0.49)</td>
<td>5 (0.83 ±1.07)</td>
<td>17 (0.94 ±0.91)</td>
<td></td>
</tr>
<tr>
<td>SAE: Number of Deaths (mean ±SD)</td>
<td>1 (0.18 ±0.38)</td>
<td>0 (0.00 ±0.00)</td>
<td>2 (0.14 ±0.15)</td>
<td>3 (0.17 ±0.37)</td>
</tr>
</tbody>
</table>

Key: SAE Serious Adverse Event, SD Standard deviation

All of the SAEs were reported via telephone and on standardised reporting forms to both the sponsor at Philips-Respirronics and to the R & I department at UHBristol. The exact details of the events were documented, including the trial arm each participant was in, for scrutiny. Each of the SAEs were individually assessed by a research panel at Philips-Respirronics and by the research safety officer at UHBristol. The researcher was then contacted by both Philips-Respirronics and the R & I department with a report regarding the outcome assessment for each SAE. This was then logged in the trial portfolio. 14 of the SAEs were participants hospitalised for an infective exacerbation of COPD. Eight hospital admissions were in the standard care group, three hospital admissions were in the exercise on NIV in hospital group and four hospital admissions were in the NIV on exercise in hospital and home group. All of the participants needed treating with antibiotics, steroids and nebulizers. Four of the admissions in the standard care group and two of the participants who had hospital admissions needed acute treatment of their uncompensated type two respiratory failure with NIV. All of the SAEs were evaluated as being related to the severity of the participants’ COPD. The trial was not stopped at any time because of SAEs. There were no incidents of equipment failure or breakages during the trial. At no time did any participants ask to stop the exercise or intervention.

### 6.2.9 Hospital Admission data

The hospital admission data were not normally distributed, therefore medians were used within the descriptive statistics. There was a trend that the standard care group and the exercise on NIV in hospital and at home group decreased their
hospital admissions from the six months before the trial to the six months after the trial, however there was an increase in admissions post trial for the exercise on NIV in hospital group (see table 6.6).

Table 6.6 Median number of hospital admissions in all groups within the six months pre-trial, in-trial time and six months post-trial

<table>
<thead>
<tr>
<th></th>
<th>Standard care</th>
<th>Exercise on NIV in hospital</th>
<th>Exercise on NIV in hospital &amp; home</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>number of admissions</td>
<td>2 (0-5)</td>
<td>0 (0-2)</td>
<td>1 (0-2)</td>
<td>1 (0-2)</td>
</tr>
<tr>
<td>(IQR)</td>
<td>(n = 7)</td>
<td>(n = 5)</td>
<td>(n = 6)</td>
<td>(n = 18)</td>
</tr>
<tr>
<td><strong>During study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>number of admissions</td>
<td>2 (0-3)</td>
<td>0 (0-1)</td>
<td>1 (0-2)</td>
<td>1 (0-2)</td>
</tr>
<tr>
<td>(IQR)</td>
<td>(n = 6)</td>
<td>(n = 5)</td>
<td>(n = 5)</td>
<td>(n = 16)</td>
</tr>
<tr>
<td><strong>After study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>number of admissions</td>
<td>2 (0-5)</td>
<td>1 (0-7)</td>
<td>1 (0-3)</td>
<td>1 (0-4)</td>
</tr>
<tr>
<td>(IQR)</td>
<td>(n = 6)</td>
<td>(n = 5)</td>
<td>(n = 4)</td>
<td>(n = 15)</td>
</tr>
</tbody>
</table>

**Abbreviation Key:** IQR Interquartile range, n = number of participants.

There was a trend for the exercise on NIV in hospital and home group to have the longest median length of stay (LOS) during the trial. There was a trend for the standard care group to have the longest median LOS within the 6 months following the trial, see table 6.7 for the admission length of stay data.

Table 6.7 Median length of stay (days) of hospital admissions between groups within the six months pre-trial, in-trial time and within the six months post-trial

<table>
<thead>
<tr>
<th></th>
<th>Standard care</th>
<th>Exercise on NIV in hospital</th>
<th>Exercise on NIV in hospital &amp; home</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOS days of admissions (IQR)</td>
<td>4 (2-7.5)</td>
<td>1 (0-3)</td>
<td>1 (0.25-7)</td>
<td>2 (1-7)</td>
</tr>
<tr>
<td>(n = 7)</td>
<td>(n = 5)</td>
<td>(n = 6)</td>
<td></td>
<td>(n = 18)</td>
</tr>
<tr>
<td><strong>During study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOS days of admissions (IQR)</td>
<td>4 (1-10)</td>
<td>3.6 (0-9)</td>
<td>4.5 (1-25)</td>
<td>4 (0-10)</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>(n = 5)</td>
<td>(n = 5)</td>
<td></td>
<td>(n = 16)</td>
</tr>
<tr>
<td>After study LOS of admissions (IQR)</td>
<td>Standard care 5 (1.25-9) ((n = 6))</td>
<td>Exercise on NIV in hospital 2.5 (1-9.5) ((n = 5))</td>
<td>Exercise on NIV in hospital &amp; home 2 (0-18.5) ((n = 4))</td>
<td>Total 4 (1-9) ((n = 15))</td>
</tr>
</tbody>
</table>

**Abbreviation Key:** IQR Interquartile range, LOS Length of stay, \(n = \) number of participants.

### 6.2.10 Participant diary information

These data were self-recorded during the trial. It included information regarding medication use and access to health care. All participants successfully kept diaries and completed entries for each day of the trial.

### 6.2.11 Medication use

The record of medication use kept by the patients in their diary was not normally distributed, therefore the medians and Interquartile ranges (IQRs) were presented. There was a trend that the group that had the most days of antibiotic use was the standard care group at 38.5 median numbers of days compared with the exercise on NIV in hospital group that had the least at 22 median days use.

There was a trend for the standard care group to have the most days of steroid use at median days of 33.5 compared with a median of 22 days of steroid use for participants in the exercise on NIV in hospital group and a median of 19 days use in the exercise on NIV in hospital and home group.

The extra medication taken was calculated from the diaries. The participants marked on their diary all the medication taken that day and if they had used more than their normal dose, for example extra doses of bronchodilators. There was a trend for the standard care group to have documented the most median days of increased medication at 33 days, see table 6.8.
### Table 6.8 The median days increase in total patient reported extra medication use between groups from hospital discharge over the three month trial period

<table>
<thead>
<tr>
<th></th>
<th>Standard care (n = 7)</th>
<th>Exercise on NIV in hospital (n = 5)</th>
<th>Exercise on NIV in hospital &amp; home (n = 6)</th>
<th>Total (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median days (IQR)</td>
<td>38.5 (9-45)</td>
<td>22 (8-43)</td>
<td>26 (0-48)</td>
<td>25 (9-43)</td>
</tr>
<tr>
<td>Steroid use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median days (IQR)</td>
<td>33.5 (20-45)</td>
<td>22 (12-51)</td>
<td>19 (0-48)</td>
<td>24 (13-44)</td>
</tr>
<tr>
<td>Increased dose/issues of prescribed medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median days (IQR)</td>
<td>33 (22-41)</td>
<td>22 (15-70)</td>
<td>11 (0-49)</td>
<td>25 (11-51)</td>
</tr>
</tbody>
</table>

**Abbreviation Key:** IQR Interquartile range

There was a trend for the exercise on NIV in hospital and home group to have documented the least median days of extra doses of medication.

### 6.2.12 GP access from hospital discharge to month three

Table 6.9 shows the differences in GP contacts between the groups. There was a trend that the exercise on NIV in hospital group had three times as many home visits compared to the exercise on NIV in hospital and home exercise group. One participant in the exercise on NIV in hospital group received 10 home visits from the GP within the three month follow up research period.

#### Table 6.9 Table of GP access: Recorded by participants from hospital discharge to month three

<table>
<thead>
<tr>
<th></th>
<th>Standard care (n = 6)</th>
<th>Exercise on NIV in Hospital (n = 5)</th>
<th>Exercise on NIV Hospital &amp; home (n = 6)</th>
<th>Total (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of visits to GP Practice (IQR)</td>
<td>0.5 (0.1-3)</td>
<td>0 (0-2.5)</td>
<td>0 (0-0.8)</td>
<td>0 (0-2.5)</td>
</tr>
<tr>
<td>Number of home visits by GP (IQR)</td>
<td>1 (0-2)</td>
<td>3 (0.5-6.5)</td>
<td>0 (0.5)</td>
<td>1 (0-2)</td>
</tr>
<tr>
<td>Number of phone consults by GP (IQR)</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>0 (0-2)</td>
<td>0 (0-1)</td>
</tr>
</tbody>
</table>

**Abbreviation Key:** GP General Practitioner, IQR Interquartile range.
6.2.13 Part 1 conclusions

In summary a total of 18 patients were recruited and 15 completed the study. 30 patients met the exclusion criteria, three declined to participate. The recruitment rate equates to 29% of those assessed (18/63) or 55% of those eligible for recruitment (18/33). A large proportion (30%) of those eligible died during admission (10/33) but only 9% (3/33) declined to participate. Randomisation after screening allocated seven to the standard care group, five to the exercise on NIV in hospital group and six to the exercise on NIV in hospital and home group. Three participants died and had incomplete follow up. There were no other reasons participants were lost to follow up. A mean of 5.72 patients were screened each month and 1.63 patients were recruited each month. Overall the consent rate of 55% (of those eligible) was good, particularly considering how ill this population is and may be promising for recruitment into a future trial.

The participant diaries were returned by all live participants. The standard care group demonstrated a trend for increased use of usual medication compared to the other groups. There was a trend for the exercise on hospital and home group to have accessed their GP less than the other two groups.

6.3 Part 2 Participant Baseline Information

6.3.1 Introduction

The baseline characteristics of the sample consisted of descriptive information including ethnicity, gender and weight. Information on disease severity included smoking history, lung function and previous admissions. Social information is reported including factors of social isolation and deprivation. Further disease severity is expressed through ABG results and the calculation of BODE scores predicting mortality.

6.3.2 Statistical Analysis

Details of how data were recorded and analysed can be found in Chapter 4 (‘Quantitative Methods’), section 4.23 Data Analysis. Missing data were caused by deaths of participants within the sample; there was no incomplete outcome measure data through researcher error or participant choice. The participants who
died were excluded from the analyses after their last data collection. Consequently one participant from the standard care group was excluded following baseline assessments and two participants from the exercise on NIV in hospital and home group were excluded, one after month one assessment and another after month two assessment respectively.

Initially the descriptive statistics were calculated. All the outcome measure scores were normally distributed, with the exception of the ActiCal data and participant diary data. Not all of the baseline characteristics were normally distributed, therefore median and interquartile range were used to describe the data and non-parametric testing were applied to the data (Kruskall-Wallis) to assess for any differences between the groups.

The researcher analysed the data to identify any trends. Any further statistical analysis was not attempted because of the small sample size of each group.

6.3.3 Differences in the Baseline Characteristics of the sample in each trial arm

There were trends for differences in baseline characteristics between the exercise on NIV in hospital group and the other groups. The exercise on NIV group had a mean age of 73.4 years which is 11.2 years older than the mean age of 62.2 years in the exercise on NIV in hospital and home group and 8.1 years older than the standard care mean age of 65.3 years. The exercise in hospital group had more males but had a lower pack year history of smoking. The exercise on NIV in hospital group had a higher mean number of co-morbidities than the exercise on NIV in hospital and home group but not the standard care group. The exercise on NIV in hospital and at home group had a trend for more hospital admissions requiring acute NIV (see Table 6.10). However there were no significant differences between groups.

A selection of the severity raw data (Age, FEV₁% predicted, Pack year history) has been included in Appendix 21. This was to allow for a selection of individual and group data to be reviewed. All the raw data was not included due to the sheer quantity of data.
Table 6.10 Baseline characteristics. Data are shown as mean ±SD (95% CI) or median (IQR range)

<table>
<thead>
<tr>
<th></th>
<th>Standard care (n = 7)</th>
<th>Exercise on NIV in hospital (n = 5)</th>
<th>Exercise on NIV in hospital and home (n = 6)</th>
<th>Total: (n = 18)</th>
<th>p-value (ANOVA unless stated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% female)</td>
<td>71.4</td>
<td>40.0</td>
<td>66.6</td>
<td>55.5</td>
<td>0.22 X²</td>
</tr>
<tr>
<td>Ethnicity (% white British)</td>
<td>85.7</td>
<td>80.0</td>
<td>83.3</td>
<td>88.2</td>
<td>0.40 X²</td>
</tr>
<tr>
<td>Age (years) Mean ±SD</td>
<td>65.3 ±6.5</td>
<td>73.4 ±19.3</td>
<td>62.2 ±6.1</td>
<td>66.5 ±11.6</td>
<td>0.28</td>
</tr>
<tr>
<td>FEV₁ (% predicted) Mean ±SD (95% CI)</td>
<td>27.8 ±16.9</td>
<td>28.2 ±14.3</td>
<td>25.8 ±12.1</td>
<td>27.2 ±13.7</td>
<td>0.96</td>
</tr>
<tr>
<td>Pack year history (number of cigarettes smoked per day (20) × number of years smoked) Mean ±SD (95% CI)</td>
<td>39.3 ±7.3</td>
<td>27.0 ±16.4</td>
<td>38.3 ±18.6</td>
<td>35.6 ±14.6</td>
<td>0.32</td>
</tr>
<tr>
<td>Previous admissions treated with NIV (number) Median (IQR))</td>
<td>0 (0-3)</td>
<td>0 (0-3)</td>
<td>1 (0-2.25)</td>
<td>0 (0-2.25)</td>
<td>0.85 (Kruskal-Wallis)</td>
</tr>
<tr>
<td>Co-morbidities (number) Mean ±SD (95% CI)</td>
<td>5.9 ±3.6</td>
<td>5.0 ±3.1</td>
<td>4.2 ±1.7</td>
<td>5.1 ±2.9</td>
<td>0.27</td>
</tr>
</tbody>
</table>

**Abbreviation Key:** CI Confidence interval, IQR Interquartile range, SD standard Deviation.
6.3.4 Other severity factors

There was a trend for the highest proportion of LTOT users to be in the exercise on NIV in hospital and home group at 83.3% presented in table 6.11. There was no significant difference between the groups for mean arterial pH and arterial pCO₂ at initiation of medical treatment with acute NIV.

Table 6.11 Other severity factors

<table>
<thead>
<tr>
<th></th>
<th>Standard care (n = 7)</th>
<th>Exercise on NIV in hospital (n = 5)</th>
<th>Exercise on NIV in Hospital and home (n = 6)</th>
<th>Total (n = 18)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pH at initiation of NIV</td>
<td>7.24 ±0.08</td>
<td>7.23 ±0.11</td>
<td>7.29 ±0.04</td>
<td>7.26 ±0.08</td>
<td>0.69</td>
</tr>
<tr>
<td>Arterial pCO₂ at initiation of NIV (kPa) Mean ±SD</td>
<td>11.14 ±2.52</td>
<td>10.42±2.59</td>
<td>10.47±1.97</td>
<td>10.70 ±2.41</td>
<td>0.92</td>
</tr>
<tr>
<td>LTOT user at Baseline (number (%))</td>
<td>3 (42.8)</td>
<td>2 (40.0)</td>
<td>5 (83.3)</td>
<td>10 (55.5)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Abbreviation Key: LTOT Long term oxygen therapy, pCO₂ Partial pressure of carbon dioxide in the arterial blood, SD Standard deviation.

6.3.5 The BODE index score of predicted mortality

The BODE index score was calculated at discharge for each of the participants. There was one participant within the standard care group who died prior to discharge so the BODE score was not calculated (see the quantitative method, section 4.21.1). The mean BODE score by group and percentage chance of mortality by 52 months is presented in table 6.12.
Table 6.12 Table of Mean BODE scores at baseline and % chance of mortality at 52 months. Data are mean ±SD

<table>
<thead>
<tr>
<th></th>
<th>Standard care (n = 7)</th>
<th>Exercise on NIV in hospital (n = 5)</th>
<th>Exercise on NIV in hospital and home (n = 6)</th>
<th>Total (n = 18)</th>
<th>P-value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline BODE score</td>
<td>8.17 ±2.19</td>
<td>8.40 ±1.20</td>
<td>7.83 ±1.57</td>
<td>8.12 ±1.74</td>
<td>0.88</td>
</tr>
<tr>
<td>Mortality at 52 months (% chance)</td>
<td>76.67 ±7.45</td>
<td>80.00 ±0.00</td>
<td>78.33 ±3.73</td>
<td>78.24 ±5.13</td>
<td>0.61</td>
</tr>
</tbody>
</table>

All groups demonstrated high predicted mortality, in line with their known disease severity.

6.3.6 Social History

The table of smoking and illegal drugs users (Table 6.13) presents the intake of harmful substances within the sample.
Table 6.13 Smoking and illegal drug use within the group

<table>
<thead>
<tr>
<th></th>
<th>Standard care (n = 7)</th>
<th>Exercise on NIV in hospital (n = 5)</th>
<th>Exercise on NIV hospital and home (n = 6)</th>
<th>Total (n = 18)</th>
<th>P-value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Smoker (n)</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>0.62</td>
</tr>
<tr>
<td>Ex-smoker (n)</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>12</td>
<td>0.29</td>
</tr>
<tr>
<td>Never smoker (n)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0.28</td>
</tr>
<tr>
<td>Current drug user (n)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0.53</td>
</tr>
<tr>
<td>Ex-drug user (n)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.48</td>
</tr>
<tr>
<td>Current alcohol abuser (n)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0.69</td>
</tr>
<tr>
<td>Ex-alcohol abuser (n)</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>0.28</td>
</tr>
</tbody>
</table>
6.3.7 Body Mass Index (BMI)

There was no significant difference between the three groups in their BMI results. The weight distribution across the groups is presented in table 6.14. There was a trend for the exercise on NIV in hospital and home group to have an overweight BMI, with a mean BMI of 27.5Kg/m\(^2\), however there was no significant difference between the three groups in their BMI results.
Table 6.14 Body Mass Index (BMI) of the groups (mean ±SD) (World Health Organisation (WHO), 2000)

<table>
<thead>
<tr>
<th></th>
<th>Standard Care (n = 7)</th>
<th>Exercise on NIV in hospital (n = 5)</th>
<th>Exercise on NIV in hospital and home (n = 6)</th>
<th>Total (n = 18)</th>
<th>P value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI mean kg/m$^2$ ±SD</td>
<td>22 ±5</td>
<td>20 ±2</td>
<td>28 ±12</td>
<td>23 ±8</td>
<td>0.33</td>
</tr>
<tr>
<td>Underweight, n (%) &lt; 18.5kg/m$^2$</td>
<td>2 (29)</td>
<td>3 (60)</td>
<td>2 (33)</td>
<td>7 (39)</td>
<td>0.56</td>
</tr>
<tr>
<td>Healthy weight, n (%) 18.5-25kg/m$^2$</td>
<td>2 (29)</td>
<td>1 (20)</td>
<td>0 (0)</td>
<td>3 (17)</td>
<td>0.42</td>
</tr>
<tr>
<td>Overweight, n (%) 25-30kg/m$^2$</td>
<td>3 (43)</td>
<td>0 (0)</td>
<td>1 (17)</td>
<td>4 (22)</td>
<td>0.22</td>
</tr>
<tr>
<td>Obese, n (%) &gt; 30kg/m$^2$</td>
<td>0 (0)</td>
<td>1 (20)</td>
<td>3 (50)</td>
<td>4 (22)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

**Abbreviation Key:** BMI Body Mass Index, n number, SD Standard deviation.
6.3.8 Social Isolation

Over a quarter of the total number of participants lived alone (38.9%) see 6.15 table of isolation. Overall the group had poor activity levels and 72.2% of the sample were unable to climb stairs.
Table 6.15 Social Isolation

<table>
<thead>
<tr>
<th></th>
<th>Standard care (n = 7)</th>
<th>Exercise on NIV in hospital (n = 5)</th>
<th>Exercise on NIV in hospital and home (n = 6)</th>
<th>Total (n = 18)</th>
<th>P value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lives alone, n (%)</td>
<td>2 (28)</td>
<td>4 (80)</td>
<td>1 (17)</td>
<td>7 (39)</td>
<td>0.08</td>
</tr>
<tr>
<td>House bound, n (%)</td>
<td>4 (57)</td>
<td>2 (40)</td>
<td>2 (33)</td>
<td>8 (44)</td>
<td>0.71</td>
</tr>
<tr>
<td>Unable to do stairs, n (%)</td>
<td>4 (57)</td>
<td>4 (80)</td>
<td>5 (83)</td>
<td>13 (72)</td>
<td>0.56</td>
</tr>
<tr>
<td>Uses walking aid, n (%)</td>
<td>4 (57)</td>
<td>1 (20)</td>
<td>2 (33)</td>
<td>7 (39)</td>
<td>0.45</td>
</tr>
<tr>
<td>Unable to visit GP, n (%)</td>
<td>4 (57)</td>
<td>2 (40)</td>
<td>4 (67)</td>
<td>10 (55)</td>
<td>0.71</td>
</tr>
<tr>
<td>Unable to visit hospital, n (%)</td>
<td>3 (43)</td>
<td>2 (40)</td>
<td>4 (67)</td>
<td>9 (50)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

**Abbreviation Key:** GP General Practitioner, n Number.
There was a trend for more participants within the exercise on NIV in hospital group to live alone, suggesting they may experience more isolation. There was a trend for more participants in the standard care group to be able to do the stairs and use a walking aid, suggesting they had higher activity levels than in the other two groups.

6.3.9 Deprivation

All three groups had participants living within socially deprived areas, see Table 6.16 for details of social deprivation across the groups. There was a trend for the exercise on NIV in hospital group to have the greatest deprivation with 60% living in England’s worst 10% of deprived areas, 80% experienced any form of deprivation and 80% experienced crime deprivation.
### Table 6.16 Table of deprivation

<table>
<thead>
<tr>
<th></th>
<th>Standard care (n = 7)</th>
<th>Exercise on NIV in hospital (n = 5)</th>
<th>Exercise on NIV in hospital and home (n = 6)</th>
<th>Total (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area in top 10% of England’s overall deprived wards (2010), n (%)</td>
<td>2 (28)</td>
<td>3 (60)</td>
<td>2 (33)</td>
<td>7 (39)</td>
</tr>
<tr>
<td>Area within top 10% of England wards for crime deprivation, n (%)</td>
<td>4 (57)</td>
<td>4 (80)</td>
<td>3 (50)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Area in top 10% of England wards for education deprivation, n (%)</td>
<td>3 (43)</td>
<td>2 (40)</td>
<td>1 (16)</td>
<td>6 (33)</td>
</tr>
<tr>
<td>Living in a ward experiencing any form of deprivation, n (%)</td>
<td>4 (57)</td>
<td>4 (80)</td>
<td>3 (50)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Lives in council property, n (%)</td>
<td>5 (71)</td>
<td>2 (40)</td>
<td>4 (67)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Receives paid benefit, n (%)</td>
<td>5 (71)</td>
<td>2 (40)</td>
<td>4 (67)</td>
<td>11 (61)</td>
</tr>
</tbody>
</table>
6.3.10 Part 2 Conclusion

In summary there was a 55% consent rate for the study which may indicate good recruitment potential for a future study. There were no statistical differences between baseline characteristics of the three groups, although there were trends for differences. The exercise on NIV in hospital group were older, sicker and more isolated than the other groups. Interestingly both NIV groups remained unwell with decompensated acidosis requiring acute NIV for longer than the standard care group.
6.4 Part 3 Clinical Outcome results

6.4.1 6MWT results

The walking distance in six minutes for healthy individuals ranges between 400 and 700m (Enright, 2003). This study is used a 30m change in distance as the MCID. Using SPSS version 17, (IBM: Chicago, Illinois, USA) the Kolmogorov-Smirnov and Shapiro-wilk tests were used to assess the distribution of the data. The results demonstrated that data were normally distributed. It is clear from Figure 6.2 that there is a trend for improvement in mean walking distance for the home and hospital exercise on NIV treatment group from baseline over all time points. The mean and standard deviation are presented in full in Appendix 22.

![6MWT means of groups](image)

*Figure 6.3 6MWT means of groups. (B-Baseline, DC-Discharge, M1-Month one, M2-Month two, M3-Month three) presented with SDs.*
There is a trend for improvement both in the exercise on NIV in hospital group and exercise on NIV in hospital and home group from baseline to discharge, however in contrast to the exercise on NIV in hospital and home group, both the standard care and exercise on NIV in hospital groups demonstrate a decline in walking distance following hospital discharge. Standard care and exercise on NIV in hospital and home groups both had one participant who walked further than other participants at baseline, 306m and 315m respectively, (see Appendix 22 for raw data). The individual participant results by group are presented in figure 6.4. This is presented to demonstrate the detail of the variability between participants and groups.
Figure 6.4 6MWT total scores measured over all time points, for all participants in the standard care group, exercise on NIV in hospital and home group and exercise on NIV in hospital and home group. (B-Baseline, DC-Discharge, M1-Month one, M2-Month two, M3-Month three)
6.4.2 SGRQ results

The SGRQ results are weighted from 0-100. The higher the score the worse the impairment. The average total score for healthy individuals is six (Ferrer et al. 2002). There was a trend for improvement in total scores within the exercise on NIV in hospital and home group (see Figure 6.5).

![Figure 6.5 SGRQ results of the 3 groups mean score. (B-Baseline, DC-Discharge, M1-Month one, M2-Month two, M3-Month three)](image)

The exercise on NIV in hospital group had minimal change from baseline (mean score = 74.27, 95% CI 100.28, 48.27) to discharge (mean score = 73.58, 95% CI 96.40, 50.77), however there was a decline in impairment for this group at month 1 (mean score = 80.17, 95% CI 94.95, 65.40) and month 3 (mean score = 80.11, 95% CI 96.45-63.78). There was a trend for the exercise on NIV in hospital and at home group of an improved SGRQ total score from baseline (mean score = 69.54, 95% CI 84.60, 54.48) to month 3 (mean score = 50.24, 95% CI 89.32, 11.19). See Appendix 23 for the raw data SGRQ results.

6.4.3 SGRQ Impact score

The average impact score for healthy individuals has been reported as two (Ferrer et al, 2002). The hospital and home exercise on NIV participants demonstrated a
trend for the greatest mean improvement from baseline (mean score = 55.8, 95% CI 39.8, 71.8) to month three (mean score = 33.0 CI 9.68, 56.32), see figure 6.6.

![Graph demonstrating the mean SGRQ impact scores by group.](image)

Figure 6.6 Graph demonstrating the mean SGRQ impact scores by group. (B- Baseline, DC-Discharge, M1-Month one, M2-Month two, M3-Month three) with SDs.

6.4.4 SGRQ activity component

The average activity score for healthy people was reported as nine (Ferrer et al, 2002). There was a trend for both the standard care group and the exercise on NIV in hospital and at home group to have improved their activity scores by month 1, however some of this improvement was lost by month two. Over all time points there was a trend for the standard care group to improve their mean score, from 100 (SD 0.0) at baseline to 66 (95 % CI 44.46, 88.14) at month 3, and the exercise on NIV in hospital and at home group from 89 (95% CI 81.38, 95.62) at baseline to 59 (95% CI 36.75, 80.45) at month three. See figure 6.7 for a comparison of results across the groups.
6.4.5 SGRQ symptoms component score

The normal score for symptoms in healthy people is 12 (Ferrer et al, 2002). The greatest trend for improvement in symptoms scores was in the exercise on NIV in hospital and home group. This improved from a baseline score of 79 (95% CI 67.4, 89.8) to 59 (95% CI 36.75, 80.45) at month three; this can be seen in comparison to the other groups within figure 6.8.

Figure 6.7 SGRQ mean activity scores across the groups. (B-Baseline, DC-Discharge, M1-Month one, M2-Month two, M3-Month three) with SDs.
6.4.6 LCADL

The LCADL total score is scored out of 75, the higher the score then the more likely the patient is unable to undertake a daily activity because of dyspnoea (Garrod et al, 2002). There was a trend that the exercise on NIV in hospital and home group had the greatest improvement in their LCADL score from baseline 50 (95% CI 37.24, 62.36) to 41 (95% CI 27.18-54.42) at month three. The exercise on NIV in hospital group demonstrated a decline in their mean score from 47 (95% CI 38.67, 55.33) at baseline to 57 (95% CI 51.78, 61.42) by month three. See Appendix 24 for the raw data. The comparison between group means is demonstrated in figure 6.9.

Figure 6.8 SGRQ mean symptom score. (B-Baseline, DC-Discharge, M1-Month one, M2-Month two, M3-Month three) with SDs.
6.4.7 Breathlessness scores

The following sections consider the results of the breathlessness outcome measures of Modified Medical Research Council (MMRC) Dyspnoea score (0 – “not troubled by breathlessness” to 4 – “unable to leave the house because of breathlessness”), and MBORG scores (0 – “no breathlessness” to 10 – “maximum breathlessness”).

6.4.7a Modified Medical Research Council (MMRC) Dyspnoea Score

There was a trend for the standard care and exercise on NIV in hospital groups to both demonstrate deterioration in their mean MRC scores. At discharge there is a trend for the exercise on NIV in hospital group to have deteriorated from 3.20 (95% CI 2.15, 4.25) to 3.6 (95% CI 3.16, 4.04), this deteriorates further to 4.0 (SD 0) by month one. This is in contrast to both the exercise on NIV in hospital and home group (baseline 3.7 (95% CI 3.3, 4.1) to discharge 3.2 (95% CI 2.32, 4.08) and the standard care group (baseline 3.4 (95% CI 2.66, 4.14) to discharge 2.8 261
(95% CI 1.92, 3.68). For the exercise on NIV in hospital group the score increased from 3.20 (95% CI 2.15, 4.15) at baseline to 4.00 (SD 0) at month three. The exercise on NIV in hospital and home group demonstrated a trend for improvement from a mean score of 3.67 (95% CI 1.42, 3.58) at baseline to 2.50 (95% CI 1.42, 3.58) by month three. The comparisons of means across groups is shown in figure 6.10. (See Appendix 25 for the raw data).

Figure 6.10 MMRC Dyspnoea mean score by group. (B-Baseline, DC-Discharge, M1-Month one, M2-Month two, M3-Month three) with SDs
6.4.7b MBORG Score at rest

There was a trend for improvement in all three groups from baseline to discharge, however only standard care improved their scores from discharge of 4.3 (95% CI 2.46, 6.14) to month one 3.9 (95% CI 1.9, 5.9) compared with exercise on NIV in hospital at discharge 4.0 (95% CI 2.16, 5.84) to month one 4.8 (95% CI 1.9, 5.9) and NIV with exercise at home from discharge 1.6 (95% CI 0, 3.2) and to month one 2.5 (95% CI 1.86, 3.14). Over the complete time period there was a trend for improvement in both the standard care and exercise on NIV in hospital and at home groups from baseline 5.57 (95% CI 4.12, 7.08) (standard care), 2.50 (95% CI 0.5, 4.0) (exercise on NIV hospital and home) to month three, 3.25 (95% CI 2.02, 4.58) (standard care) and 2.13 (95% CI 0.25, 4.45) (exercise on NIV hospital and home). The exercise on NIV in hospital group demonstrated a trend for a decline in BORG score from a baseline score of 4.3 (95% CI 2.02, 6.58) to a month three score of 7 (95% CI 5.2, 8.0). The difference in group means is demonstrated in figure 6.11. See Appendix 26 for the raw data.
Figure 6.11 Mean MBORG breathlessness scores at rest. (B-Baseline, DC-Discharge, M1-Month one, M2-Month two, M3-Month three) with SDs.

6.4.10 European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Score

A MCID is recognised as 0.03 for the utility score and 1.00 is regarded as best health (Brooks, 2003).

6.4.10a EQ-5D-5L utility scores

The mean utility scores demonstrated a trend for an improvement in the exercise on NIV in hospital and home group from 0.30 (95% CI 1.16, 0.64) at baseline to 0.66 (0.5, 0.9) at month three (see Appendix 27 for the raw data). There was a trend for both the standard care group and the exercise on NIV in hospital group to report a worsening in their mean utility score from baseline to month three.
There was a trend for a large decrease in utility score for the standard care group between month one (0.46 95% CI 0.18, 0.82) and month two (0.08 95% CI 0.04, 0.44). A comparison of group mean utility scores can be seen in figure 6.12.

![EQ-5D-5L mean utility scores](image)

**Figure 6.12** EQ-5D-5L mean utility scores. (B-Baseline, DC-Discharge, M1-Month one, M2-Month two, M3-Month three) with SDs

6.4.10b EQ-5D-5L visual analogue scores (VAS)

There was a trend for a deterioration in the exercise on NIV in hospital group from a mean score of 44 (95% CI 18.0, 69.95) at baseline to 39 (95% CI 25.24, 52.76) at month three. Both standard care and exercise on NIV in hospital and home groups demonstrated improvements from baseline with a mean score of 37 (95% CI 22.8, 51.92) (standard care) and 40 (95% CI 20.96, 59.04) (exercise on NIV in hospital and home) to month three scores of 39 (95% CI 20.96, 57.44) (standard care) and 58 (95% CI 43, 72) (exercise on NIV in hospital and home). See figure 6.13 for the differences in mean VAS score between groups.
Figure 6.13 EQ-5D-5L mean group visual analogue scores (VAS) scores. (B-Baseline, DC-Discharge, M1-Month one, M2-Month two, M3-Month three) with SDs

6.4.11 Activity monitoring

The ActiCal collated three months’ worth of data from discharge. The data were evaluated and the total daily median step count for each group from all three months of data were calculated. Due to incomplete data the analysis included four participants from each group, see figure 6.14.
Each available daily total has been plotted for Standard Care (n = 378 days), Exercise on NIV in Hospital (n = 336 days) and Exercise on NIV in Hospital and Home (n = 332 days).

The exercise on NIV in the hospital and home group improved from 4020 steps at month 1 to 6017 by month 2. However by month 3 the step count declined. The standard care group had a much lower step count at month 1 of 1009, but this continued to improve to 3843 at month 3. The exercise on NIV in hospital group, whilst beginning with a higher step count at 2515 than the standard care group, plateaued over the three months, see table 6.17.
Table 6.17 Median daily step count over the three months following discharge

<table>
<thead>
<tr>
<th></th>
<th>Standard care</th>
<th>Exercise on NIV in hospital</th>
<th>Exercise on NIV in hospital and home</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Month one</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median daily step count</td>
<td>1255</td>
<td>2515</td>
<td>4020</td>
<td>3606</td>
</tr>
<tr>
<td>(IQR)</td>
<td>(1009-4149)</td>
<td>(2421-4274)</td>
<td>(3606-7588)</td>
<td>(2138-4519)</td>
</tr>
<tr>
<td>(n = 5)</td>
<td></td>
<td>(n = 5)</td>
<td>(n = 5)</td>
<td>(n = 15)</td>
</tr>
<tr>
<td><strong>Month Two</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median daily step count</td>
<td>3442</td>
<td>2543</td>
<td>6017</td>
<td>2860</td>
</tr>
<tr>
<td>(IQR)</td>
<td>(1742-5234)</td>
<td>(2374-2745)</td>
<td>(2881-9569)</td>
<td>(2587-5233)</td>
</tr>
<tr>
<td>(n = 4)</td>
<td></td>
<td>(n = 4)</td>
<td>(n = 4)</td>
<td>(n = 12)</td>
</tr>
<tr>
<td><strong>Month Three</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median daily step count</td>
<td>3843</td>
<td>2367</td>
<td>5843</td>
<td>2832</td>
</tr>
<tr>
<td>(IQR)</td>
<td>(2137-4931)</td>
<td>(1937-4180)</td>
<td>(2397-9660)</td>
<td>(1931-5166)</td>
</tr>
<tr>
<td>(n = 4)</td>
<td></td>
<td>(n = 5)</td>
<td>(n = 4)</td>
<td>(n = 13)</td>
</tr>
</tbody>
</table>

Abbreviation Key: IQR Interquartile range, n = Number of participants

6.4.13 Conclusion

The exercise on NIV in hospital and home group demonstrated a trend for improvement in all outcome measures. The exercise on NIV in hospital and home group was the only group to have improved outcomes for the 6MWT, LCADL, MRC and EQ-5D-5L. A summary table of the outcome measures is presented in table 6.18. The ‘improved’ or ‘worse’ measures refer to a positive or negative change in excess of the MCID. ‘Unchanged’ represents a change below the established MCID. MMRC, BORG and total step count do not have a known MCID, therefore any improvement is classified as ‘improved’.
Table 6.18 Summary table of the outcome measure results in each group from baseline to month three

<table>
<thead>
<tr>
<th></th>
<th>MCID</th>
<th>Standard care</th>
<th>Exercise on NIV in hospital</th>
<th>Exercise on NIV in hospital and home</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWT</td>
<td>30m</td>
<td>Unchanged</td>
<td>Unchanged</td>
<td>Improved</td>
</tr>
<tr>
<td>SGRQ: Total score</td>
<td>4</td>
<td>Improved</td>
<td>Worse</td>
<td>Improved</td>
</tr>
<tr>
<td>SGRQ: Impact</td>
<td>4</td>
<td>Improved</td>
<td>Worse</td>
<td>Improved</td>
</tr>
<tr>
<td>SGRQ: Activity</td>
<td>4</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>SGRQ: Symptoms</td>
<td>4</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>LCADL</td>
<td>4</td>
<td>Unchanged</td>
<td>Worse</td>
<td>Improved</td>
</tr>
<tr>
<td>MRC</td>
<td>Not known</td>
<td>Worse</td>
<td>Worse</td>
<td>Improved</td>
</tr>
<tr>
<td>MBORG</td>
<td>Not known</td>
<td>Improved</td>
<td>Worse</td>
<td>Improved</td>
</tr>
<tr>
<td>EQ-5D-5L: Utility Score</td>
<td>0.03</td>
<td>Unchanged</td>
<td>Worse</td>
<td>Improved</td>
</tr>
<tr>
<td>EQ-5D-5L: VAS score</td>
<td>8</td>
<td>Unchanged</td>
<td>Unchanged</td>
<td>Improved</td>
</tr>
<tr>
<td>Total step count</td>
<td>Not known</td>
<td>Improved</td>
<td>Worse</td>
<td>Improved</td>
</tr>
</tbody>
</table>

**Abbreviation Key:** EQ-5D-5L European quality of life - 5 dimensions - 5 levels, LCADL London Chest activity of living questionnaire, MCID Minimum Clinically Important Difference, SGRQ St George’s respiratory questionnaire, 6MWT Six minute walk test.

6.5 Overall Conclusions

The quantitative results presented in this chapter demonstrated that the trial had a good recruitment and retention rate despite the disease severity of the population. This may offer positive information to inform a future trial. The study sample included a wide range of participants of variable, gender, age and ethnicity. They were reflective of the type of patients with severe unstable COPD seen in clinical practice, thus they seemed to represent the desired target population. The participants in the intervention limbs were able to exercise with NIV on the higher PS, recommended from the literature review. All outcome measures, except the ActiCal data were collated, including the participant reported diary. A trend for improvement was demonstrated for the NIV on exercise hospital and home group in 6MWT, LCADL, SGRQ and EQ-5D-5L. Unexpectedly the exercise on NIV in hospital group demonstrated a trend for deterioration in 6/7 of the outcome measures. The statistical analysis was limited because of the small sample size. A powered future trial may be able to address this problem. The recruitment success, outcome measure completion and trend for 269
improvement may suggest that a future trial is feasible, but it is also important to assess the acceptability of the intervention to the participants. This will be explored within Chapter 7 Qualitative Findings, analysis and researcher interpretation of the 'participant experience'. These quantitative results will be combined with the qualitative findings and discussed together within the Discussion in chapter 9.
Chapter 7 Qualitative findings, analysis and researcher interpretation of ‘the participant experience’.

7.1 Introduction

This chapter presents the findings and analysis from the semi-structured interviews of the four surviving participants who were randomised into the hospital and home NIV arm of the study. They experienced both the use of exercise on NIV during their hospital stay and continued with exercise on NIV for a further three months at home. Three women and one man were interviewed and the age range was 52-65 years.

The aim of this chapter is to enable the reader to hear the participants’ voices to enable a rich and true reflection of the interview material. The main themes were analysed and are discussed under the concepts of the experience of living with severe COPD, the feasibility of the study and directions for clinical practice. These concepts were developed from the aims of the study, researcher influence, literature review and the voices of the participants. This analysis meets the secondary aims of the research, Chapter 1 (‘Background’), section 1.21 Data Analysis.

The researcher acknowledges that there is often overlap between samples of transcript. This is because the interviews were with human beings who do not speak in a unidirectional way and their thoughts often meant that conversation covered many areas. Therefore although an attempt has been made to identify specific themes to make sense of the data, these themes cannot truly be seen in isolation from one another.

7.2 The interviews

All four interviews took place within a week of the three months post discharge time period. The first interview took place on the 4/6/2013. The last interview took place on 24/3/2014. They all took place at the participants’ homes. Two of the participants needed rest breaks from the interview for breathlessness and fatigue management. The researcher’s reflection of undertaking the interviews can be found in Chapter 8 (‘Reflexivity’), section 8.5 finding my space as an interviewer.
7.3 The experience of living with severe COPD

The themes that were identified under the experience of living with severe COPD are presented in figure 7.1.

Figure 7.1 The experience of living with severe COPD

The following sections will address each of the themes identified in Fig 7.1 beginning with the participants' voices and then followed by analysis and discussion. To allow greater understanding of the participant experience the discussion includes assimilation with other sources of literature, informal discussions with patients and observations. For clarity the researcher has differentiated in the text where thoughts are from her own observations or other interaction with the participants and not direct analysis of the transcription. The separation is to allow for the possibility that the researcher's role as a clinician may have clouded some of these observations (see Chapter 8 Reflexivity).
7.3.1 Symptoms and exacerbation

The participants discussed the physical symptoms of having a diagnosis of COPD with particular emphasis upon their breathing and exacerbations:

“...Bad...Breathing...Bad it was all bad...but then you don't realise how bad you are til you go in there do you…” (Gert)

“...things like the breathing problem and although you tell me my levels are fine for some reason they don't feel fine and the confusion I've had and the light headedness and things like that...erm ones I cancelled oh what was it it's hard for me to remember what it was it was see this is the (tut) memory problem I've got…” (Vanessa)

Breathlessness was reported as the main symptom by participants, which is consistent with previous literature (Habraken et al., 2008; Elkington et al., 2004). Despite improved medication in the form of inhaled therapy this was still the overwhelming experience in this group. In the literature breathlessness is often described vividly by COPD patients and compared to suffocation (Seamark et al., 2004). None of the participants in the course of the study ever used these vivid descriptions. The participants in this study always spoke of breathlessness in relation to activity and tasks.

For one participant her memory was affected. Cognitive loss has been reported to be present in 77% of patients with COPD and hypoxaemia (Grant et al., 1982). Cognitive deficit may also worsen over time, memory and attention problems can increase in presentation during an exacerbation and this is heightened in patients who have received hospital NIV (Hung et al., 2009; Kirkil et al., 2007; Ambrosino, 2002). Cognitive symptoms developed during a severe exacerbation can last up to 6 months following the hospital admission (Ambrosino et al., 2002). In an alternative study fatigue was the participants’ main concern (Lewko et al., 2014) however most of the other symptoms experienced were not referred to during the interview but in every day conversation with the researcher. Whilst some were specific to COPD respiratory symptoms (for example, wheeze, sputum and fatigue), others were not specific to COPD (for example low back pain, leg oedema and knee pain). Whilst COPD is acknowledged to be a multi-component disorder (Agusti, 2005), these symptoms may be because of the age and co-morbidities of the participants.
7.3.2 Impact on living: daily tasks

The participants emphasised the daily struggle of completing their activities of daily living and the balancing act between task, time and breathing:

“...mainly because I think I I'm struggling too much just to get through each day erm doing the main things I need to do you know like eating and clearing up and things like that...” (Vanessa)

“...I mean I couldn't tell you it was probably about eight months ago that I walked around the supermarket with a trolley...cause a lot of people...even this morning said where's your scooter...” (Elsie)

“...whereas I used to sit in the chair and let him (nodding at husband) do everything...” (Gert)

“... I was struggling to perhaps go to the shops that type of thing and stopping off...” (Neil)

The participants describe the struggle of carrying out daily tasks (for example, shopping). Through analysis of their descriptions it would seem that the participants have developed coping strategies to function including: slowing down either the speed of an activity or by having rests during the activity (for example Neil continually stopping for breaks); adaptation of the daily task (for example Elsie using a scooter for shopping); and activity avoidance (for example Gert letting her husband take on her role). This is supported by the studies carried out by Habraken et al. (2008) and Wortz et al. (2012). They undertook interviews of patients with end stage COPD and participants reported that they modified their activities, took breaks between activities or avoided activities altogether. These methods of coping with breathlessness were also supported by researcher observations throughout the study. An example of slowing down tasks was to allow longer for tasks and to break them up with rest (for example, walk to the next lamp post or stop for coffee). An example of changing tasks was ironing in sitting or using the microwave to heat coffee. An example of avoidance was one participant who only dressed in pyjamas to avoid the activity of dressing and changed their pattern of sleep to wake later in the day so as not to have to make breakfast or deal with people calling at the door.

Whilst the impact of breathlessness on daily activities is widely reported in the literature, from a clinical perspective I had failed to realise the impact on every small task, leading to adaptation and avoidance.
As a clinician I had witnessed these patients when they were at their sickest, bed bound, attached to a tight fitting mask, and often unable to communicate fully. Then if the patient improved there followed brief 30 minute treatment sessions e.g. transfer out of bed, onto commode, mobilise to the toilet and then at this point they are often deemed medically fit and to have reached the minimal status for discharge home. This brief interaction is carried out in a safe hospital environment with an adapted environment (for example, hospital bed, raised toilet and O2 or assistance if indicated), with all daily needs met (for example, cup of tea brought to bed). There are no life interruptions such as the doorbell or environmental hazards (such as stairs) to negotiate. As a physiotherapist it is important to be able to be patient centric and focus on patient led goals to adapt treatment to the needs of the patient however, it is easy to forget that hospital is not home and the symptoms experienced by patients are not just one off events but ongoing, multi-dimensional and they affect every aspect of living. What seemed surprising was just how limited their lifestyle was, whilst for the participants it seemed normal.

This was reflected by Habraken et al. (2008) who concluded that because COPD patients spend a long time in end stage illness, unlike other pathologies, they have time to modify to each deterioration and time to become used to their limitations. Therefore, life with limitations becomes normal. This is a problem as positive social relationships and social support are linked with better QOL and personal integrity (Nicholson and Anderson, 2003; Leidy and Haase, 1999).

7.3.3 Time

The theme of time was identified in many aspects of the transcripts:

“…erm that was in order to do my hair I had to have my arms lifted up above my head for quite a few minutes it took me about twenty minutes to half an hour to do my hair and that was quite tiring on my arms and my shoulders so by the time I’d finished doing my hair yeah my arms and shoulders were quite tired and sore…” (Vanessa)

“…in the last three months I think before I was struggling…” (Neil)

…not being able to sort the oxygen quick enough if I’m not getting…” (Vanessa)

“…I was out Christmas time but I don’t think I went out after that….it always seem like Christmas time that I go down…sighs…” (Elsie)
The participants focused on time by assessing how long they have been unable to perform tasks well. They discussed the anxiety around doing tasks quickly (for example attaching oxygen). Strang, Ekberg-Jansson and Henoch (2014) reported that anxiety often materialises in combination with dyspnoea in patients with COPD. There appeared to be little documented about how patients with COPD perceive time. Environmental factors seemed to define activity, with winter months being seen as challenging for one participant and linked with exacerbations. Habraken et al. (2008) supported this with his findings that sometimes patients did not leave the house for months due to bad weather.

7.3.4 Emotions

“... cause before then I was just I was miserable...I gotta admit...and things was worrying me as well...” (Gert)

There was also anxiety attached to having an exacerbation:

“...No not worried I just think about...Is it every time I get a cold will I end up in hospital...yeah...I mean I've got my tablets...” (Elsie)

For one participant it felt that there were no treatment options left:

“...No...No and this is where you come in (tearful)...I really appreciate it... Erm...sighs well...there was no other choice really because I just want to get better...sighs...” (Elsie)

In this research study during the informal discussions with the researcher the participants often spoke of being depressed and anxious. The participants spoke of loss in terms of not being able to do previous activities. This is similar to findings from the literature. Wortz, et al. (2012) carried out in-depth interviews that identified loss as a major theme in relation to loss of normal functioning, loss of independence, loss associated with co-morbidities and loss of social contact.

7.3.5 Isolation

The participants commented on a feeling of isolation:

“...They haven’t seen it (the ventilator)...I don’t get a lot of people up here...so...it’s just as well really there aren’t a lot of people that come up here...” (Gert)

“...Erm... it can be I mean I've got loads of friends but I just don't see them now... I mean I had a friend we used to go out in the car and we used to go shopping and everything together but I don't even ask now and she doesn't
ask me sometimes you can feel very cut off I mean the girls I used to work with before at work you know in a job you keep in touch for a while and then everything wears off and you don’t hear anything for a while…a couple of people on Facebook…that I used to work with and all that…but you can get very lonely…very lonely…” (Elsie)

One participant discussed the opinions of others regarding her own responsibility for causing her disease:

“… Oh Burt’s attitude, that’s my son, his attitude very much is that most of what’s happened to me I deserve because I haven’t completely given up smoking so he tends to fluctuate between feeling that there’s no point in having any treatment at all while I still smoke and making use of treatment that will help and that if it helps enough maybe it will help me give up smoking if you understand that…” (Vanessa)

During the informal discussions had with the researcher participants discussed the stigma they felt by both health care professionals and family towards their condition. The literature suggests that the loss of social support leads to being isolated from society and stigmatisation of their symptoms and disability. Blame from others and self-blame can lead to poor self-esteem (Nicholson and Anderson, 2003; Toms and Harrison, 2002). Interviews carried out by Halding et al. (2010) suggested that people with COPD were judged by society because their disease was perceived as being self-inflicted. This was spoken of by one participant (Vanessa) and her son’s attitude of her not deserving treatment.

Participants suffered from negative emotions and the urge to apologise. Of the four participants interviewed two were still current smokers. Researcher observations throughout the study had observed that, whilst one participant was apologetic for smoking and had expressed the blame by relatives, the other participant felt no guilt and blamed boredom and no other pleasure as the reason for continuing with smoking. Halding, et al. (2011) supported this by demonstrating that the interviewees revealed actions to diminish strain from stigmatisation and self-blame such as non-disclosure of smoking habits and pointing out excuses.

Interestingly throughout this research study the participants were observed by the researcher as often referring to others as more deserving of care and considering them to be worse off. This related to other patients seen on the wards, often unbeknown to the patient but with less severe disease.
The participants spoke of losses, which is supported in the literature by the interview findings of a study (Seamark et al., 2004) where participants described losses in relation to jobs, tasks around the garden and growing dependence on carers. Most of the participants discussed a loss of activity around the home and growing dependence on others to do tasks from washing up to withdrawing money. One of the participants, who was the only one still working at the start of the study, had to drop his hours considerably by the end of the study and was considering retiring.

The researcher’s personal perspective is that the isolation experienced was a direct result of not being able to participate in social activities due to activity avoidance worsened by hospitalisation, however research by Halding et al. (2010) suggested that patients no longer felt that they were full members of society right from the point of diagnosis.

7.3.6 Healthcare

The participants often discussed their past experiences of healthcare. Hospital care was mentioned directly and in terms of the inevitability of admission:

“...I gotta be…the hospital…they do treat you well I gotta say they they did everything for me in there without them I wouldn’t be here I don’t think ….but they are good…” (Gert)

“...erm...sighs well...there was no other choice really because I just want to get better…sighs…” (Elsie)

They often had negative preconceptions about NIV:

“...reminds me of that I had in hospital of the mask that’s what it reminds me of and I didn’t like that either…” (Gert)

“...It would have frightened me...Yeah I was thinking about the other one laughs...yeah...alright in the beginning with the other one I was scared...erm and I...No I think it was just having that over my face and it was very hard to get to sleep with it because it was the way it was going and I think I must have just given in and just laid down to it and that was it...but it seemed to be like I was fighting it for some reason but I started going through the night then with with it ok...And... erm... it’s as I said it’s not because the thing is you breathe with that one the other one does the breathing for you…” (Elsie)

One participant had preconceptions about PR and being sedentary:

“...I turned it (PR) down quite a few times...Because people had told me they are very pushy...Force you to do things...the worse thing you can do is just sit there as with this illness…” (Elsie)
Regardless of the fact that the participants often have a long time living with their symptoms it was unanticipated that exacerbations still surprised them. There is a government push for the public to avoid using A&E in favour of GP or walk in centres (NHS England, 2014), however for this group of patients A&E is still frequently utilised. An exacerbation of COPD is the second biggest cause of admission to hospital in the UK (one in eight admissions) (Healthcare Commission, 2006). For this group despite having had frequent exacerbations and having suffered with COPD for many years an exacerbation was still unexpected. One participant waited for some time with symptoms trying to avoid hospitalisation, however this may potentially have led to a more severe exacerbation. There was much emphasis by the participants on self-management, self-monitoring of symptoms and self-prescription. It was also clear, however, that ultimately there was an acceptance that they would have to go into hospital.

The interview findings suggested that there will always be a need for this group of patients to access hospital care. Whilst self-monitoring was important, exacerbations were still unpredictable and their severity will inevitably lead to admission.

7.4 Acceptability: The participants experience of being involved in the study

This section will present the concept of acceptability of the research to the participants. The themes that underpin this concept are illustrated in figure 7.2.
7.4.1 Impact

This concept relates directly to the aim of the thesis (see Chapter 1 Background, Section 1.22 Aims of the Research and Thesis). This theme encompasses the possible impact the intervention has had on each participant both physically and emotionally. They found the intervention contributed to physical changes:

“…From going in erm I feel about 70% better but now as the time has gone on now it’s escalated…” (Elsie)

There was a physical improvement often described by participants in terms of daily activities:

“…yeah definitely Oh yeah I can walk a little bit better than what I did...and I do feel a little bit better I gotta say…” (Gert)

“…erm small amount of additional strength in my limbs especially my legs err you know where which is what we worked on mainly…” (Vanessa)

“…Erm I think in the last three months I think before I was struggling to to perhaps go to the shops that type of thing and stopping off I just presumed that type of condition but since I have exercised and so forth erm you know I was able to walk to my shops and back without stopping…” (Neil)

“…Erm I can walk round the shops, I go up and down the stairs, I walk out to the front with the oxygen obviously erm I’ve been out a few times...been to
the hospital...been to the doctors...been to my cousins...went out for a meal which is something I haven’t done for a long long time.” (Elsie)

Fatigue was described as being counterproductive:

“...I suppose my main feeling is that I haven’t really been physically up to it that I haven’t had such as much benefit from... from the sessions as I could have had because of being unable to erm do any exercises on my own in the daytime when you haven’t called...mainly because I think I I’m struggling too much just to get through each day erm doing the main things I need to do you know like eating and clearing up and things like that...difficulties in exercising?...” (Vanessa)

The participants expressed how the intervention affected them emotionally:

“...Oh yeah definitely Oh yeah I can walk a little bit better than what I did...and I do feel a little bit better I gotta say...cause before then I was just I was miserable...I gotta admit...and things was worrying me as well but at the Yeah I was really down and yeah I was but at the moment no I’m alright....moment now I’m fine...I’m much better now I do say....” (Gert)

“...I was lying (laughs)... erm... oh did I do that (laughs)... I don’t know what to say erm... well yeah it did seem to have a good effect on my mood and my feeling physically even though I was a bit tired afterwards and needed a little sleep or nap... erm... generally speaking I did feel better...” (Vanessa)

“...laughs erm yeah I suppose my stress levels improved mainly because you were as good as your word that I didn't feel pressured that I had to do anything I didn’t want to do...” (Vanessa)

(Interviewer) “...So now you’ve finished this research...are you feeling a bit more positive about life?” “(tearful) very much...very much (laughs) but I’ll tell you why I’m laughing I’ll tell you soon...” (Elsie)

Confidence levels were commented on as improving:

“...erm actually confidence that my breathing is better than I realised by having the machine the little thing showing me every time you came that my sats levels were good and stuff...” (Vanessa)

“...don’t know because you talked to me about it I’ll be honest with you it seems to give you the will to try things erm you know you sort of done it with that and then you think let me try it without it and its surprising...” (Elsie)

(Post interview Elsie said the other main change she wanted to thank me for was increasing her confidence and making her feel like the old Elsie again...making her feel human. But she didn’t want to say this on tape because she knew she would get upset but was happy for me to document this.)

The participants described a feeling of fear and dread regarding the intervention:
“...Very difficult (laughs) cause I didn’t like using it without you being here mind...cause I was frightened that I was going to break it or I was gonna do something that’s why I never ever used it but erm once…” (Gert)

“...I don’t dread you coming so much as the purpose of your visit that’s what I dread really… erm… I suppose it’s the thought of having to do the exercise erm... use the mask erm... and the worst bit is taking the mask off afterwards and getting my breath back…” (Vanessa)

“...erm a little bit daunting initially (laughs)...” (Neil)

Guilt, blame and regret were recognised by the participants:

“...I suppose my main feeling is that I haven’t really been physically up to it that I haven’t had such as much benefit from... from the sessions as I could have had because of being unable to erm do any exercises on my own in the daytime when you haven’t called…” (Vanessa)

“... I don’t want to let you down…” (Vanessa)

“... erm no I just wish that I wasn’t so that my condition wasn’t so poor to start with a year or two ago I’d have probably benefited much more than this than I am doing now…” (Vanessa)

“...erm Jason (son) and Sam (nephew) think it’s great they think that erm I should make more use of it and they are happy to help me use it if I want to...Oh Burt’s attitude, that’s my son, his attitude very much is that most of what’s happened to me I deserve because I haven’t completely given up smoking so he tends to fluctuate between feeling that there’s no point in having any treatment at all while I still smoke and making use of treatment that will help…” (Vanessa)

The participant’s commented on the negative effects of the exercise programme and outcome measures:

“...the walk tests erm I did find difficulty with them sometimes because I would put quite a lot into it erm and obviously the nurse would monitor me erm how I was and so forth but when doing a full exercise and then you know going to work I did find it it did take quite a lot out of…” (Neil)

“...Aching limbs ((laughs)) yeah but that could have been the stairs as well though mind…” (Elsie)

The participants divulged the potential benefit of the device, although for some their thoughts were contradictory:
“...Well it's obviously a positive thing otherwise I wouldn't be using it would I? So it is obviously positive but err... some things you get used to and some things you don't do you? And that I didn't get used to...” (Gert)

“...I expect it has been a positive experience yes. Well it does I think it does help you with your exercise erm I think that's the positive thing because I realised pretty early on that I erm that you need to do some sort of exercise to stabilise your condition and erm help you in future years...”.(Neil)

“...erm I'll say positive overall (laughing) even though I hate to admit that (laughing)...” (Vanessa)

“...It's improved on my breathing erm it doesn't make me want to stop and overall it is a good thing for like people in my condition to use...” (Elsie)

“...When you've actually got it on it can feel quite relaxing...” (Vanessa)

The clinician within the researcher had not appreciated the reality that some of the participants felt that they had to choose between activities due to fatigue. For one participant choosing to put her hair up (a weekly task) meant she would not be able to exercise that day.

For another participant it was the assessment of the 6 minute walk test in combination with the exercise and still working which was tiring.

It would seem that the adaptations the participants had made, with their daily activities of living, carried over to include the exercise regime. Therefore fatigue and graded exercise may need to be considered in future studies.

7.4.2 Equipment/Logistics

The participants expressed difficulties with both application of the mask and the claustrophobia it created:

“...no I don't know I don't think so although I'm quite nervous about using it and putting it on and stuff... yeah I don't find that easy to put on plus as well because I have to take my glasses off then I can't see properly so that makes me nervous not being able to see properly if I am doing it on my own...” (Vanessa)

“...Well if I was sort of on it most of the time I don't think I would have liked it because obviously the glasses and it's not very nice...this one's ok but the bipap with false teeth...” (Elsie)

“...Ok the only thing that I did find difficult at times was putting the mask on to be quite honest with you erm again I think it's the claustrophobic aspect to
it and also I don’t know which brought on a little bit of a what we discussed just now a little bit of a panic err to so you know so you were probably breathing more heavily which you know is not natural…” (Neil)

The participants discussed the equipment dimensions specifically:

“…because it’s light… the designs alright in it…it’s just a matter of putting it on the floor really so yeah that’s alright…” (Gert)

“…I find the weight of the equipment heavy to lift but then that can be put in place you know it’s not too heavy for me to move I could put it in place first and then put the equipment on and stuff you know at the side of the bed erm…” (Vanessa)

“…No because I charged it once since I’ve come out of hospital…” (Elsie)

“…No...because it’s compact...very compact... and I mean everything’s in the bag so you haven't got to oh where I put that and where is that…it’s all there…” (Elsie)

The participants focused on the practicalities of using the NIV at home to exercise:

“…I could walk alright with it…” (Gert)

“…erm connecting it up properly and you know not having....yeah to the oxygen and not being able to sort the oxygen quick enough if I’m not getting...yeah I don't find that easy to put on plus as well because I have to take my glasses off then I can't see properly so that makes me nervous not being able to see properly if I am doing it on my own…” (Vanessa)

“…erm a little bit daunting initially (laughs) but once you use it and you experience it you get very much used to it and erm it is no problem at all really so you know you find it well the whole equipment and so forth you find useful really…” (Neil)

Overall the participants rated the equipment as compact and a good weight, although one participant felt the device was too heavy to move. However most of the participants tended to position the ventilator on the floor and exercise around it. This meant that the exercises used needed to be adapted for this. However the researcher had already considered this and most of the exercises were easily achieved with the ventilator on the floor. However walking and stair climbing could only be carried out with the assistance of the researcher because of the weight of the device. Therefore there is a need to develop a more portable device to allow participants to wear it for activity. However within this very severe disease group most exercises may initially be in sitting. The home environment may additionally impinge on the space required for exercising so portability of the device may be redundant in the house-bound patient.
Similarly to many nocturnal home ventilator users the mask was a concern. All of the participants reported claustrophobia associated with the mask particularly on initial use. There was also an issue involving participants who wore glasses but needed the full face mask as this meant they were unable to wear them during the exercise sessions. This also caused difficulty when donning the mask. One participant reported difficulties with loose dentures although this was more with the hospital acute NIV than the NIV during the study. Since the completion of the study new mask technology has been developed. There are now full face masks without a head strap which glasses can be worn over to avoid the problems experienced by the participants in this study. One participant was able to use a nasal mask but this was not tolerated by other participants. Some participant’s experienced dry mouth after using the NIV device. This is a common side effect of home NIV often cured by a full face mask or adding a humidifier. A humidifier is a heated water bath that the air runs through prior to reaching the mask. Adding a humidifier may increase resistance in the circuit changing, inspiratory flow and pressure to the patient. Thus the addition of a humidifier into the study would need further investigation.

7.4.3 Ventilator settings

The participants discussed the sensation of the positive pressure from the ventilator which for one of them was an unpleasant sensation:

“…Yeah…I tell you Roger I don’t like it up your nose…it’s the air going through your nose…because if it’s too high obviously it covers your breathing and it reminds me of that I had in hospital of the mask that’s what it reminds me of and I didn’t like that either (laughs)…” (Gert)

“…I didn’t like the pressure on it either… no…I didn’t …no…” (Gert)

But for others it provided relief: The sensation of the pressure from the ventilator was for some of the participants an unpleasant sensation but for others it provided relief:

“…It wasn’t so overpowering on the face and the mask didn’t feel half as bad…” (Elsie)

“…And… erm… it’s as I said it’s not because the thing is you breathe with that one the other one does the breathing for you…Erm…if… if…you don’t work with it you get all the noise the bubbling…it’s just concentrating on using it and using it the right way…No…No cause you’d already talked me through
it erm as I said if you don’t use it in the right sequence it doesn’t work properly
does it…” (Elsie)

“…It helps you breathe a little bit better with it on it does…when you’re
exercising….otherwise you’re out of breath so bloody quick that did help…
but other than that …no…” (Gert)

“…the worst bit is taking the mask off afterwards and getting my breath
back…” (Vanessa)

“…I feel it actually gives me dry mouth which I don’t I don’t like very much
and I don’t like taking it off because of you know the transition back to you
know the normal oxygen machine…” (Vanessa)

Only the participant using a nasal mask commented on the pressure being an
unpleasant sensation. This was given as a reason why the participant did not use
the ventilator often without supervision. More time could be spent titrating
pressures and exploring mask interfaces as this patient may have benefitted from
an alternative mask type to assist distribution of pressure. One of the participants
found the pressures easier to tolerate than those provided by acute ventilation
devices. This may be a reason as to why the participants in this study were
concordant with ventilation use because they had already experienced much
greater pressures acutely. It is clear from the response of participants that they
valued lots of explanation and reassurance from the researcher on the use of the
ventilator.

7.4.4 Outcome measure choice

The outcome measures were specifically mentioned:

“…Yeah I… I the diaries are useful erm the walk tests erm I did find difficulty
with them sometimes because I would put a lot into it erm and obviously
the nurse would monitor me erm how I was and so forth but when doing a full
exercise and then you know going to work I did find it it did take quite a lot
out of me err not that I was thinking it would take a lot out of me but erm it I
did actually find that it did a little bit…” (Neil)

“…Well diaries and questionnaires I absolutely hate in any form for anything
so erm that’s something that I would have struggled to do you know anyway
erm…” (Vanessa)

“…Yeah I think over the weeks it starts to build up more and more and more
…the last time was twenty seven times weren’t it… I mean I couldn’t believe
I done that many and then we done steps you know I think it’s progression
you done that and then you think oh I’ll achieve this or that the next time I
just go for it…” (Elsie)
Only one participant commented on strongly disliking completing questionnaires or diaries, however despite stating this all patient reported outcome measures were completed by this participant. Most participants actually sought comfort in the outcome measures as proof of their health improvement. Therefore the specific timing of the outcome measures needs to be considered for a future study. The researcher had anticipated the 6MWT as being fatiguing to patients and that it would probably mean that the exercise session would not take place. The researcher had not considered that the questionnaires would be considered as tiring and for some participants these had to be carried out in isolation to exercise. Therefore the type and length of completion of outcome measures does need to be considered carefully for a further trial.

7.4.5 Exercise sessions

The participants differed in their views between using the ventilator to exercise and unsupported exercise:

“…I mean the exercising that’s alright I don’t mind things like that…it was just that... (looking at the ventilator) but other than that yeah it was alright. Well it helped you didn’t it when you did your exercises…it does help you...It helps you breathe a little bit better with it on it does...when you’re exercising....otherwise you’re out of breath so bloody quick that did help… but other than that …no…” (Gert)

(Interviewer) “Did you find it easy exercising in your home?”

“Yeah I did yeah…I did. What without it…Oh yeah you don’t get the same benefit do you? If you haven’t got it on you don’t get the same benefit...so...yeah having it on did make a lot of difference...” (Gert)

“…Ok the only thing that I did find difficult at times was putting the mask on to be quite honest with you and then I’d try try and try sometimes I have used it a couple of times erm and then you think oh blow it I’ll just do the exercises without using the equipment so that’s the only down side I mean I would have used it if I could you know fit it on better...to be quite honest with you I didn’t see a lot of difference from using the ventilator to erm there were a couple of times where we didn’t use it and erm I didn’t see any difference between actually using it and erm doing it without the ventilator…” (Neil)

“…No…because I that can be a lot easier than to do it without it…Its improved on my breathing erm it doesn’t make me want to stop and overall it is a good thing for like people in my condition to use...Yeah…yep…I mean I can do it with or without I could do it with or without it but as I was supposed to be using it I carried on using it… even if you don’t do the full amount like you were doing on that at least you are doing something and that is the way I looked at it as well I did try as much as I could but obviously I done more with that…” (Elsie)
There was anticipation that the exercise would be a negative experience:

“…I don’t dread you coming so much as the purpose of your visit that’s what I dread really… erm… I suppose it’s the thought of having to do the exercise… because I know that what I dread well it isn’t as bad as the sessions gonna be what I dread really… erm… I suppose it’s the thought of having to do the exercise…” (Vanessa)

“…the exercise did…it’s like you said if you are not used to it you will you will feel it…” (Elsie)

The participants discussed their experience of exercising on NIV without supervision:

“…Very difficult (laughs) cause I didn’t like using it without you being here mind...cause I was frightened that I was going to break it or I was gonna do something that’s why I never ever used it but erm once…” (Gert)

“…I suppose my main feeling is that I haven’t really been physically up to it that I haven’t had such as much benefit from... from the sessions as I could have had because of being unable to erm do any exercises on my own in the daytime when you haven’t called…” (Vanessa)

“…No...No...I mean you are not here every day so you know you’ve helped me...so what I’ve done every day is like a pattern every day right eleven o’clock it’s time to do this and I got myself into that (laugh’s) I mean you gotta have a timetable or a you know obviously if I had doctors or anything...but I still done it not said oh well I’m going to the doctors so I won’t...or I can’t be bothered with that today…I done it…” (Elsie)

“…Erm it was just getting used to it and I as you know I didn’t really walk with it it was only with you that I walked with it erm but it was…” (Elsie)

The timing and frequency of the intervention was discussed:

“…erm no I just wish that I wasn’t so that my condition wasn’t so poor to start with a year or two ago I’d have probably benefitted much more than this than I am doing now…” (Vanessa)

“…erm only maybe very marginally simply because I haven’t been able to make full use of you know the opportunity to do the exercises I think if I’d have managed to do it more times in the week then I think I would have benefitted quite significantly…” (Vanessa)

“…No...no...it seems ...how many weeks have we done this now... (So twelve (Interviewer))...Yeah that’s surprising isn’t it…” (Elsie)

Some of the participants reported they were unable to use the device unsupervised. As previously mentioned this may have been to do with difficulties applying the mask and connecting the O₂.
the device because of the weight of the equipment when trying to physically move it around the property. Others spoke of a lack of motivation and fatigue as preventing independent exercise. One of the participants voiced that extra supervised sessions would have been useful as part of the programme. One of the participants felt that different exercise could be achieved when supervised (for example, walking on the ventilator).

7.4.6 Research feedback

They discussed their experience of being involved in the research:

“Because it… well there’s always changes and you’ve probably come up with and another person’s probably come up with something that would be more helpful as well I really, really appreciated what you have done… Well I’d just like other people to take part it would make a lot of difference for yourselves and it would help the people cause I’ve seen what it done to me…” (Elsie)

“No as far as I was aware I would think that this is doing a cross section as to you you to erm I presume help people in in the future really that’s the way I read it…” (Neil)

They also had some advice to others embarking on the research intervention:

“… erm well just basically to go for it that it’s not as bad as you think it’s gonna be (laughing)…” (Vanessa)

“…Don’t bother (laughs) don’t bother no it is a good thing when you it is… if you…you know it is if you need something like that it is a good thing for people to use…” (Gert)

“…It’s really helped. Its improved on my breathing erm it doesn’t make me want to stop and overall it is a good thing for like people in my condition to use…Go ahead and use it…don’t be afraid because it will help. Do as you’re told (laughs) and push on through…” (Elsie)

“…Err I think the only thing is erm… I think is the keep up what you are being told by the nurse erm because it will only help you really you know I think that the advice the advice that you’re given really you’ve got to take on board because the stronger you are the more exercise is going to help your condition and help prolong your life which is what it’s all about really I suppose…” (Neil)

Overall the participants felt that being involved with the research was a positive experience. They wanted the opportunity to take part in new research and would recommend taking part to others. They reported an initial fear but their anxiety was eased with clear explanations and physiotherapy. One participant appreciated the feedback during and at the end of the research. She had
previously been involved in a research trial and after it finished she was not told whether she had received a placebo or a real drug. This was a source of anxiety for her and put her off participating in other research until this study.

The participants experienced positive physical changes. They reported increased activity levels both in being able to carry out household tasks and wider social activities. The participants reported that the intervention gave them confidence in their abilities to be able to do activities. They reported a relief from dyspnoea on exercise that allowed them to train harder and for a longer period of time. They reported an improvement in upper and lower limb strength. One participant reported she had achieved weight loss from carrying out the exercise. The participants also experienced improvements in their mood and stress levels.

7.5 Directions for clinical practice

This concept relates to the themes discussed that direct clinical practice. The themes that underpin this concept are illustrated in Figure 7.3.

*Figure 7.3 Directions for clinical practice*
7.5.1 Value placed on monitoring

The participants were concerned with their O$_2$ levels and placed importance upon this when self-evaluating their health:

“…Yeah…yeah… and another help has been me getting a sats machine as well because I can monitor…because if my sats go down then I know that there’s something wrong and then it’s not advancing more…” (Elsie)

“…erm actually confidence that my breathing is better than I realised by having the machine the little thing showing me every time you came that my sats levels were good and stuff…” (Vanessa)

Value was placed on the monitoring carried out by the physiotherapist during the research period:

“…in general I think it’s a good thing to come round like this…I never knew people would come round like this but yeah…” (Gert)

“…I don’t really know I just thought erm I mean it has been helpful obviously in the fact that you know erm I mean that somebody is I presume is you know is coming round to monitor you and erm discuss your medication and discuss your ongoing health I suppose…” (Neil)

There was much emphasis on self-management, behaviour change, self-monitoring of symptoms and self-prescription within the health-care literature and current clinical practice, however, one of the novel findings from the interviews was that the participants valued monitoring. The participants, whilst keen to carry out their own monitoring, really valued professional monitoring. They were enthused to know if their outcome measures were any better or worse, particularly the walking tests.

This finding suggested that face to face contact was important to these participants and demonstrated how community visits were perceived as valuable. This research may support the role of community matrons and community physiotherapy.

The participants seemed fixated with their O$_2$ levels and their monitoring and what this could mean clinically. A big change has occurred in the last few years in regard to self-management. One possible cause is easier access for patients to purchase their own monitoring equipment on the internet e.g. O$_2$ saturation machines, however whether this is advantageous is unclear. Whilst the participants felt reassurance in having this device it is not a full assessment of their condition. I feel as a clinician that I had been trained to complete a full
respiratory assessment. I was taught not to focus on O₂ saturations but I have undergraduate students who do so, seeing this as a quick and easy measure of respiratory status.

7.5.2 Time: set up/removal

The participants described the intervention as something that takes time to get used to:

“…It’s the beginning that’s the worse once you’ve got it on you are alright cause you’ve got to get used to it…..but it is the beginning puts you right off….but once you’ve got it on you’re alright…” (Gert)

“…Yeah…it got better as time went on…yeah…” (Elsie)

“…erm a little bit daunting initially (laughs) but once you use it and you experience it you get very much used to it and erm it is no problem at all really so you know you find it well the whole equipment and so forth you find useful really err initially not no erm it took several goes actually when I say several probably about two to three err goes before erm I got used to it really…” (Neil)

The participants identified that there is a recovery period after the intervention:

“…I don’t dread you coming so much as the purpose of your visit that’s what I dread really…erm… I suppose it’s the thought of having to do the exercise erm… use the mask erm… and the worst bit is taking the mask off afterwards and getting my breath back and I don’t like taking it off because of you know the transition back to you know the normal oxygen machine…” (Vanessa)

The participants reported it took them quite a long time to get used to the NIV. This should be taken into consideration for both acute patients and home NIV patients. It is also a consideration for taking exercise on NIV forward into clinical practice. Adequate time must be given to ensuring patients feel confident with the device. Not all of the participants felt confident enough to exercise on their own with the device. More time could have been spent by the researcher encouraging independent use rather than just focusing on an exercise session. More time was needed to demonstrate connection of additional O₂ to the ventilator as this increased anxiety in one participant.

At the other end of the spectrum patients also found their work of breathing increased on removal of NIV. This could have deterred them from using NIV. Certainly in clinical practice home ventilation patients often describe a period of breathlessness in the morning when they first wake up and take off the ventilator. It may be that a longer time is needed to rest on the ventilator when stopping...
exercise to restore breathing back to pre-exercise levels. More research is needed to assess the optimum time for NIV removal post exercise.

7.5.3 Hospital management of NIV

The participants commented on their experience of having NIV acutely in comparison to the NIV experienced in the study:

“…reminds me of that I had in hospital of the mask that’s what it reminds me of and I didn’t like that either…” (Gert)

“…It wasn’t so overpowering on the face and the mask didn’t feel half as bad…” (Elsie)

“…It would have frightened me…Yeah I was thinking about the other one laughs…yeah…alright in the beginning with the other one I was scared…erm and I…No I think it was just having that over my face and it was very hard to get to sleep with it because it was the way it was going and I think I must have just given in and just laid down to it and that was it…but it seemed to be like I was fighting it for some reason but I started going through the night then with with it ok…And…erm… it’s as I said it’s not because the thing is you breathe with that one the other one does the breathing for you…” (Elsie)

The participants expressed lots of anxiety around their acute NIV experience. Fear of whether they would ever come off the ventilator and discomfort from the mask were their main concerns. More explanation from health care staff about NIV, how it works and how long the treatment may be on for, may all have relieved anxiety in these participants. Equally, spending more time fitting the acute NIV mask and introducing the ventilator slowly may also have benefited this patient group. However, within the acute setting where time is important, a leisurely approach may not be available.

7.5.4 Other uses of NIV: pacing

“…Yeah…erm… you...you obviously you’ve got to work with the machine you’ve got to work with the machine but you’ve got to concentrate on what you are doing as well otherwise it would just be a waste of time…” (Elsie)

“…It’s been a good teacher…very good teacher…” (Elsie)

Another novel finding from this study was the role NIV may play in pacing of breathing during exercise. One of the participants described the ventilator as a teacher that taught the patient how to slow and correct breathing. Traditional respiratory physiotherapy encompasses pacing and positions of ease to improve
breathlessness. However time limitations in the acute environment often make this management strategy less frequently taught to patients.

It could be that NIV is used clinically to assist the patient in pacing activities. Additionally the NIV could be used for activities of daily living (for example put on for hoovering or bed making to allow for paced breathing and decrease work of breathing). There is a need to look further at the role of NIV and more portable devices may increase the possibilities for use.

The participants reported that the NIV felt relaxing and had a re-training role. NIV could be useful clinically in reducing the work of breathing post exercise and in supporting exercise to assist recovery.

7.5.5 On-going care: including information

The interaction and information from the clinician was discussed:

“...laughs erm yeah I suppose my stress levels improved mainly because you were as good as your word that I didn't feel pressured that I had to do anything I didn't want to do...” (Vanessa)

“...Yeah...yeah...cause I thought I was gonna be on it all the time...I think it was when you came round talking to me and told me it was just when I needed it at night and whatever...” (Elsie)

The method of initiating NIV was considered:

“...No...No cause you'd already talked me through it erm as I said if you don't use it in the right sequence it doesn't work properly does it your blowing back into it so you are breathing it in as it is giving it to you and then out again...” (Elsie)

“...No because you explained everything ...you explained to me in hospital and then when we got together the first time you showed me and you explained all that it does and you said like you can turn it up you can adjust it an everything which is good...” (Elsie)

“...And talked more about it as well...cause they don't really tell you what they are actually doing all they say is that we've got to put a mask on you and that's...” (Elsie)

There was a feeling of being given one chance for health care:

“...Yeah...yeah cause once well obviously once you're discharged from the hospital from the doctor you know you just report back to your doctor if you're not well but again that worries me if I went to the doctors with a chest infection will it automatically mean back in hospital cause I mean is he going to give you a chance to see if you come out of it...and that is one thing that worries me or don't worry me I think about I mean...” (Elsie)
“No I’d had a letter to go but that was cancelled by the hospital cause it was snow then the next one I had my aunty had died and it was her funeral so I rang and then I had another letter saying that cause I hadn’t been to 5 appointments which wasn’t true it was 2 appointments they closed the book on me and they were going to write to my doctor and if anything my doctor would have to refer me back.” (Elsie)

The participants wanted to have the opportunity to experience other treatment options and having access to treatment:

“…No...No and this is where you come in (tearful)...I really appreciate it. Everything...everything it has opened my eyes more knowing that there is something else out there that will help.” (Elsie)

“...do like the idea of having access to it even though I haven’t used it on my own if I didn’t have so many other things stressing me out (laughs) then I’d probably put more effort into having a go and using it on its own cause I think that. I think it would help me... with some of the erm daily problems I’ve had...” (Vanessa)

“...monitor you and erm discuss your medication and discuss your ongoing health I suppose...” (Neil)

“...There probably is... if you look around but who do you contact...... I know there is a phone number for the British Lung foundation and all that but there’s nothing is there now really... (Sighs and yawns)” (Elsie)

“...I turned it (PR) down quite a few times...Because people had told me they are very pushy...Force you to do things...but I’ve learnt now you shouldn’t listen to other people (coughs)... I read it this time in a booklet from the hospital I came away with the other day...they won’t force you to do anything you don’t want to do (laughs)...” (Elsie)

The participants valued the time spent explaining the therapy and improvements seen. One participant felt more time should be spent on planning treatment with the patient and explaining the treatment options in response to individual health care needs. Understanding and trust from health personnel can positively impact the lives of patients with COPD (Leidy and Haase, 1999). Non-supportive health care encounters generated feelings of discredit, self-blame and guilt (Haldine et al., 2010).

The findings suggested that participants felt that they were discharged from hospital care back to their GP because there was nothing more that could be done for them. They also reported that they were often discharged from hospital care if they could not make outpatient appointments. In the literature Seamark, et al. (2004) described the desire for patients to go to clinics but the exhaustion of getting there made it distressing. Some patients in this research study spoke of
negative comments from receptionists when they were unable to make their appointments. In this study the participants were unsure of the benefit of having a nurse visit who was a stranger but for carers it was reassuring. Although the participants did value more frank, open communication and monitoring there was anxiety experienced that GP care would not be as good and would lead to hospital admission. This is similar to the findings of Habraken et al. (2008) where patients were told by physicians that their lungs would only get worse and nothing more could be done.

The participants wanted to have the opportunity to access health care even if they choose not to accept. As previously stated chronic patients may not be re-offered therapy (for example smoking cessation and PR) if they have previously declined. Mann and Stuenkel (2006) suggest that health care professionals should be aware of the problems of stigma and should examine their own values, although they may be difficult to change. The participants wanted knowledge of new treatments and research to optimise their care.

7.5.6 The need for home exercise sessions

“...erm I feel that I should you know which we discussed earlier that I should keep up some of the exercises which I think are important I think that is really about it...” (Neil)

The participants felt the benefit of having an exercise plan at home. They reported that they would benefit from having PR and exercise classes explained to them in full. One participant would have liked knowledge of other groups that meet and alternative exercise groups.

7.6 What did they not say that I had expected them to?

No participant openly expressed that they felt the NIV added a burden to their life. Some participants were ambivalent about the benefit of the device. O₂ has previously been expressed as both a lifeline and a restriction (Elkington et al., 2004). I had wondered if the acceptability of the device would be poor and whether another piece of medical kit in their home would not be viewed positively. However, in this instance the participants were only using NIV for a short period of time and they always knew that the NIV use was temporary. There have been conflicting reports as to whether or not home nocturnal NIV improves the QOL of patients with COPD (McEvoy et al., 2009; Meecham Jones et al., 1995).
Despite the severity of their lung disease not one participant discussed dying. On personal reflection their proximity to death was well known to the researcher from researched statistics and clinical practice. Thus that is why it maybe seemed strange to me as the clinician and researcher that they did not discuss this either formally or informally, however the literature demonstrated a lack of understanding by COPD patients about the severity of disease and eventual death (Sorenson, 2013; Horton et al., 2013). This is potentially because health care professionals do not discuss dying with patients (Lau et al., 2010) and palliative care provision remains inferior to that offered for other pathologies (du Covedic et al., 2012). Perhaps their abstaining from discussing death is not surprising because I did not ask them a direct question concerning it.

7.7 Overall experience

Overall the interviews have provided new knowledge on the acceptability of the research into exercise on NIV in patients with COPD. Existing literature has been further enhanced by in-depth rich finding about the experiences of an under researched group of patients with severe COPD.

It is clear that the participants wanted active treatment. One possible solution is that this should be carried out in tandem with palliative care. Most literature focuses on the lack of palliation and lack of advanced decision making, which can be difficult to initiate in COPD because it is difficult to predict death. A difficulty arises when patients are told that they are dying and then stop being active or stop certain treatments but then do not actually die in the subsequent few months. Then the patient ends up in limbo, receiving neither active nor palliative care.

The participants found being involved in research a positive experience and were keen to have the opportunity to be involved in further research. The participants all found the intervention beneficial. They felt that the NIV relieved breathlessness, allowing them to exercise more and they gained physical and emotional benefits from being involved in the study.
7.8 Summary

The main themes have been presented through the voices of the four participants. Although sometimes the participants’ comments were repetitive it was still important that they were heard and considered under the different themes. This chapter has presented an analysis of the research findings and discussed the main concepts which developed from the themes of the findings. It has addressed the secondary aim of the research project and discussed the experience of the participant. The chapter has also discussed the acceptability of the research and intervention to the participants. The integration of the qualitative synthesis and the qualitative results is presented within the discussion chapter (Chapter 9 Discussion).
Chapter 8 Reflexivity

8.1 Reflexivity: finding the ‘me’ in the research process

This section of the chapter will be written in the first person as it is a direct reflection of the research process. A core part of qualitative research is to embrace reflexivity. Whilst quantitative methods seek to be as objective as possible, qualitative researchers accept that the researcher is an active participant in the research process and shapes methods and analysis (Robson, 2011). Some key researchers (Silverman, 2001) try to identify and separate subjectivity. However, whilst I sought to identify what personal factors may have influenced the research I also chose to embrace them within a reflexive diary, which other qualitative researchers have considered useful, as an account of my relationship with the research process (Banister, 1994).

Reflexivity is the ability to critically reflect on the research process and the individual’s own role as researcher (Maso, 2003; Finlay 2002) and recognises that researchers bring their own emotions, intuitions, values, commitments, perspectives, prejudices and personal agendas to research. This chapter of my reflexivity should allow me to be open about how this has impinged and shaped the research process thus improving the integrity and trustworthiness of this research (Finlay, 2002).

Initially I found the qualitative concept of embracing subjectivity as challenging, possibly because I was so used to reading and reviewing professionally with scientific objectivity. In contrast the process of reflection felt more familiar. Within physiotherapy it is a very common process initiated at undergraduate level, nurtured with compulsory documented continued professional development (CPD) and has become so ingrained in my professional practice that almost all my clinical decisions were reflective. In contrast Finlay and Gough (2003) suggested that reflection is thought after the event, whereas reflexivity is an instant, vigorous, non-stop, consciousness.

For the purpose of this chapter key stages from my reflective diary have been selected and discussed. This is to help the reader understand the importance of my values and beliefs, and how they may have influenced this piece of research.
As part of the qualitative component of my mixed methods design I understood that it was important to use reflexivity to resonate these values and beliefs at all phases of the research process to allow for credibility of my research findings (Pope and Mays, 1999; Wellington and Austin, 1996).

8.2 Separating the self

It is important to understand the many roles that I had and how they may have influenced the research I chose. Within the research I was going to be physiotherapist, researcher and an interviewer. Each of these roles is very different but I questioned how far I would really be able to separate them. I also questioned whether realistically the participants would separate me into three different roles. Additionally to these roles I am a mother and wife and thus my personhood is affected by these influences. Equally would I as a researcher be able to separate the patient, from the participant, from the individual? I decided from the beginning to wear my uniform for all clinical exercise sessions. When I was undertaking outcome measures I wore a white shirt and black trousers. When I carried out the interviews I wore jeans and casual clothes. On reflection I felt this would help me and the patients to differentiate roles, however I was not naive to think that I could filter out the other roles but I thought it may allow the patients to think of me differently for each task.

This section is a snapshot of what makes up my personhood, although, all roles overlap and influence each other. This helped me to clearly see who I was and gave insight into my role in this research.

At the time of the research I had been a respiratory physiotherapist for 10 years. My enjoyment of respiratory physiotherapy came from the problem based assessment and thus appropriate treatment selection. I enjoyed the multidisciplinary team approach and comradery when working with a team. On reflection I recognised that I was a practical person who likes practical solutions to problems. I think this was why it was important for the research to be something relevant and easily slotted into clinical practice. Unlike other colleagues within respiratory care, who focused on treatment for sputum retention, it was always rehabilitation that interested me. In particular the careful clinical balance required when weaning patients from ventilation and progressing rehabilitation.
I considered myself to be quite bossy and I like to lead, again this often influenced my physiotherapy practice. I wondered how this desire to lead may influence my role as interviewer in the research, when I needed to ensure it was the participant’s experience captured and not my own. I was passionate about social injustice. I had a concern for the ‘underdog’ stemming from childhood. My mother recounts stories of how I would always ask her to buy the teddy in the shop no one wanted (for example the bear with no eye). This developed to stray animals and befriending children at school that no one else liked. I was though, unclear as to what was the trigger for this concern, however, this concern extended into my role as a physiotherapist.

On completion of my junior rotations I shunned the desirable outpatient specialty in favour of respiratory care, an area that was considered then as a less desirable speciality. When delving into my thoughts about this, I realised this went further. I did not choose surgical respiratory or ITU but chose the even less desirable Medical care speciality. I did not choose the well-funded and more desirable area of Cystic Fibrosis but patients with COPD. Again I thought of myself as the underdog champion, working with a group of patients with less funding and equipment than other groups and with a stigma of blame related to their smoking. Through this reflective process I can see how my interest in this group came about and how the research question developed. Although it was beneficial to sum up the history behind the research, I was concerned about how my sympathy for this group of patients might have affected the research.

8.3 How I chose the question?

In order to fully appreciate how I would interact with the research process, I needed to be clear as to my subjective investment in the research question (See Chapter 1 Background, section 1.21.1 Personal Perspective). I needed to think about what had influenced my decisions. Why did I consider research into this chosen patient group to be so important and why did I want to do this piece of research?

Maso (2003) suggested that the research question should be personally relevant, provoke passion and initiate a meaningful research endeavour. I spent considerable time reflecting upon these questions. As a result of this reflection, I
concluded that the true research question was actually to confirm if what I was already doing in clinical practice (for example exercising patients with severe COPD on NIV) was actually beneficial to the patient. I was concerned that it may just seem like it is better. I was also aware that junior staff may see me as hypocritical when I questioned them on the evidence behind their treatment, when there was limited information on the treatment I was advocating.

8.4 Reflecting on reflecting

As a physiotherapist I am used to reflecting on my clinical practice in regard to applying evidence as part of my CPD. This is a very structured process often involving models of reflection which I have undertaken since my undergraduate studies, however I had not necessarily reflected on my own personal feelings and influences. Thus initially reflexivity did not come easily to me. Over the research period I kept a reflective diary of my thoughts and feelings. Initially it was quite factual and structured but over the course of the research my notes became more reflective and less descriptive by including my thoughts and feelings not just actions and events. Overall reflexivity seemed to be a skill that was dynamic and changed throughout the research process (Finlay and Gough, 2003). Towards the end of the research period I became aware of reflecting on reflections. The following section details key reflection points within the research period.

8.4.1 Tension between researcher and physiotherapist

Initially, when carrying out the 6MWT I became conscious that I was possibly encouraging the standard care group more than the other two groups. Even though there was a SOP that I was following, I was anxious to not favour the two treatment groups. Then I reflected whether by doing this I was covertly disadvantaging these participants. However by the time the discharge outcome measures were assessed I reflected that my physiotherapy role had taken over. On reflection I realised that the physiotherapist in me wanted each patient to succeed and improve. Again there was the conflict of keeping the researcher collating the outcome measures separate to the physiotherapist wanting improvement. It was interesting to reflect on how I seemed to have two separate roles but yet was one person, although from one diary entry it would seem that I felt there were multiple roles:
25th May 2013

“It would seem that I have 3 different characters that I play one is the researcher keen to extract data and remain aloof, one is the physiotherapist keen for the patient to progress and to do well, one is the concerned empathiser who seeks to comfort and agree with the participants.”

Over the course of the research I was surprised at the success of the completion of questionnaires. There was only one participant who did not automatically give me her diary cards each month and needed prompting. I had reflected on watching the participants complete the questionnaires at hospital discharge and wondered if any of them would continue with such a time consuming task. I reflected on the wisdom of evaluating completion of outcome measures as part of the feasibility aim.

I felt that less bias was introduced by not evaluating any of the questionnaires or ActiCal data until the end of the study. It was only through the 6MWT that I was aware I could possibly see the progress of participants, however it was a month between tests so I could not always remember previous events. Despite my best efforts to reduce bias in the outcome measures, the participants were always keen to tell me how they had fared.

22nd October 2013

“I was feeling pleased today that despite the challenge of keeping the researcher role separate to the physiotherapy role, I really could not remember the distance Neil (pseudonym) had walked at last assessment, thus I was unlikely to influence this result today. However no-one told Neil today that I was keeping my roles distinct and he disclosed full distance measure of last assessment a few seconds before initiation of the assessment. I had forgotten the participants are an added complication when separating the self…”

Additionally I had reflected upon the challenge of using the mixed methods design. As a researcher within the quantitative method I needed to remain objective and
unbiased. However within the qualitative methods my personal involvement was an integral component of analysis.

8.5 Finding my space as an interviewer? A reflection

There was a tension through being clinician, researcher and interviewer. As a physiotherapist I thought I would be quite good at conducting the interviews. I had prided myself as having good communication and felt I was skilled at getting a patient history to create a diagnosis and problem list. However, I am also used to curtailing patients who are poor historians and move away from the facts. Within qualitative methods it is important to be able to let the participants dictate to a certain extent the direction of conversation to ensure that their experience can be truly understood (Braun and Clarke, 2013). With qualitative research there was a need to step outside of physiotherapy or what Braun and Clarke (2013) refer to as cultural membership. This was the ability to put aside my own assumptions.

I wrote in the reflective diary after each interview and during the analysis. I found it useful to make field notes as I interviewed. In the first interview I wrote very little as I engaged in questions and focused on the interview guide. However my ability to reflect within the interview improved with each interview. I also made sure I spent time after each interview reflecting on the environment, the participants and also my immediate reaction to the interview responses.

30th May 2013

“Throughout the interview I found my mind drifting. I was aware that I experienced a conflict between being a non-judgemental NHS physiotherapist, to a judgemental person and to a researcher. For example in my physiotherapy thoughts on the participant still smoking, to a researcher wanting the patients to have found the experience beneficial and also as a person who wanted to offer the participant comfort.”

I also reflected upon times within the interviews when I disagreed with the participant and how this may have shaped the interview. Further to this I even wondered if I even liked the participant. This was even harder for me to express. The professional physiotherapist within me would suggest they were challenging or non-concordant. It was a relief to actually say “I don't like that person” in my
diary after interview. Although, yet again I had to evaluate how my dislike may have shaped the research and interview.

In contrast to this another reflection related to wondering if a patient had given good feedback to try and please me. I recall one participant explaining that she never cancelled a session because she did not want to let me down. My diary reflected on my thoughts that I wondered if I had somehow unintentionally communicated my desire for the research to work and to complete the PhD onto the participants. I debated whether this was something that all patients experienced. That patients felt they had to please health care professionals in return for continued treatment and involvement. Yet again, these thoughts made me change my behaviour as a researcher. I endeavoured further to not knowingly put my own or the research agenda on individuals. I found benefit from discussing with my supervisors my initial reaction to the interviews and immediate reflections on how I undertook them. This de-brief after each interview was really important as it helped me to see how others interpreted the environment and interview content. It helped me to reflect on why I may have thought and reacted as I did. It helped me to identify how my thought processes shaped the rest of the interviews.

All these reflections during the interview were challenging for me in my role as researcher. It was difficult to be able to listen to what was being said by the participant and to also reflect on this to guide further conversation. Braun and Clarke (2013) referred to this as being able to have double consciousness.

I felt that the final interview produced the most in-depth and revealing data. I think this was because of a combination of factors. The final interviewee was an outspoken Bristolian female who enjoyed conversation. Overall the research study had been a positive experience for her and this therefore made conversation flow easily. I knew from discussion with other post graduate students that often the majority of information can come from one key interviewee, the ‘golden participant’ as we referred to them at postgraduate study days. I reflected that I am pretty sure that the fourth interviewee was my golden participant

28th April 2014
“Yippee…That went so well…it works…my research made her better…I think I have some real good nuggets of information…finally I relaxed enough to get the full patient experience”

I was also aware that the better content of the last interview may have been the result of my improved skills as an interviewer. I felt that as I knew it was the final interview I relaxed. I finally heeded the advice of my supervisors to become freer with the interview guide. I became less conscious of time and the need to meet the aims of the research and researcher agenda. I allowed more time for the participant to lead the conversation and to discuss the experience of living with COPD. I also felt that I had learnt from the previous interviews and was able to ask questions at opportune moments and allow for silence when waiting for a response.

8.6 Finding my role as analyser

Braun and Clarke (2006) suggested that the researcher needs to ensure that they have ongoing reflexive discussion with themselves through the process of analysis. Therefore the reflective diary was continued during this process to assist with decisions.

8.6.1 Transcribing

It was at this stage that I decided to give participants names with the same letter, associated with the same age and economic circumstances.

3rd July 2013

“Writing an allocated ID number on top of the transcription seems very cold, objective and too quantitative. I want to still be able to picture the participant and apply a human face to them rather than just a number”

During transcription I became aware of my views on each of the comments said by the interviewee. Especially if it was positive about the study it made me feel happy that the research worked, equally I worried I was potentially dismissing the negative comments. I had to think how this may influence my interpretation of what was said.

Transcribing was a frustrating and slow process the participants often speaking in Bristolian tones making for difficult transcribing. Being a part time researcher it
was difficult to find enough time to immerse myself in the transcription. Initially learning to use the transcription pedal was frustrating. At some low points it did feel like a waste of time especially as some postgraduate peers had outsourced their transcriptions. It was also difficult to ensure the tone and mood was captured throughout. The tedium of transcription has been reported by other authors (Reissman, 1993), however because there were only four interviews I felt that transcription, although tedious, was manageable and essential to allow for full immersion into the data (Braun and Clarke, 2013). As transcription became easier I was able to reflect upon my immediate thoughts as I re-heard the interview. This included reflecting upon my own interaction with the participants. I reflected on the way I had asked questions and meaningful pauses. These all helped me to reflect on how I may have influenced responses and allowed for deeper insight into what a participant may have actually been saying.

8.6.2 Coding

When undertaking the initial coding it was difficult not to focus on specific words but this often meant that the context was lost. Bryman (2001) commented on the importance of keeping the surrounding data to ensure it is meaningful. It was also difficult to not just focus on the aims of the research and feasibility of the intervention. The researcher had to remember to just code as seen initially then move onto what this may mean as part of the production of themes and analysis.

After piecing all the codes together to form themes I was beginning to have a sense of what I felt were the more important ones and also which met the feasibility aim. I tried to distance myself again from the aims of the project to make sure that I had captured the patient experience within the themes. What I may consider an important theme others (including the participants) may not. I also found that the ‘golden participant’ quotes were frequently appearing. I reflected on whether this was because I thought that what she said was valuable or just because her interview was the longest. Braun and Clarke (2006) suggested that coding needs to be thorough and not just from a few key examples. This was challenging when there were only four participants and one talked for much longer than the others.
8.6.3 The findings

This was difficult as I was not sure how this should look. Whilst my primary concern was addressing the aims of the research I also wanted to capture the patient experience. It was difficult as the last interviewee produced the longest data set and so often had the most quotes to use. It was challenging to ensure coded quotations were included from all four interviewees. Another challenge was avoiding too much duplication as often the same piece of data were used for multiple themes. On reflection and discussion with my supervisors I acknowledged that overlap is a natural consequence of being human and thoughts are not distinct from one another. I therefore decided to embrace the repetition and overlap within the findings. Nevertheless there needed to be enough data within the synthesis to evidence the themes. Braun and Clarke (2006) suggested that it is important to avoid repetition but still ensure a full story is explained. The researcher used mind maps to illustrate the separate themes and to break up the chosen quotes. A narrative was used to explain each of the themes.

8.7 The integration of the qualitative findings with the quantitative results

One of my aims of using a mixed methods methodology was to ensure true integration of qualitative and quantitative research methods, however I also wanted to ensure enough detail was given in the thesis to the outcome of each method. There was a lack of evidence in the literature as to how qualitative and quantitative data could be integrated as part of a mixed methods approach (Bryman, 2006; Ivankova, Cresswell and Stick, 2006). Therefore to achieve this both the quantitative results and qualitative analysis were presented separately but they would be discussed together in the overall discussion chapter.

8.8 Conclusion

In this chapter I have focused on my reflective journey encompassing the important attribute of qualitative research in reflexivity. I have reflected on why the research question was chosen, my interaction within the research process from development of the research question, to carrying out the data collection and interviews, and the analysis. By presenting my reflections throughout the
research I hoped to inform the reader of my interaction with the process and improve the credibility of my research findings. The next chapter combines the mixed methods results and discusses them in relation to the aims of the feasibility study.
Chapter 9 Discussion

9.1 Introduction

This chapter reflects on the aims and objectives of the research and how well they were achieved. It discusses how the study met the aim of feasibility (Aim 3 and Aim 4). It discusses the combined quantitative results of the research and briefly compares this with the existing literature on exercising on NIV (Aim 2). It also reflects on the experience of patients with COPD of participating in the research process relating to the acceptability of the trial (Aim 1 and Aim 2). Furthermore it unites the quantitative and qualitative findings from the research. In addition this chapter summarises the main findings of the study and considers the contributions it has made to new knowledge. It evaluates the strengths and limitations of the research and discusses possible alternative methods and direction of future research.

9.2 Research Aim: Feasibility and Acceptability

9.2.1 Recruitment sample

From the mixed methods results it can be concluded that it seemed feasible and acceptable to undertake a RCT exercising participants with severe COPD on NIV. The participants were recruited and retained in the study from baseline assessment to three months following hospital discharge. The research process was acceptable to participants and they commented that they would repeat the experience and recommend it to others. No participants expressed concern regarding randomised allocation and this was not given as a reason for patients not participating. It seems feasible and acceptable to participants to undertake exercise on NIV from hospital to home following an acute admission for an exacerbation of COPD. The participants completed the training course of exercise on NIV and found relief from the sensation of dyspnoea possibly allowing them to train harder and for a longer duration. The sample size obtained for this study (n = 18 split into three groups: n = 7, n = 6, n = 5) is similar to that used in previous studies investigating exercise on NIV with sample numbers ranging from two to twelve participants in the NIV treatment group (Dyer et al., 2011; Borghi Silva et al., 2010; Reuveny et al., 2005; Costes et al., 2003).
Recruitment of patients with COPD into research studies is considered challenging. In a contemporary Cochrane review of NIV for exercise training in COPD six RCTs recruited sample sizes of 18-32 participants (Menadue \textit{et al.}, 2014). When presenting this research at conference (European Respiratory Conference, 2014; BTS Conference-winter 2014) the researcher was commonly asked how it was achievable to recruit and retain participants into this type of study. The possible reasons for successful recruitment were that the present study looked at a specific group of patients post acidosis, who are not routinely picked up by discharge schemes and generally have a longer hospital stay this may have allowed the patients to get used to the NIV device. Another possibility is that often this group is overlooked to take part in research because they are excluded, considered palliative or perhaps it is assumed that they do not want to take part. An alternative view is that feasibility studies in patients with conditions considered as palliative are very important (Hagen \textit{et al.}, 2011). There were 17 SAEs and three deaths that took place during this study thus demonstrating the potential challenges of retaining patients with severe COPD into a RCT.

The successful recruitment may be because it is critical in studies of this type for the patient to have confidence in the researcher. The researcher was a respiratory physiotherapist who may have instilled confidence in the patients, thereby influencing their participation. This research has demonstrated that it is feasible to recruit into and retain participants into this type of study, but because of the small numbers recruited and increased possibility for participants to die a definitive multi-centre trial over a longer recruitment period would be necessary.

This group of patients all had severe lung disease, demonstrated by their lung function results on discharge from hospital. They all had a large number of co-morbidities indicating overall general poor health. All groups presented a poor predicted mortality based on their BODE score. The group would seem to be a good representation of the type of patients seen clinically. There were no significant differences in the characteristics of the groups, which is important because it means that they were broadly homogenous and group differences were unlikely to have affected outcome. There were more LTOT users within the intervention hospital and home exercise on NIV group. This could be indicative of the worsening severity of this group. However O\textsubscript{2} use may be a compounding
factor as discussed in the limitations in section 9.6 Problems and limitations of the research. Therefore the inclusion and documentation of O₂ use in a future study may be important.

9.2.2 Inclusion/exclusion criteria

One of the objectives (objective 5) was for this research to be useful and relevant to clinicians. Often research is explanatory in design evaluating the effectiveness of an intervention in a controlled laboratory environment compared to a pragmatic trial that seeks to test effectiveness of the intervention in the clinical environment (Zwarenstein et al., 2008). Often explanatory trials are only useful within the controlled laboratory conditions in which they were undertaken. Explanatory trial results can be difficult to generalize and apply to clinical practice (Patsopoulos, 2011). An example of this is that most patients with COPD have co-morbidities and are an elderly population. It would be extremely difficult to control for this and exclusions often used in explanatory studies may lead to the study being not representative of the patients seen clinically. The inclusion and exclusion criteria used in this trial seem sensible for a future study. The exclusion criterion surrounding mental capacity represented a challenging decision as to whether this should be reviewed for a future trial. It may have been possible to exercise and train patients with mental capacity issues on NIV but it possibly would have been more time consuming and may not have been possible in the time frame required. Therefore this may need to be considered in a larger RCT because this group is often excluded from research (Parker, Penhale and Stanley, 2010). There were two patients who lived out of area this had not previously been considered when planning the exclusions as it was expected that most of the participants would live within the local Bristol area. Due to the lone researcher and time limitations of the PhD they could not be included in the study. An area inclusion zone would need to be considered in the future RCT. Multi-site research would capture different post code areas.

9.2.3 Access to health care

There was a trend that overall the hospital and home exercise on NIV group accessed less health care than the standard care group. This was demonstrated with medication use, including antibiotics, steroids and existing medication. This group had less access to their GP and number of hospital admissions in-trial and
post-trial. However the length of stay in-trial was greater than standard care, although this was considerably less than standard care in the post-trial admissions. This trend is important as, if replicated in an RCT, it could lead to considerable health benefits for patients and economic benefits for the NHS.

9.2.4 Physiotherapy input

During the hospital admission there was no extra physiotherapy time or treatment sessions needed for the hospital and home exercise group than those offered to the standard care group. Therefore this demonstrates that it is feasible to set up NIV and begin the training with no extra time needed. However the researcher is an experienced specialist in NIV so it is unclear if it would be more time consuming for a less experienced staff member. Most of the home patients experienced 24 sessions of approximately one hour with a senior physiotherapist. This is considerably more than the once a week for six weeks that is often allocated for community physiotherapy caseload, although this extra cost may be worthwhile if the trend for decreased hospital length of stay post trial and decrease in extra medication use is upheld in an RCT. So a rigorous economic analysis within a future RCT is required to assess whether the extra cost required to carry out the intervention is beneficial long term to both the patient but also economically in terms of health and societal costs. It seems feasible to collect the data required to inform, including resource use and the EQ-5D-5L.

9.2.5 Acceptability

Only three participants refused to participate in the trial therefore the suggestion of the research seems acceptable to patients. There were no drop outs of live participants in the trial supporting that the research design is acceptable to patients. The participants in the exercise on NIV in hospital and home group were asked to comment on the research process including intervention and completion of outcome measures and although fatigue was mentioned for both the intervention and completion of outcome measures, no one expressed that they would not take part, or that they did not want to complete the measures and all would recommend the trial to others. The completion of all measures, except the ActiCal, and concordance with all supervised intervention provide strong evidence that the research design and intervention was acceptable to participants.
9.3 Research Aim: Outcome measures and combined results

It seems feasible to carry out the majority of the outcome measures used in the study. All of the patient reported measures were completed. The only data which was incomplete was the ActiCal data. Any challenges and difficulties associated with the collation of this data is discussed later within the limitations. A trend for improvement was demonstrated for the NIV on exercise hospital and home group in 6MWT, LCADL, SGRQ and EQ-5D-5L. Unexpectedly the exercise on NIV in hospital group demonstrated a trend for deterioration in six out of seven of the outcome measures. If the outcomes of this study were replicated in a larger study it could establish that NIV on exercise is an important intervention.

9.3.1 How do the results of the outcome measures compare to the existing literature.

9.3.1a Walking and Activity

The exercise on NIV in hospital and home group improved their mean walking distance by 220m (311% increase) from baseline to month three compared to 4m (8% increase) and 9m (53% increase) in the standard and exercise on NIV in hospital groups respectively. In comparison an updated Cochrane analysis of the 6MWT following a course of PR found a mean treatment effect of 44m from a meta-analysis of 38 studies (McCarthy et al., 2015). Despite there being a clinically important difference in the exercise on NIV in hospital and home group, the final walking distance was less than 334m which is the distance proven to predict an increased risk of death and hospital admission (Polkey et al., 2013). Equally all three groups demonstrated an improvement, which is important because research has suggested that a 30m decline in 6MWT is associated with worsening clinical status (Pinto-plata et al., 2004). The participants in this study were much more deconditioned but still able to achieve a much greater improvement in 6MWT than other studies with greater effects on walking distance than PR, LVRS and AOT (McCarthy et al., 2015; Criner et al., 1999; Leach et al., 1992).

The exercise on NIV in hospital and home group improved from 4,020 steps at month one post discharge to 6,017 by month two but by month three the step count declined. The standard care group had a much lower step count at month
one of 1,009, but this continued to improve to 3,843 at month three. The exercise on NIV in hospital group, whilst beginning with a higher step count at 2,515 than the standard care group, plateaued over the three months. However there was incomplete data from this measure.

The existing literature demonstrated that in patients with COPD who have not undergone PR their daily physical activity levels decrease over time (Donaldson et al., 2005). One study measured step count in men with COPD and concluded that the average step count for mildest lung disease, GOLD 1 was 5856 decreasing to 3707 with the most severe stage of disease, GOLD IV (Moy et al., 2012). The exercise on NIV in hospital and at home in the current study ended their average daily step count at 5843, considerably more than their equal disease severity from the previously mentioned study.

In COPD, a higher daily step count, when objectively measured, has been linked with lower mortality in COPD, independent of lung function. Physical activity was the best predictor of all-cause mortality (Waschki et al., 2011). In this prospective cohort study patients with COPD who survived 48 months had a mean daily step count of 6,424 compared with the patients who did not survive who had a mean daily step count of 3,006. (Waschki et al., 2011).

If the data had been complete it would have been useful to study the energy expenditure of the participants. Energy expenditure is the total amount of calories burnt each day, therefore it is the amount of energy a person needs each day to carry out their activities from breathing to walking (Crouter, Churilla and Bassett, 2006). The ActiCal device may not be the most advanced device for this because it does not address isometric exercise, carrying of loads or hill walking (Spierer et al., 2011). Therefore there may be a cost element to using a device that more accurately measures energy expenditure. The ActiCal was the only incomplete outcome collated therefore in the future RCT it may be necessary to consider an activity questionnaire. This would be low in cost and easily completed, however there is often a low completion rate and recall bias when documenting activity (Lissner et al., 2004). The activity may need to consider lower level activities because of how deconditioned the participants are. A SR of activity assessment in chronic disease including COPD suggested that the LCADL is a useful
assessment of activity for patients completing PR (Williams et al., 2012). This was included in this trial and may be relevant to use in the planned RCT.

9.3.1b QOL questionnaires

There was a trend for an improvement in excess of the MCID (4 units) in the SGRQ in the hospital and home exercise on NIV group. The standard care group also demonstrated an improvement in QOL by 7 units from baseline to month three but this was not as great as the 19 unit improvement found in the exercise on NIV in hospital and home group. The exercise on NIV in hospital group demonstrated a clinical worsening with an increase in score by 6. At discharge after the use of NIV during the hospital stay there was an improvement in total score of 2 units but it did not reach the MCID.

A Cochrane review examining the effect of PR on QOL in patients with COPD found that the mean effect of PR exceeded the MCID of 4 units (McCarthy et al., 2015). The most recent review meta-analysis of 19 studies demonstrated a mean improvement of 7 units in the total SGRQ score in participants who underwent PR (McCarthy et al., 2015). However the improvement in SGRQ differed from the results of the review into the use of NIV for exercise training in COPD, which demonstrated that total scores failed to reach the MCID (Menadue et al., 2014). This may have been because it considered only two studies and there were methodological limitations. A study researching home PR demonstrated a significant improvement in SGRQ total score by 10 units (p < 0.001). Activity improved by 9 units (p < 0.008) and impact scores by 14 units (p < 0.001) and these were also significantly greater than in the control group (Pinto et al., 2014), however symptom scores were not significantly different.

The exercise on NIV in hospital and at home group were the only group to demonstrate a MDC (4 units) in LCADL total score from baseline (mean score 50 units) to three months (41 units). MDC is not the same measure of change as MCID and has limitations because although it may signify statistical significance this is not the same as being clinically meaningful to patients or clinicians. The patients may not be able to perceive the benefit and clinicians may not change their management or treatment dependent on the results of MDC (Crosby,
Kolotkin and Williams, 2003). The exercise on NIV in hospital group demonstrated a worse LCADL score by 10 units. None of the existing studies of exercise on NIV used LCADL as an outcome measure, however a home exercise programme for patients with COPD also demonstrated an improvement in total LCADL score of 3 units. Although that change was significantly different from the control group, it was not a MDC (de Sousa Pinto et al., 2014). Therefore it would seem that this measure of activities of daily living designed for patients with severe COPD detected a greater change in the present study’s exercise on NIV in hospital and home group than other studies, supporting the potential value of the intervention to this patient group (de Sousa Pinto et al., 2014; Garrod et al., 2000)

This study only demonstrated an improved QOL score on the EQ-5D-5L in exercise on NIV in hospital and home group (+ 0.27 utility score). This research is novel as no other studies evaluating exercise on NIV have used the EQ-5D-5L measure. One study reviewing the effects of PR found that QOL decreased at eight and twenty weeks following PR despite improvements in other outcome measures (Egan et al., 2012).

9.3.1c Breathlessness measures

In this research study there was a trend for improvement in MBORG in both the standard care and exercise on NIV in hospital and at home groups from a baseline of 5.57 units (standard care) and 2.50 units (exercise on NIV hospital and home) to month three, 3.25 (standard care) and 2.13 units (exercise on NIV hospital and home). The exercise on NIV in hospital group demonstrated a trend for an increase in MBORG score from a baseline score of 4.3 units to a month three score of 7 units.

Garrod, Paul and Wedzicha (2000) demonstrated that NIV on exercise decreased BORG scores from 6 to 4 units.

A study carried out by Egan et al., (2012) demonstrated a statistical improvement \( p = 0.008 \) in modified MRC dyspnoea score from baseline to week 20 following a course of 7 weeks PR, although when rounded to complete scores there was a small change in score number (week 0 = 2.3 to week 20 = 2.1). However there was no control group for comparison. The researcher could find no other studies
looking at modified MRC as an outcome. Mostly it is used as an inclusion criterion similar to age and lung function.

The numerical breathlessness scores are important but more important are the words used to describe each score. The mean exercise on NIV in hospital and home group rating changed from being ‘too breathless to leave the house or I am breathless on dressing’ to ‘I stop for breath after walking about 100 yards or a few minutes on level ground’ suggesting a very positive improvement.

9.3.2 Summary

It was feasible to collate the majority of the outcome measures (only the ActiCal device had missing data). It was acceptable for participants to complete the questionnaires and diaries, but one of the interviewed participants did feel that they were tiring to complete. Exercise on NIV in hospital and home improved physical objective measures of the 6MWT and activity levels compared to standard care. Exercise on NIV in hospital and home improved patient reported QOL measures. These improvements were supported by the participants' voice in being able to walk further outside of the home, carry out more daily tasks and reports of both physical and emotional benefits following the study.

9.4 What might the findings and results mean?

Overall there was a trend for improvement in the hospital and home exercise group in both patient reported and objective measures. The greatest surprise to the researcher was just how poorly the exercise on NIV in hospital group did compared to the standard care group and the exercise on NIV in hospital and home group. Although there was no statistical difference in baseline characteristics, this group did spend longer on NIV in hospital, suggesting a prolonged recovery from exacerbation.

9.4.1 What may have contributed to this trend for improvement in quantitative results and qualitative findings?

The main symptom expressed at interview was breathlessness. Therefore the intervention possibly relieved breathlessness to allow the participants to exercise. There are a few possible theories as to how it may have achieved this. The literature revealed that NIV may offload respiratory muscles and improve DLH or
change the provision of blood supply to the peripheral limbs allowing exercise at a greater intensity (Aliverti and Macklem, 2008; O'Donnell and Webb, 2008). This research study used higher pressures than previous studies (mean PS = 16 cm H₂O), however this research did not measure diaphragm fatigue or respiratory muscle action. Therefore it is difficult to know whether this was the mechanism for improvement.

Alternatively the increased monitoring the patient received throughout the research process may have contributed to the trend in improvement in outcome measures. The interview findings suggested that the participants found monitoring beneficial. However all participants experienced increased monitoring and access to a health care professional.

Another contributing cause could be a placebo effect from using the ventilator. This trial did not use blinding of participants with the use of a sham device due to the severity of the patients and the researcher had concerns that breathing suboptimal pressures would be detrimental to the participants.

The sample characteristics used may also have influenced the trend for improvement. They were a group with severe COPD. Menadue et al., (2011) reported positive results in patients with more severe lung disease. The timing of the intervention may have provided an opportune moment for rehabilitation. The literature demonstrates success with PR post exacerbation (Puhan et al., 2011).

Additionally selecting sicker patients on NIV had the advantage of spending longer time in hospital allowing for greater adjustment to NIV on discharge. By bridging the intervention from hospital to home it allowed patients to continue with a rehabilitation programme in their own home and avoid the problems of accessing outpatient based rehabilitation.

9.5 Strengths of the study

One strength of this study was that it trialled a new intervention producing novel results. There were no other studies that trained patients with severe COPD following an acidotic exacerbation of COPD requiring hospitalisation and treatment acutely with NIV. There were no other studies that exercised from the acute to community setting over a three month period of time using high ventilator pressures. This study was developed from a clinical idea so has direct relevance
to clinical practice. It was further developed from the existing literature and used the learning points of these previous studies to develop the intervention package. Through the process of developing the clinical question into a research project other clinicians may feel empowered to develop their own clinical questions into research ideas.

A strength specifically related to the study design was that it was a feasibility study. This means that it will help to contribute to the success of a further study. As discussed in Chapter 3 (‘Methodology: Justification’), section 3.7 Justification of change of primary outcome to feasibility it is important that adequate time is given to test that an intervention works as it is supposed to (MRC, 2008). By choosing the research aim of feasibility it means that any parts of the research study which were unclear, or if doubt was cast as to whether or not certain aspects would work, they could be assessed before a more costly larger study was embarked on (Feeley, 2009). However, it is also important that the research and intervention are acceptable to patients and clinicians (Feeley, 2009). The feasibility study design allowed for the researcher to study a difficult to research group, notoriously difficult to recruit into studies, a sick group, across both the acute and community setting.

Another design related strength was the successful execution of a mixed methods study enabling evaluation of both feasibility and acceptability. The usefulness of the qualitative approach was that it also gave a voice to an under researched group of patients with severe COPD. Contributions to the literature of their experience of living with COPD and their involvement in the study have been made. The use of semi-structured interviews allowed for a depth and complexity in the qualitative data gathered. The detail of the easy to follow qualitative method, analysis and reflexivity have added to the evaluation of trustworthiness and rigour throughout the research process.

The quantitative methods produced novel research because it is the first study to use activity as an outcome measure for the intervention of hospital and home exercise on NIV in severe COPD. The limitation of this measure was that the data were incomplete, so future studies would need to consider how they ensure use of activity devices by participants. This is an important outcome measure gaining more use within research and an essential part of a future research study.
The pragmatic study design was a key strength to avoid unnecessary exclusion of participants, using equipment and methods similar to clinical practice. The research took place in realistic clinical settings from the busy medical assessment unit to cluttered homes. This met one of the methodological objectives of producing real world research that is directly relevant to applied settings and clinical practice.

An additional strength of the study is that it investigated a topical area and contributed to developing a research base in NIV, COPD and physiotherapy. Since the study was undertaken, exercising on NIV has been a focus at two key respiratory conferences (ERS conference 2014 and Journees Internationals De Ventilation A Domicile (JIVD) 2015). The research is therefore topical and further knowledge seems keenly desired within the respiratory professions.

**9.6 Problems and limitations of the research**

This feasibility study had a number of challenges and limitations. Despite being a major strength that this study was a feasibility study, it was also a limitation. The small sample means that statistical significance was not able to be demonstrated due to the low statistical power. However there were positive trends in results observed.

One of the areas which proved challenging was in recruitment. It was challenging trying to recruit on a busy medical assessment unit. It was also difficult as often the patients flagged up for potential recruitment died. There was a need to ensure recruitment could take place every day (including at weekends) to maximise the time available to initiate therapy within the hospital environment. Although the total sample used was small, it was not dissimilar to other research studies. This knowledge is useful because it demonstrates to other researchers that it is feasible to recruit patients with severe lung disease into such trials. However it also determines the necessity for a multi-centre RCT. The researcher had two initial refusals to participate in the research, which may have been because of the inexperience of the researcher in recruitment. The timing of recruitment was also different for each participant as they were required to be improving medically and have a stable pH level on ABG. They also had different lengths of hospital stay leading to different lengths of treatment time within the hospital. However methods
to resolve this issue are not immediately apparent in this acutely unwell group. One possible solution could be to have a total time of inclusion in the study or set a number of sessions but this also has limitations. An additional limitation of recruitment is that it only occurred at one hospital site. Therefore it is difficult to predict if the research would be feasible within a different hospital or location.

A further limitation is that the researcher considered behaviour change within the literature retrospectively and the research protocol had already been designed and initiated. This was possibly because at the time of initiating the research idea behaviour change was not commonly considered in clinical physiotherapy practice and unfamiliar to the researcher. Behaviour change techniques have been successfully applied in smoking cessation, managing chronic low back pain and pelvic floor weakness (Hay-Smith, McClurg, Frawly and Dean, 2016; Bartlett, Sheeran and Hawley, 2014; Harman et al., 2014). Therefore behaviour change techniques could be advantageous when using an exercise intervention with patients with COPD.

There were limitations with the method because the study was unblinded, although this is difficult to achieve with a single researcher. This may have meant that bias was introduced into the trial. It is also challenging to issue a sham device in this group as sham devices are poorly researched and may increase the work of breathing in the sham group, affecting outcome. However the researcher did use randomisation to allocate participants to different groups and used sealed envelopes to try to decrease possible bias associated with group allocation. Documented SOPs for measuring the 6MWT ensured equal instructions were issued to the participants independent of group.

Another limitation was that AEs were not reported. This was because the patients were not specifically asked about a checklist of symptoms. The feasibility study was reliant on self-reporting. All of the SAEs were reported as planned and this is further reflected upon in section 9.8. This limitation would be addressed in the future RCT and a specific checklist of AE questions would be asked of all the participants and they would keep a copy for daily/weekly reporting.

One potential confounding factor could have been the use of O$_2$ with NIV. The study by Dreher et al. (2009) demonstrated PaO$_2$ increased by 14.0 ±16.66mm Hg following the walk with NIV and O$_2$ compared to just O$_2$ alone (p < 0.003).
unfortunately there was no NIV alone group, or NIV and double dose O\textsubscript{2} entrained for comparison. Interestingly the distance walked was less with NIV and O\textsubscript{2} (555 ±227m) compared with usual O\textsubscript{2} (619 ±210m) and double dose O\textsubscript{2} (622 ±215m) (p < 0.024). Five of the six participants had LTOT and thus used O\textsubscript{2} entrained to their NIV.

In this current study two of the five participants of the Exercise on NIV in hospital group and three of the five participants in the Standard care group and five of the six participants in the Exercise on NIV in hospital and home group were receiving LTOT. All three participants that died were on LTOT. There was one participant in the exercise on NIV group who did not have O\textsubscript{2} entrained when exercising with NIV but still achieved an improvement in their 6MWT of 179m. None of the participants undertook their 6MWT on NIV so the weight of device could not have reduced the 6MWT distance in this instance (no O\textsubscript{2} users carried their cylinders either). However, whether those on LTOT and thus walking on O\textsubscript{2} were able to walk further because of the O\textsubscript{2} is unknown. The amount of O\textsubscript{2} entrained with NIV may need consideration in a future study. AOT is still an area of current debate (BTS, 2015). As further research is carried out into which patients may benefit from ambulatory AOT this may help inform further studies involving exercising on NIV. Another potential problem is with the inclusion of participants on home NIV. There may be some benefit from using additional nocturnal NIV in patients with hypercapnic COPD. However there were no participants on nocturnal home NIV during this study.

There were difficulties with the collation of outcome measures. When assessing the 6MWT it was difficult to ensure the area was clear of people within the hospital environment. Within the home environment it was difficult to find an area big enough and so often the garden or street was used. This was not ideal in the winter in poor weather conditions. These challenges were very helpful in planning a subsequent trial as they need careful review and planning, given the disease severity of the participants. The outcome measures were time consuming to complete and additional days to exercise days were needed just to complete the outcome measures. These issues have implications for staffing a successful RCT. It was challenging being a part-time researcher and balancing clinical duties with research. A particular challenge was during the trial when the needs of the clinical
service required the research to be undertaken on two consecutive days. This took lots of negotiation to change because it was not acceptable to patients to exercise on two consecutive days because of fatigue.

Another consideration of this trial is that it was sponsored by a commercial company and this may be viewed negatively by other researchers. However because the researcher retained intellectual property of the research data and freedom to publish negative results it should offer balance to the criticism. Furthermore if the equipment and back fill time had not been funded this research would not have been able to occur. The study’s commercial sponsor meant that intellectual property rights had to be negotiated which was time consuming and eroded the recruitment period.

One of the biggest limitations to this study is that it did not include a group just receiving exercise training at home (i.e. it did not compare exercise with exercise on NIV for three months). The findings of Pinto et al.’s (2014) home PR study were similar to this study because they showed an improvement in health status. This may cause conflict as it could be that home exercise is a confounding factor and the participants in this study may have done well just with exercise and not NIV on exercise. However the changes in health status observed by Pinto et al. (2014) were not as great as those observed in the present study (10 units improvement for total SGRQ score compared with 19 units in the current study). However it does suggest a future RCT may benefit from having an exercise at home only arm for comparison.

The aim of this study was feasibility of an RCT and it was not clear at the outset if recruitment would be possible. Initially it was thought there may be value from just exercising the patients on NIV during their time in hospital. Therefore this was one of the researched groups. At the time of the study development of home exercise for COPD was a novel area of research and some of the initial studies were negative. However further research produced more positive results allowing justification for inclusion of a hospital and home exercise group, although the inclusion of another limb would impact upon study recruitment numbers and future research.

With regard to the qualitative methods it would have been insightful to have interviewed all participants from all groups, but the time limitations of being a
single researcher did not allow for this. It would have also been useful to have interviewed on more than one occasion. This would have assisted identification of time points for improvement and captured information from participants who died later in the trial.

On reflection I regret that there was no opportunity to discuss the themes in person with the participants, however the time taken for analysis meant it was completed a considerable time after the last interview which would have made it disjointed. Posting out the themes to participants was less invasive but may have contributed to the lack of response.

9.7 Implications of findings for further research

It is clear there is a need for a multi-centre RCT with a large number of participants comparing exercise to exercise on NIV for three months post discharge. A sample size calculation (Fieller, 2007) for a future definitive trial was made using data collected as part of this feasibility trial. The 6MWT at three months following discharge was chosen as the primary outcome, with a clinically relevant difference of 30m, a SD of 73.25 (the SD of the standard care group at 3 months), alpha = 0.05 and 80% power. Based on three independent groups a prospective sample size of \( n = 127 \) per group would be required. A trial including just two independent groups would need a prospective sample size of \( n = 95 \) per group. This would determine if there is any significant benefit on 6MWT from using NIV on exercise in patients with severe COPD following an acidotic exacerbation resulting in hospitalisation and NIV use. Initially the researcher had wanted to preserve the three group model because of wanting to review any benefit for the current practice of exercising whilst in hospital on NIV but on reflection this finding can be extracted from the discharge outcome measure timing, therefore only two groups are required potentially meaning less research centres are required or a shorter length of trial. There would be no standard care group but on reflection there are multiple studies that look at the morbidity and mortality of this group that could be used as comparison with the future RCT findings. An outline of the research protocol for the proposed RCT is included in section 9.10.
9.8 Implications of findings for clinicians now

Clinically there was a trend for improvement in 6MWT and QOL measures. Sadly two of the participants died in the NIV on exercise in hospital and at home group and one participant in the standard care arm. These SAEs did not occur whilst using the intervention or within three days of an exercise session. They were all formally investigated and the trial was not discontinued. Additionally ten patients died prior to approaching for inclusion into the study. There was also a large number of SAEs. All of this reflects just how unwell this group was and demonstrates a realistic representation of patients with end stage COPD. Therefore in a future trial reporting of SAEs and AEs will be important to fully assess the safety of exercising patients with severe COPD and its use in clinical practice. Examining the data from the two participants who died in the exercise on NIV in hospital and at home group there was a trend for improvement in their 6MWT at their last recorded measure thus suggesting benefit. Therefore a suggestion from this research is that clinicians continue to use NIV as an adjunct for exercise in those who seem to benefit, particularly if this can be continued at home.

9.9 Implications for patients

This study has provided more evidence into the potential benefits of NIV in patients with severe COPD. Therefore it has given patients another choice of intervention. It has given this severe disease group a voice and added to the literature on the experiences of patients with severe COPD. The research has demonstrated that patients with severe COPD wanted to be involved in research and wanted to exercise. This study may influence other researchers to research this sample group. For the participants in the study they were all referred to PR and may now have been able to access this outpatient service.

9.10 Clear vision of the future RCT

This feasibility study has demonstrated the value and possibility for a successful RCT. This intervention was complex because it was involving a complex patient group who are severely unwell, the intervention spans complex organisations (both primary and secondary care) and the intervention had to be adjusted for the
individual in terms of both exercise and ventilation settings (MRC, 2008). This feasibility study has fulfilled MRC complex intervention requirements because it has allowed the researcher to be confident that the intervention can be used as intended. It has allowed for the rates of recruitment and retention to be fully evaluated to enable a sample size calculation to be completed for planning a further RCT (MRC, 2008). The future multi-centre trial research process is presented in Figure 9.1
Figure 9.1 Diagram of the future RCT
9.11 Outline of the future research protocol and justification provided by feasibility study

One of the aims of this feasibility study was to inform a future trial. The researcher has been able to plan an outline of the proposal for a future trial. A full protocol is beyond the scope of this thesis and would need further planning to complete. This outline protocol is based on the WHO (2016) recommended format for a research protocol.

9.11.1a Study Ethics and procedure

Full NHS ethical and R&I permissions will be sought for the trial. The trial will be registered as an RCT. Full ethical and R & I protocol will be followed in line with good research clinical practice including the keeping of a trial portfolio.

9.11.1b Justification

There are no anticipated or unknown ethical issues based on the feasibility study.

9.11.2 Study objective and null hypothesis

9.11.2a Study objective

Do patients walk further when exercised on NIV following a hospital admission with an exacerbation of COPD with uncompensated type II respiratory failure on NIV compared to exercise alone?

9.11.2b Null hypothesis

That there is no difference in outcome in exercising patients with severe COPD following a hospital admission with an exacerbation of COPD with uncompensated type II respiratory failure on NIV to exercise alone.

9.11.3 Study Design

9.11.3a Design

A multi-centre randomised controlled trial.

9.11.3b Justification

This trial is multi-centre to allow for recruitment of a greater sample size. This is because the sample size calculation demonstrated that a sample size of \( n = 95 \)
per group (total sample size n = 190) would be needed to identify a clinically significant difference between groups in the 6MWT as statistically significant. Therefore five centres would need to be involved for a trial period of two years. There would be one group for supervised exercise hospital and home and one group supervised exercise on NIV hospital to home. This would mean 38 participants per centre, at a rate of n = 1.5 participants per month. Additional participants would need to be considered if participants dropped out.

9.11.4 Research Team

Research team required at all 5 centres:

0.25 Full Time Equivalent (FTE) Researcher for screening and consenting

0.5 (FTE) Band 6/7 Physiotherapist for intervention

0.25 (FTE) Band 5/6 Physiotherapist for outcome measure assessment

Research team main centre:

0.5 (FTE) Researcher for data entry and analyser

0.5 (FTE) Health Economist

0.25 (FTE) Statistical Analyser

9.11.4a Justification

This staffing is based upon the feasibility study which identified that different clinicians and researchers blinded to group were needed for undertaking the intervention, outcome measures and data analysis. The Physiotherapy time is derived from the feasibility of one year 0.5 (FTE) Band 7 required to do all the research tasks. The exact cost of the staff required would need to be considered at the timing of grant or commercial funding application as this will be dependent on location of centre and pay inflation. The role of a health economist inclusion into the study has been reflected upon. For the purpose of the proposed study this would be included but cost effectiveness of the intervention would be a secondary outcome.
9.11.5 Equipment

There would need to be 10 NIV devices per centre. This would mean a loan or purchase of 50 NIV devices. These cost £3,500 per NIV device and additionally there are consumables and maintenance. Therefore if purchased the cost of equipment would be £35,000. It would be preferable to seek an agreement for borrow or loan of the ventilators, each NIV device will last from five to eight years to make this a viable option.

9.11.5a Justification

Commercial funding was sought and granted for the feasibility trial. Commercial providers of NIV frequently offer NIV equipment on loan for trials.

9.11.6 Recruitment

9.11.6a Screening

All Patients admitted to hospital following an acute exacerbation of COPD requiring treatment with NIV.

9.11.6b Location

A & E, Assessment Medical Unit and acute respiratory wards of the five acute hospital centres.

9.11.6c Inclusion/exclusion criteria:

Inclusion: All Patients admitted to hospital following an acute exacerbation of COPD requiring treatment with NIV.

1. Exclusion: Primary diagnosis not COPD
2. Not had a respiratory acidosis diagnosed through ABG analysis
3. Not had NIV treatment
4. Under 25 years of age
5. Unable to follow commands or unable to consent
6. Known contraindication to NIV (Royal College of Physicians, 2008)
7. Unable to tolerate acute hospital NIV
8. Unable to or refused to comply with physiotherapy
9. Patients already attending PR
10. Patient home environment unsafe for lone researcher
11. Had an additional pathology that limited ability to mobilise
12. Dying/receiving end of life care and not expected to survive hospital admission
13. Do not live more than one hour from the hospital

9.11.6d Justification

There would be no changes to the inclusion criteria used in the feasibility study. The exclusion criteria would be more detailed and patient unable to or refused to comply will be separated out. There will be three extra exclusion criteria 9, 10 and 13 in regards to PR, home safety and home location.

9.11.7 Outcomes

Primary outcome:

6MWT

Secondary outcomes:

SGRQ for HQOL assessment
EQ5D-5L and economic evaluation
MBORG

ActiCal: Step count, energy expenditure and LCADL

Extra measures

Spirometry will be undertaken at baseline and BODE score calculated at hospital discharge to capture disease severity data. Other baseline data will mirror that obtained in the feasibility data including age, BMI, smoking history, social status, hospital admission history, acute NIV use and LOS. This will ensure that the baseline characteristics are assessed for homogeneity.
9.11.7a Justification

The trial would use 6MWT as the primary outcome because it was easily collated in the feasibility study from the acute to community environment and is meaningful to both clinicians and patients.

Activity is still an important outcome to assess as the impact of NIV on exercise in activity in patients with COPD is unknown. During the feasibility study the ActiCal was the only measure incomplete. Additionally to step count data it may be beneficial to review energy expenditure of the participant when collating the ActiCal data. It would also be beneficial to have an additional activity questionnaire in case there is missing data and the ActiCal is not worn by enough participants. LCADL can present some details about activities but not the amount or quantity. Further discussion and piloting of an activity questionnaire with expert patient groups may be needed to decide upon an activity questionnaire to supplement the ActiCal device.

The other area still undecided upon would be the role of qualitative methods. There is a tension between wanting to fully capture the voice of the participant in their experience of NIV and impact on QOL and balancing this with understanding the financial cost of including interviews in the final study. For the feasibility study it was essential to include qualitative methods to completely understand the acceptability of the trial and to truly understand the participants’ experience of the research. The qualitative findings show that the trial is acceptable and a positive experience to the participants. Therefore in the proposed RCTs skeleton study protocol the interviews have been omitted. The QOL measures assessed should offer insight into participants’ perceived benefits. The qualitative findings suggested that breathlessness is the main symptom that they experienced therefore MBORG is chosen as a secondary outcome. There may be a need to record symptom reported diary information which was successfully collated during the trial and this may be dependent on the health economic requirement of the trial.
9.11.7 Timing

The baseline measurements will be taken in hospital on the ward within 24 hours of consent following stability of cardiovascular system and respiratory acidosis.

The discharge measurements will be taken on morning of discharge on the ward.

The month one, two and three measurements will be taken in the participant’s home at four weeks, eight weeks and twelve weeks following discharge. These will be undertaken at the same time and location for each individual participant.

The outcome measures will not be assessed on the same day as an intervention session. The outcome measures will take between 30-45 minutes to complete. This will allow for rest time following the 6MWT to allow the participants to recover from breathlessness. A standardised SOP for each of the outcome measures will be completed for example 6MWT SOP will be based on Appendix 18.

The order of the assessment of the outcome measures will be:

1. 6MWT
2. SGRQ
3. EQ5D-5L
4. LCADL
5. MBORG

ActiCal monitoring (Is a continuous measure that will be applied at hospital discharge). The ActiCal monitor will be downloaded at the end of the trial. The ventilator data will be downloaded at the end of the trial.

9.11.8 Randomisation and Blinding

Randomisation of participants to groups would be decided prior to the trial starting in sealed envelopes or via a clinical trials unit randomisation service to reduce selection bias. Bias would also be reduced by having a different therapist performing the outcome measures and the interventions. The physiotherapist assessing outcomes would be blinded to how the patients had been randomised. The quantitative analysis would also be carried out by a researcher blinded to group allocation. It is not possible to blind the clinician providing the intervention or the participant as there is no known sham NIV.
9.11.9 Intervention

9.11.9a NIV

NIV using the Trilogy 100 (Philips-Respironics), with a minimum PS target of 16cmH\textsubscript{2}O. Set up will be based on the SOP in Appendix 13.

The circuit will be single limb with a leak valve in the mask. The mask will be full face mask but if a patient is claustrophobic an alternative nasal mask will be considered. No humidifier will be put into the circuit.

\( \text{O}_2 \) will be entrained into the NIV circuit if the patient uses LTOT and if the patient desaturates to <90% \( \text{SpO}_2 \) during exercise.

NIV will be initiated at rest at the PS used during the acute exacerbation unless patient reports unable to tolerate this then it will be decreased by 2cmH\textsubscript{2}O every 5 minutes until patient is able to tolerate. The NIV will then be titrated during exercise in-line with patient feedback, \( \text{SpO}_2 \) <85% and asking the participant the MBORG score. If the MBORG score increases by one unit score on the MBORG scale the pressure is increased by 2cmH\textsubscript{2}O.

9.11.9b Exercise

This will follow PR guidelines (BTS, 2013). This will consist of pedal cycling, walking, step ups and the use of free weights. The same exercise will be undertaken in both groups. The same exercise will be used during the hospital stay and at home. This will be based on the SOP in Appendix 12. MBORG will be used to increase or decrease the exercise intensity in both groups. The exercise will be stopped at a participant’s request, if \( \text{SpO}_2 \) falls below 85% or persisting RR >40 breaths per minute despite upward titration of PS.

9.11.9c Sessions

The sessions will be supervised twice weekly for a maximum of 30 minute of exercise time. No additional sessions will occur in either group. If the participant is admitted to hospital during the trial the training sessions will continue as planned once their condition has stabilised in both cardiovascular observations and resolved respiratory acidosis. No extra sessions will be offered to participants if sessions are missed for any reason.
9.11.9d Justification

The exercise used will be based on the exercise in the feasibility study. Due to the extent of the deconditioned patients recruited the intensity of training suggested by PR guidelines and within the exercise SOP was not initially possible. Therefore further consideration of this is required. To clarify this future work may need to occur on deciding how to progress the patients with very severe COPD to optimised PS on NIV and exercise training duration and intensity. A focus group of professionals who rehabilitate with NIV or rehabilitation patients with very severe COPD would be useful as there is currently no standardised method. Further discussion of clinical criteria of when to stop the exercise session would also be sought.

9.11.10 Safety

9.11.10a SAEs and AEs

The SAEs and AEs will be reported as to the requirements of the individual NHS R & I centres and/or Sponsor. The participants will be individually asked about specific AEs and SAEs at each intervention session and outcome measure assessment. Contact details of the principal researcher at each of the centres will be provided to each of the participants to report any concerns. This will be available for participants for three months after they have completed the trial.

9.11.10b Intervention

The participant will be monitored with pulse oximetry for SpO\textsubscript{2} and HR throughout, RR and MBORG will be evaluated every two minutes and patient feedback obtained. If RR >40 breaths per minute or SpO\textsubscript{2} stays < 85% despite optimising NIV the session will be stopped. The session will be discontinued at the participant’s request. Any NIV equipment failure means the session will be terminated and the NIV equipment replaced prior to the next session and the AE recorded and reported to trial Sponsor.

9.11.10c Justification

A shortcoming of the feasibility trial was that AEs were not routinely sought via a check list. Thus this will be rectified for the RCT. The SAEs will be clearly reported as there were three deaths within the feasibility study and 14 hospital admissions.
These should therefore be fully evaluated to ensure the intervention or unsupported exercise is not the cause. Further discussion at a focus group of experts who rehabilitate patients with very severe COPD would add to the decision making within the protocol for clinical signs/methods to assess the cessation of an exercise session.

9.11.11 Data Analysis

Formal standardised outcome measure data collection sheets will be used at all of the sites, participants will only identifiable on the sheets by their participant number. All forms will be collated at one research site and collated by the research assistant who is blinded to participant group. The forms data will be recorded in Microsoft Excel version 13, selected and exported into SPSS version 20, (IBM: Chicago, Illinois, USA) for statistical analysis. Descriptive statistics will be calculated for the baseline data and outcome measures and the data will be assessed for normal distribution. When the data is normally distributed a one-way ANOVA will be carried out to assess for differences in the data between groups at each time point. Further statistical analysis will be provided by a statistician. All medical and personal information will be treated as confidential. Data will be anonymised as far as possible and as early as possible in the process. Data will be collected and retained in accordance with the Data Protection Act 1998.

9.11.12 Expected outcome

If the results of the study prove that NIV enables participants to exercise and gain benefits enabling them to walk further NIV could prove a useful adjunct to both PR and acute hospital rehabilitation. It may offer an alternative treatment for patients with very severe lung disease who only have palliative treatments available currently.

9.11.13 Dissemination

The aim for the dissemination of the RCT would be to publish the results in the scientific journals of Thorax or European Respiratory Journal. The results will also be fed back to other health care professional at conferences of the British Thoracic Society, European Respiratory Society and Chartered Society of Physiotherapy. The results would be disseminated in written form to any participants who would like to receive a summary of the trial results.
9.14 Conclusion

This chapter has demonstrated how the research aims and objectives were met. It reflected on the feasibility of the research trial, the clinical outcome results and interview synthesis. This chapter has also compared the findings of this study with existing literature. It has united the results of the quantitative and qualitative data. The chapter has discussed the strengths and the limitations of the feasibility study, revisiting alternative methodology and methods that could have been used. It concludes with a protocol outline that could be implemented as the basis of the future RCT.
Chapter 10 Conclusions

10.1 Introduction

This final chapter re-examines the original aims, objectives and research question considering the degree that they have been achieved. It then concludes with implications of the findings for future research and concludes with the contribution to new knowledge the doctoral research has made.

10.2 Revisit the research aims and objectives

This theses has sought to answer these aims:

10.2.1 Aim 1:

To evaluate the acceptability of applying non-invasive ventilation (NIV) during exercise in both the hospital environment and at home to patients with severe COPD who have been hospitalised for an acute exacerbation with acidotic respiratory failure.

The research has successfully achieved this aim by presenting the attrition rates, concordance with outcome measures and qualitative interview data from the participants regarding their experience of the research.

10.2.2 Aim 2:

To gather qualitative data to aid understanding of the patient experience of participation in the intervention arm of the research trial to enhance quantitative acceptability data.

The qualitative research enabled the acceptability of the research intervention to be fully understood through the patient experience. The themes identified from the interview material revealed the intervention to be a positive experience for the exercise on NIV in hospital and home group. Therefore the qualitative information identified that the research and intervention was acceptable to this group. Acceptability is an important component of concordance and thus the feasibility of the research.
10.2.3 Aim 3:

To evaluate the feasibility of a randomised controlled trial design including:

- Ability to complete the design in clinical environment with available resources
- Availability of the participant sample pool
- Recruitment numbers and recruitment time period
- Randomisation process and acceptability
- Participant retention in the trial, dropout rate and reasons

The quantitative results enabled evaluation of the feasibility of the trial design by presenting an evaluation of recruitment and retention in the consort diagram, figure 6.1. The design was evaluated for completion within a clearly described clinical environment, timing required and the available resources documented.

10.2.4 Aim 4:

To evaluate the feasibility of collating and completion of the quantitative outcome measures. To inform a future trial of the potential primary outcome and secondary outcomes. These measures included:

- Six minute walk test (6MWT)
- St George’s respiratory questionnaire (SGRQ)
- European Quality of Life - 5 Dimensions - 5 Levels (EQ-5D-5L): Utility score and visual analogue score
- The London Chest Activity of Daily Living Questionnaire (LADL)
- Modified BORG (MBORG) breathlessness score
- Modified Medical Research Council (MMRC) dyspnoea score
- Activity levels: assessed by ActiCal activity monitor
- Self-reported medication use, access to healthcare and hospital admissions

The feasibility of collation and participant completion of the quantitative outcome measures was evaluated. The NIV on exercise in hospital and home intervention package generated a trend for improvement in the outcome measures with the most obvious improvement seen in the 6MWT, this was
selected as the primary outcome in the outline of the protocol for a future trial. This outcome was used to calculate the sample size required for statistical significance in the future trial.

10.3 Final conclusions

This doctoral research investigated the feasibility of exercising patients with severe COPD on NIV from hospital to home over three months.

This study demonstrated a contribution to new knowledge in this area by demonstrating that it is feasible and acceptable to patients with severe COPD to exercise on NIV. It demonstrated that this can be carried out in both the hospital and home environment. This study demonstrated that this type of study can be recruited into but to achieve sufficient numbers and to ensure reduced bias a multi-centre trial would be required. This study successfully took a mixed-methods approach and successfully balanced the methods with comprehensive integration. This work was important because it demonstrated that patients with severe COPD wanted to be actively treated, including engaging in exercise, and wanted to be involved in research. The trend for improvement in outcome measures and positive experiences expressed by participants at interview strengthen the existing literature on exercise on NIV in patients with COPD. Future research is needed in the form of a multicentre randomised trial to assess whether the findings have any statistical significance, clinical significance and are cost effective.
Reference List


Corner, E. and Garrod, R. (2010). Does the addition of non-invasive ventilation during pulmonary rehabilitation in patients with chronic obstructive pulmonary


Cote, C.G. and Celli, B.R. (1998) In patients with COPD, the 6 minute walking distance is a better predictor of health care utilization than FEV1, blood gases, and dyspnea [abstract]. *European Respiratory Journal*. 383


359


374


Kendrick, A.H. (2014) COPD [lecture to Association for Respiratory Technology and Physiology NIV Course], Holiday Inn, Birmingham. 22 October.


understanding, unanswered questions, and research needs. *Chest.* 134 (Supplement 4), pp 43-56.


391


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422


Appendix

Appendix 1 Literature Review Part B: Excluded studies

<table>
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<th>Reason for exclusion: Review not individual study</th>
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Reason for exclusion: Review not individual study


Reason for exclusion: Not COPD sample


Reason for exclusion: Included in an SR


### Reason for exclusion: Included in an SR


### Reason for exclusion: Not published in English


**Reason for exclusion: Not NIV**


**Reason for exclusion: Nocturnal long term use of NIV**

## Reason for exclusion: Nocturnal long term use of NIV

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## Reason for exclusion: Not exercise

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Appendix 2a Ethical Approval University Hospitals Bristol

Health Research Authority
NRES Committee South West - Central Bristol
Bristol Research Ethics Committee Centre
Whitefriars
Level 3, Block B
Lewin’s Mead
Bristol BS1 2NT
Email: ubh-tr.SouthWest3@nhs.net
Telephone: 0117 342 1335
Facsimile: 0117 342 0445

24 September 2012

Mrs Kathryn AM Buchan
Highly Specialist Respiratory Physiotherapist

Dear Mrs Buchan

Study title: A randomized control trial of non-invasive ventilation during an exercise programme following acute acidic exacerbation of COPD in hospital and follow-up use at home: feasibility of using the Trilogy Ventilator.

REC reference: 12/SW/0228
Protocol number: EAME2011Trilogy01

Thank you for your letter of 03 September 2012, responding to the Committee’s request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a sub-committee of the REC. A list of the sub-committee members is attached.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

A Research Ethics Committee established by the Health Research Authority
Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

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<tr>
<th>Document</th>
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<th>Date</th>
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<td>Evidence of insurance or indemnity</td>
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<td>GP/Consultant Information Sheets</td>
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<td>Investigator CV</td>
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<td>Letter from Sponsor</td>
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<tr>
<td>Other: Clinical Investigation Agreement</td>
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<tr>
<td>Participant Consent Form</td>
<td>2</td>
<td>24 August 2012</td>
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<tr>
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</tr>
<tr>
<td>Response to Request for Further Information</td>
<td></td>
<td>03 September 2012</td>
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</table>

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

A Research Ethics Committee established by the Health Research Authority
After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/SW/0228 Please quote this number on all correspondence.

With the Committee’s best wishes for the success of this project

Yours sincerely

Email: ubh-tr.southwest3@nhs.net

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

Copy to: 

A Research Ethics Committee established by the Health Research Authority

433
NRES Committee South West - Central Bristol

Attendance at Sub-Committee of the REC meeting on 14 September 2012

Committee Members:

<table>
<thead>
<tr>
<th>Name</th>
<th>Profession</th>
<th>Present</th>
<th>Notes</th>
</tr>
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<td></td>
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Also in attendance:

<table>
<thead>
<tr>
<th>Name</th>
<th>Position (or reason for attending)</th>
</tr>
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<tbody>
<tr>
<td>[Redacted]</td>
<td>Coordinator</td>
</tr>
</tbody>
</table>
Appendix 2b Ethical Approval University Hospital Bristol Amendment

18 March 2013

Mrs Kathryn AM Buchan
Highly Specialist Respiratory Physiotherapist

Dear Mrs Buchan

Study title: A randomized control trial of non-invasive ventilation during an exercise programme following acute acidic exacerbation of COPD in hospital and follow-up use at home: feasibility of using the Trilogy Ventilator.

REC reference: 12/SW/0228
Protocol number: EAME2011Trilogy01
Amendment number: 1
Amendment date: 12 February 2013
IRAS project ID: 106328

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation, with the requirement that a Lone Worker Policy is adhered to.

Approved documents
The documents reviewed and approved at the meeting were:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor agreement</td>
<td>email</td>
<td>11 February 2013</td>
</tr>
<tr>
<td>Interview Schedules/Topic Guides</td>
<td>1</td>
<td>11 January 2013</td>
</tr>
<tr>
<td>GP/Consultant Information Sheets</td>
<td>3</td>
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</tr>
<tr>
<td>Participant Consent Form</td>
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<td>15 January 2013</td>
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<td>6</td>
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<tr>
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<td>15 January 2013</td>
</tr>
<tr>
<td>Notice of Substantial Amendment (non-CTIMPs)</td>
<td>1</td>
<td>12 February 2013</td>
</tr>
</tbody>
</table>

A Research Ethics Committee established by the Health Research Authority
Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members’ training days – see details at http://www.hra.nhs.uk/hra-training/

12/SW/0229: Please quote this number on all correspondence

Yours sincerely

pp.
Chair

Copy to:

NRES Committee South West - Central Bristol

Attendance at Sub-Committee of the REC meeting on 28 February 2013

<table>
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<th>Name</th>
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Also in attendance:

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<th>Position (or reason for attending)</th>
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A Research Ethics Committee established by the Health Research Authority
Appendix 2c Ethical Approval University of Western England

Our ref: JW/lt

30th October 2012

Mrs Kathryn AM Buchan
Highly Specialist Respiratory Physiotherapist

Dear Kathryn

Application number: HLS/12/10/104
Application title: A randomized control trial of non-invasive ventilation during an exercise programme following acute acidic exacerbation of COPD in hospital and follow-up use at home: feasibility of using the Trilogy Ventilator
REC reference: 12/SW/0228

Your NHS Ethics application and approval conditions have been considered by the Faculty Research Ethics Committee on behalf of the University. It has been given ethical approval to proceed with the following conditions:

- You comply with the conditions of the NHS Ethics approval.
- You notify the Faculty Research Ethics Committee of any further correspondence with the NHS Ethics Committee.
- You must notify the Faculty Research Ethics Committee in advance if you wish to make any significant amendments to the original application.
- If you have to terminate your research before completion, please inform the Faculty Research Ethics Committee within 14 days, indicating the reasons.
- Please notify the Faculty Research Ethics Committee if there are any serious events or developments in the research that have an ethical dimension.
- Any changes to the study protocol, which have an ethical dimension, will need to be approved by the Faculty Research Ethics Committee. You should send details of any such amendments to the committee with an
explanation of the reason for the proposed changes. Any changes approved by an external research ethics committee must also be communicated to the relevant UWE committee.

- Please note that all information sheets and consent forms should be on UWE headed paper.
- Please be advised that as principal investigator you are responsible for the secure storage and destruction of data at the end of the specified period. A copy of the 'Guidance on Managing Research Records' is enclosed for your information.
- Please note that the University Research Ethics Committee (UREC) is required to monitor and audit the ethical conduct of research involving human participants, data and tissue conducted by academic staff, students and researchers. Your project may be selected for audit from the research projects submitted to and approved by the UREC and its committees.

Please note that your study should not commence at any NHS site until you have obtained final management approval from the R&D department for the relevant NHS care organisation. A copy of the approval letter(s) must be forwarded to Leigh Taylor in line with Research Governance requirements.

We wish you well with your research.

Yours sincerely

Chair
Faculty Research Ethics Committee

c.c. Margaret Fletcher
Appendix 3 Participant Information Sheet

Participant Information Sheet

A randomized control trial of non-invasive ventilation (NIV) during an exercise programme following acute acidotic exacerbation of COPD in hospital and follow-up use at home: feasibility of using the Trilogy Ventilator.

You are being invited to take part in a research study.

We are providing you with this information today so that you may have time to consider whether you wish to participate.

You need to understand why the research is being done and what it involves.

Please feel free to ask any questions or discuss this with your doctor, friends and relatives.
1. Why have I been chosen?
You have been admitted with an exacerbation of COPD which needed treatment with NIV in the ward. If you meet all the inclusion criteria for the study, we will ask you if you wish to participate in the study.

2. What is the purpose of this study?
Chronic Obstructive Pulmonary disease (COPD) is a lung condition which causes frequent infections and flare ups called exacerbations. One of the symptoms of COPD is shortness of breath. This may decrease general activity and can lead to a loss of physical fitness, which may lead to more hospital visits. If you are admitted to hospital, this may be because your breathing has become so bad that the carbon dioxide in your blood rises and the oxygen falls. This can lead to a fall in the acidity of your blood, and so you become acidic, which may make you feel more unwell.

One treatment option for an exacerbation requiring a hospital stay is provided by a device called Non-Invasive ventilation (NIV). This device delivers two pressures via a face mask, one when you breathe in and the other when you breathe out. This helps to reduce the effort of breathing, and allows time for medication to work. It also allows the body to better use the oxygen breathed in and helps faster removal of the carbon dioxide breathed out. Most patients use NIV for a few days during a hospital stay, but a few patients require use of NIV at home after leaving hospital.

The purpose of this study, which is being undertaken as part of a PhD, is to assess a home NIV device for use both in the hospital and at home during exercise in patients who have been admitted with an exacerbation of COPD that has already been treated with NIV. This is a new approach to treating patients and we do not know how well this will work. Current care – known as standard care – does not use NIV in the way in which we are planning to use it in this study.
The NIV device is called a Trilogy, and is smaller and more portable than the one you have been treated with in hospital.

The study wishes to assess the use of the Trilogy NIV device in three groups:
1. Standard care
2. Standard care plus Trilogy, when in hospital
3. Standard care plus Trilogy when in hospital, and then discharged with Trilogy to use at home during exercise

If you agree to participate, you will be randomly allocated to one of the groups – see Section 5 for more detail.

On completion of this study, the Trilogy device will not be available for long-term use, and will therefore be removed.

3. What is the device being tested?

The device being tested is a Philips Respironics Trilogy home NIV device. This device has currently been tested and is used by patients at home to support their breathing when asleep. This device may support your breathing when exercising to allow you to exercise further and for longer. This device has been used to support patients exercising at home but this needs to be further evaluated.

4. Do I have to take part?

No – it is up to you to decide whether or not to take part. You will be given 24 hours to read and keep this information and decide whether you wish to take part. If you wish to take part, then you will be able to speak to one of the study investigators who will go through the study in more detail. You are free to withdraw any time and without giving a reason. This will have no detrimental effect on the standard of your care or treatment and we will respect your decision.

If you do not wish to take part then you will still receive standard care.
5. What will happen to me if I do take part?

After inclusion into the study, you will receive a number allocated at random and be placed into one of the three groups. Sometimes because we do not know which way of treating patients is best, we need to make comparisons. Patients are therefore put into groups, with different treatments and then compared. The groups are –

**Group 1** will receive standard care: an exercise session three times week, with two supervised sessions for 30 minutes on the ward.

**Group 2** will have the same treatment as Group 1, but use the NIV device whilst carrying out the exercise when in the ward.

**Group 3** will have the same treatment as Group 2, but you will carry on with the device and exercise at home for at least three times a week with two supervised sessions for 30 minutes for a three month period after being discharged from hospital.

You, therefore have a one in three chance of being allocated into Group 3. Neither you nor your doctor will decide which Group you are in. You will get all other usual medical and nursing care no matter which group you are in.

**Assessments in the Ward (Groups 1, 2 & 3)**

Basic assessment of your height, weight and age will be recorded.

You will also be asked to complete 3 questionnaires about your

- General Health (EQ-5D)
- Activities (London Chest Activities of Daily Living)
- Symptoms relating to your COPD (St George’s Respiratory Questionnaire).

These three questionnaires will allow us to understand how you feel. These will take about 40 minutes to fill in.

There will be one physical assessment where we will ask you to walk with a frame as far as possible on the ward within a six minute period of time. This is a standard assessment used by the ward physiotherapist that you would have to complete as part of your routine.
You will also be issued with an actical monitor, which records your activity. It is not uncomfortable to wear and is worn with a strap like a watch.

**Pre-Discharge to home**

Just before you are discharged home from the ward, we will ask you to complete the three questionnaires again and undertake the walk test for 6 minutes again.

**Post Discharge**

The questionnaires will be completed a further 3 times once per month either at home or in clinic by the physiotherapist. We will also ask you to keep a diary of your symptoms and any access you may have had to medical treatment or health professionals, such as community nurses, your practice nurses or your GP

**Groups 2 and 3**

If you are allocated to Group 2 or Group 3, then you will be asked to undertake exercise in the ward using the Trilogy NIV device. On each occasion, that you are exercised, you will be asked to wear the nasal/face mask attached to the Trilogy. The Trilogy will provide to you a pressure during breathing in, similar to that when you were on the ward ventilator just after admission. This will assist your breathing during each exercise period you undertake.

**Group 3**

If you are in Group 3, you will be given the Trilogy device to take home and whenever you undertake a period of exercise training, you will be asked to use the Trilogy to assist your breathing during exercise.

At the end of the study Group 3 members will be asked to tell us about their experiences of using the Trilogy device. The researcher will arrange to interview you either by phone or by visiting you at a place and time convenient to you. The interview will take about 35 – 45 minutes. The interview will be audio recorded and notes taken so we can be sure that what you say is remembered accurately. It is important we know about both good and less good experiences. You can ask to stop the recording and interview at any time.

**Will my taking part in the interviews be kept confidential?**

Patient Information Sheet v6:15-01-13
Yes. We will follow ethical and legal practice and all information collected from you will be treated confidentially. Your name will not be linked to anything you say, a number code will be used and any other names we mention removed so that no one can be recognised from any reports of the study. Every attempt will be made to safeguard your confidentiality, but in the unlikely event of you sharing something which we believe impacts on your health and safety, we may have a duty to act on it. This would not be done without your knowledge.

**What will happen after the Interview?**

After the interview, the audio recording will be typed up word-for-word. The interviews from all the members of group 3 will be analysed and the main themes identified. You will be given the chance to read a copy of these topics, to check that we have understood your answers correctly. What we find will be published in a written report.

6. Expenses and payments?

All visits will be made to you at home, unless you have a booked outpatient appointment at the Bristol Royal Infirmary, to see one of the medical team. You should therefore incur no costs of participating in this study.

The exception is patients in group 3, who will be using the NIV device at home. On discharge, the batteries will be fully charged giving about 4 hours of use. You will be asked to ensure that the battery remains fully charged, so after each exercise session, you will need to plug the device back into the mains.

7. What else do I have to do?

You should carry on with taking all your medication as prescribed and carry on with your normal daily routine when back at home.

8. What are the possible benefits of taking part?

The exercise achieved whilst using NIV may mean that your muscles will become more developed allowing for further general activity. If your general activity levels and fitness levels increase you may have less infections, exacerbations and therefore less hospital admissions.

It is hoped that the information that we get from the group 3 interviews will help us plan how we help patients use this device and others like it in the future.

---

Patient Information Sheet v6.15-01-13
9. What are the possible risks of taking part?

This study is non-invasive, and will be conducted initially in hospital. There are believed to be no significant risks. The following risks are the same for any patient receiving NIV and but these are not that common and can be relatively easily solved –

- Conjunctivitis – reddening and soreness of the eyes
- Skin abrasions due to non-invasive interfaces
- Gastric distension – bloated feeling in the stomach

More uncommon effects, which if they occur need to be reported to the study team as soon as possible include

- Nasal passage irritation or dryness
- Irritation of the eyes
- Headaches
- Upper airway contamination
- Re-breathing of expired air if the mask is worn and the unit is not powered up
- A reduction in blood pressure
- Lung collapse. The occurrence of this is considered a very serious adverse device effect, but would be rare in patients who have already received NIV in hospital without experiencing this.

10. What are the possible disadvantages and risks of taking part?

There will be a delay until the end of the study before you can take part in pulmonary rehabilitation (PR) classes. These are classes containing supervised exercise and advice about managing your COPD provided in the community. Although you will be referred as is standard practice at hospital discharge. The disadvantage of this is you may be more likely to lose physical fitness and therefore be at an increased risk of exacerbation whilst waiting for pulmonary rehabilitation. This is a recognized risk in all patients who do not, or are unable to attend PR classes.

At the end of the study, and if you are allocated to Group 3, you will not be able to keep the Trilogy NIV device.

If you are allocated to group 3 it is hoped that taking part in the interview will not be stressful or difficult for you. It is up to you exactly what you choose to say. However, if you find the interview
difficult it can be stopped straight away or we can pause for a while.

11. **What if I experience a problem?**
Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. In the first instance you should contact the investigators. If you do not wish to speak to the Investigators, the hospital Patient Advice and Liaison Service (PALS) liaison officers can be contacted on 0117 342 3705 or via email at pals@uhbristol.nhs.uk and may be able to help and liaise between you and the Investigators.
If you wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

12. **What will happen if I do not want to carry on with the study?**
Any data collected on you, up to the point of withdrawal will be destroyed. This will have no detrimental effect on any further care you receive. You will be referred on to pulmonary rehabilitation as planned.

13. **What if new information becomes available?**
Sometimes during the course of a research project, new information becomes available about the device that is being studied. If this happens, your researcher will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form. Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. She will explain the reasons and arrange for your care to continue.

14. **Will taking part in the study be kept confidential?**
All the information about your participation in this study will be kept confidential. All information collected from you during this research study will be kept strictly confidential. All data will be coded at the time of entry into the study so you cannot be recognized from it. The researchers at Bristol Royal Infirmary and Philips-Respironics will have access to the
raw data from your questionnaires, interviews and walking tests, which will be used to analyze the results of the study and to present data at meetings. No individual patients will be identified by name etc.

No information from this study will be passed onto any third party, including your own GP, unless written consent is obtained from you first.

15. What will happen to the results of the research study?
The results may be published in scientific journals and presented at conferences. Individuals will not be identified in any report/publication.

16. Who is funding the study?
The study is funded from Philips Respironics UK who are funding the salary of the researcher and providing the equipment for this study.

17. Who has reviewed this study?
This study has been reviewed by the South West–Central Bristol Research Ethics Committee and has received a favourable response for conduct of this research.

18. Contact Details
You may contact the two principal investigators – Katy Buchan or Adrian Kendrick - about this study if you would like any further information. If during taking part in this study, you have any concerns or you have an adverse reaction, please similarly contact the investigators –

<table>
<thead>
<tr>
<th>Email:</th>
<th><a href="mailto:Katv.buchan@UHBristol.nhs.uk">Katv.buchan@UHBristol.nhs.uk</a></th>
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<tbody>
<tr>
<td>Tel:</td>
<td></td>
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<tr>
<td>Bleep:</td>
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</tr>
<tr>
<td>Emergency:</td>
<td>You need to state that it is to do with the NIV study otherwise the switchboard will not contact us</td>
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*Thank you for taking the time to read this information sheet and considering whether to take part in this research.*
**Appendix 4 Consent to study form**

**CONSENT FORM**

**Patient Identification Number for this trial:**

**Title of Project:** A randomized control trial of non-invasive ventilation (NIV) during an exercise programme following acute acidotic exacerbation of COPD in hospital and follow-up use at home: feasibility of using the Trilogy Ventilator.

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<tr>
<td>1.</td>
<td>I confirm that I have read and understand the subject information sheet dated 15/01/13; version 6 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.</td>
</tr>
<tr>
<td>2.</td>
<td>I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.</td>
</tr>
<tr>
<td>3.</td>
<td>I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by the researchers responsible for this study. I give permission for these individuals to have access to my records.</td>
</tr>
<tr>
<td>4.</td>
<td>I understand that I may be interviewed and that this will be audio-recorded. I give permission to be interviewed, audio-recorded and give permission for these individuals to have access to the interview dialogue.</td>
</tr>
<tr>
<td>5.</td>
<td>I agree to my General Practitioner being informed of my participation in this study</td>
</tr>
<tr>
<td>6.</td>
<td>I agree to a delay in commencing Pulmonary Rehabilitation until completion of this study in 3 months’ time, and that the Pulmonary Rehabilitation service has been informed of this. In agreeing to this delay, I understand that I may have a further exacerbation of my COPD during this 3 month period.</td>
</tr>
</tbody>
</table>

Consent Form – NIV Study; v4. 15-01-13
7. I agree to take part in this study

Name of Patient   Date   Signature

Researcher   Date   Signature

When completed, 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical notes
NHS Permission for Research has been granted for the study detailed below at University Hospitals Bristol NHS Foundation Trust (UHBr). Permission is subject to any conditions and is effective from 24.01.13 until 16.03.14.

Dear Katy

RE: The application of Non-Invasive Ventilation during Pulmonary Rehabilitation in patients with Chronic Obstructive Pulmonary Disease (COPD). EAME2011 Trilogy01

R&D No: ME/2011/3913

NHS permission for the above research has been granted on the basis of the application submitted and a favourable opinion from an authorised REC.

Permission is granted on the understanding that the study is conducted in accordance with the Research Governance Framework, Good Clinical Practice, and NHS Trust policies and procedures available at http://www.uhbristol.nhs.uk/research-innovation/are-you-a-researcher/information-for-researchers/post-approval/

It is also a condition of NHS Permission at this site that local recruitment data is uploaded to the EDGE system and the study record is kept up-to-date. Please contact the Research Management Office if you are unsure how to do this.

The following conditions must be met prior to recruitment commencing:

- A site file is set-up and delegation log established

UHBr is required to monitor research to ensure compliance with the Research Governance Framework and other legal and regulatory requirements. For further details about monitoring arrangements please contact the Research Management Office. The Research Management Office will monitor recruitment on an on-going basis and can provide support and advice if you are experiencing problems in meeting your targets within the agreed time frame.
Page 2
Mrs Kathryn Buchan
24th January 2013

The Research Management Office should be notified of any urgent safety measure taken in order to protect research participants against any immediate hazard to their health or safety. This should be within the same time frame as notification to the REC and any other regulatory bodies and should include the reasons why the measures were taken and any plan for further action.

NHS indemnity is provided for the period of permission given above. Requests for changes to the period of permission (eg an extension of the study) must be made to the Research Management Office before permission ceases with an explanation as to why the change is being sought.

All amendments (including changes to the local research team) need to be submitted in accordance with regulatory and national requirements which can be found on IRAS. The Research Management Office also needs to be notified if there are any changes to the study status.

We wish you every success with this study.

Yours sincerely

[Signature]

Acting Head of Research and Innovation/Deputy Director of Research

Copy to:

[Signature]
Appendix 6 Intellectual property contract

CLINICAL INVESTIGATION AGREEMENT FOR MEDICAL TECHNOLOGY INDUSTRY
SPONSORED RESEARCH IN NHS HOSPITALS

The application of Non-Invasive Ventilation during Pulmonary Rehabilitation in
patients with Chronic Obstructive Pulmonary Disease (COPD).
EAME2011Trilogy01

This agreement dated ........................................

is between

University Hospitals Bristol NHS FOUNDATION TRUST,
Trust Headquarters, Marlborough Street, Bristol, BS1 3NU
(Hereinafter known as the “Trust”)

AND

Respironics International, Inc., a Philips Healthcare company which is registered in Delaware
with company number 2931132 and whose registered office is at c/o Corporation Service
Company, 2711 Centerville Road, Suite 400, Wilmington, Delaware 19808 (“Philips”);

WHEREAS Philips has appointed its Associated Company, Respironics UK (a business of
Philips Electronics UK Limited, a company registered in England with company number
446897 and whose registered office is at Philips Centre, Guildford Business Park, Guildford,
Surrey GU2 8XH) in the United Kingdom as its representative in respect of this Agreement;
accordingly, references to Philips shall be deemed to include Respironics UK.

(Hereinafter known as the “Sponsor”)

NOW

WHEREAS the Sponsor is a medical technology company involved in the research,
development, manufacture and sale of medical devices for use in humans

WHEREAS the Sponsor is developing new devices, treatments and interventions in the field
of Chronic Obstructive Pulmonary Disease

WHEREAS the Trust is concerned with the diagnosis, treatment and prevention of disease
and clinical research for the improvement of healthcare

WHEREAS the Trust has a particular interest and expertise in Respiratory Medicine

WHEREAS the Sponsor wishes to contract with the Trust to undertake a sponsored clinical
investigation entitled: “The application of Non-Invasive Ventilation during Pulmonary
Rehabilitation in patients with Chronic Obstructive Pulmonary Disease (COPD)* Clinical Investigation Plan EAME2011Trilogy01

It is agreed that the Trust and Sponsor shall participate in the aforementioned clinical investigation in accordance with this Agreement.

1. DEFINITIONS

1.1 The following words and phrases have the following meanings:

“Affiliate” means any business entity which controls, is controlled by, or is under the common control with the Sponsor. For the purposes of this definition, a business entity shall be deemed to control another business entity if it owns, directly or indirectly, in excess of 50% of the voting interest in such business entity or the power to direct the management of such business entity.

“Agent” shall include, but shall not be limited to, any person providing services to a Party under a contract for services or otherwise.

“Agreement” means this agreement comprising its clauses, schedules and any appendices attached to it.

“Auditor” means a person being a representative of the Sponsor who is authorised to carry out a systematic review and independent examination of Clinical Investigation related activities and documents to determine whether the evaluated Clinical Investigation related activities were conducted, and the data were recorded, analysed and accurately reported according to the Clinical Investigation Plan, the Sponsor’s Standard Operating Procedures, EN ISO 14155 or ICH GCP and the applicable regulatory requirements.


“Clinical Investigation” means the investigation to be conducted at the Investigation Site in accordance with the Clinical Investigation Plan numbered EAME2011Trilogy01.

“Clinical Investigation Completion Date” means the date that the final Clinical Investigation Subject was examined or received an intervention for the purposes of collection of data for the primary outcome.

“Clinical Investigation Plan” means the document (a copy of which is at Appendix 1 and signed by the Investigator) that states the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the Clinical Investigation and all amendments thereto as the Parties may from time to time agree in accordance with clauses 4.9, 10.2 and 14.2 and which have also been signed by the Investigator. Such amendments will be signed by the Parties and form a part of this Agreement.

“Clinical Investigation Subject” means a person recruited to participate in the Clinical Investigation.

“Confidential Information” means any and all information, data and material of any nature belonging to the Trust or to the Sponsor and/or its Affiliates which either Party may receive or obtain in connection with this Agreement which is
Personal Data or Sensitive Personal Data (as both terms are defined in the Data Protection Act 1998) which relates to any patient of the Trust or his or her treatment or medical history, or other information, the release of which is likely to prejudice the commercial interests of the Trust or the Sponsor respectively, or which is a trade secret, including Know How.

“CRF” means Case Report Form.


“ICH GCP” means the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95).

“IDE” means the Investigational Device Exemption application process by which the United States Food and Drug Administration exempts medical device companies from the Federal statute that prohibits an unapproved device from being shipped in interstate commerce.

“Inspector” means a person, acting on behalf of a Regulatory Authority, who conducts an official review of documents, facilities, records and any other resources that are deemed by the Regulatory Authority to be related to the Clinical Investigation and that may be located at the Investigation Site.

“Instructions for Use” means the information provided by the manufacturer to inform the device user of the product’s proper use and of any precautions to be taken.

“Intellectual Property Rights” means patents, trade marks, trade names, service marks, domain names copyrights, moral rights, rights in and to databases (including rights to prevent the extraction or reutilisation of information from a database), design rights, topography rights and all rights or forms of protection of a similar nature or having equivalent or the similar effect to any of them which may subsist anywhere in the world, whether or not any of them are registered and including applications for registration of any of them.

“Investigation Monitor” means a person appointed by the Sponsor responsible for ensuring the Investigator’s compliance with the Clinical Investigation Plan and for reporting to the Sponsor on the progress of the Clinical Investigation.

“Investigation Site(s)” means any premises approved by the Trust in which the Clinical Investigation will be conducted.

“Investigation Site Team Members” means the persons who will undertake the conduct of the Clinical Investigation at the Investigation Site on behalf of the NHS Trust under the supervision of the Investigator.

“Investigational Medical Device” means the CE marked or non-CE marked study device(s) or control material(s) identified in the Clinical Investigation Plan.

“Investigator” means Dr Adrian Kendrick who shall take primary responsibility for the conduct of the Clinical Investigation at the Investigation Site on behalf of the Trust or any other person as may be agreed from time to time between the Parties as a replacement.

“Know How” means all technical and other information which is not in the public domain (other than as a result of a breach of confidence), including but not limited to information comprising or relating to concepts, discoveries, data,
designs, formulae, ideas, inventions, methods, models, software, procedures, designs for experiments and tests and results of experimentation and testing, processes, specifications and techniques, laboratory records, clinical data, manufacturing data and information contained in submissions to regulatory authorities, whether or not protected by Intellectual Property Rights or any applications for such rights.

"Non-CE Marked" means not bearing a CE Mark for the intended purpose of the medical device for the purposes of the Clinical Investigation.

"Non-regulated Clinical Investigation" means a Clinical Investigation where the Investigational Medical Device is being used for the purpose for which it was CE marked and therefore the Clinical Investigation is not subject to regulatory approval under the Medical Device Regulations 2002. This includes postmarketing clinical studies.

"Party" means the Sponsor, or the Trust and "Parties" shall mean both of them.

"Regulated Clinical Investigation" means a Clinical Investigation where an Investigational Medical Device that is not CE Marked, or a CE Marked medical device being used for a new intended purpose, is being investigated following regulatory approval under the requirements of the Medical Devices Regulations 2002.

"Regulatory Authority" includes, but is not limited to, the Medicines and Healthcare products Regulatory Agency, Notified Bodies, as defined in the Medical Devices Regulations 2002, the U.S. Food and Drug Administration, Japan Ministry of Health, Labour and Welfare, and the General Medical Council.

"R&D Office" means the Trust department responsible for the administration of this Clinical Investigation on behalf of the Trust.

"Site File" means the file maintained by the Investigator containing the documentation specified in EN ISO 14155 or ICH GCP.

"Sponsor" means the medical technology company that is a signatory to this Agreement.

"Substantial Amendment" means an amendment to the terms of the Clinical Investigation Plan that requires approval by the Research Ethics Committee or is likely to significantly affect the obligations of the Parties in respect of the safety, conduct or management or costs of the Clinical Investigation.

"Timelines" means the dates set out in Appendix 2 hereto as may be amended by agreement between the Parties and Timeline shall mean any one of such dates.

"Trust" means the University Hospitals Bristol NHS FOUNDATION TRUST that is a signatory to this Agreement.

1.2 Any reference to a statutory provision, code or guidance shall be deemed to include reference to any subsequent modification or re-enactment of it.

1.3 The headings to clauses are inserted for convenience only and shall not affect the interpretation or construction of this Agreement.

1.4 Where appropriate, words denoting the singular shall include the plural and vice versa and words denoting any gender shall include all genders.

2. INVESTIGATOR AND INVESTIGATION SITE TEAM MEMBERS
2.1 The Trust represents that it is entitled to procure and the Trust will procure the services of Dr Adrian Kendrick to act as Investigator and shall ensure the performance of the obligations of the Investigator set out in Appendix 6 and elsewhere in this Agreement. Where the Trust is not the Investigator’s principal employer, it will notify the principal employer in a timely way of his proposed involvement in the Clinical Investigation. Any financial or other arrangements relating to his involvement in the Clinical Investigation will be agreed directly between the Trust and the principal employer.

2.2 The Trust represents that the Investigator holds the necessary registration and has the necessary expertise, time and resources to perform the Clinical Investigation and will ensure that the Investigator is made aware of and acknowledges the obligations applicable to the Investigator set out in Appendix 6 and elsewhere in this Agreement.

2.3 The Trust shall notify the Sponsor if the Investigator ceases to be employed by or be associated with the Trust or is otherwise unavailable to continue as Investigator, and shall use all reasonable endeavours to find a replacement acceptable to both the Sponsor and the Trust, subject to the Trust’s overriding obligations in relation to Clinical Investigation Subjects and individual patient care. If no mutually acceptable replacement can be found the Sponsor may terminate this Agreement pursuant to clause 12.3 below.

2.4 The Trust shall procure and shall ensure that the Investigator procures the performance of the obligations of the Investigation Site Team Members as set out in this Agreement.

3. CLINICAL INVESTIGATION GOVERNANCE

3.1 The Sponsor shall inform the Trust and the Investigator of the name and telephone number of the Investigation Monitor and the name of the person who will be available as a point of contact.

3.2 The Parties shall comply with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws and statutes of England including but not limited to, the Human Rights Act 1998, the Data Protection Act 1998, the Medical Devices Regulations 2002 and with all relevant guidance relating to medical devices and clinical investigations from time to time in force including, but not limited to, EN ISO 14155 or ICH GCP, the World Medical Association Declaration of Helsinki entitled ‘Ethical Principles for Medical Research Involving Human Subjects’ (1996 version), the NHS Research Governance Framework for Health and Social Care (version 2, April 2005). In addition, where the Clinical Investigation is conducted as part of an IDE, the Trust shall comply with any other relevant requirements notified by the Sponsor to the Trust.

3.3 The Sponsor shall comply with all guidelines from time to time in force and published by The Association of British Healthcare Industries in relation to clinical investigations and in particular those entitled “Clinical Investigation Compensation Guidelines” (1995) a copy of which is set out in Appendix 3.

3.4 The Sponsor shall not commit (and warrants that in entering into the Agreement it has not committed) any of the following acts:

3.4.1 provide or offer to provide to any person in the employment of or in the service of the Trust any gift or consideration not contemplated by the financial arrangements set out at clause 10 below in relation to the
negotiation or performance of this Agreement or the Clinical Investigation;

3.4.2 make payment or agree to make payment of any commission to any person in the employment of or in the service of the Trust in relation to this Agreement or the Clinical Investigation.

3.5 If the Sponsor or any of its employees, Agents or sub-contractors, or any person acting on their behalf, commits any of the acts referred to in clause 3.4 above or commits any offence under the Bribery Act 2010, in relation to this Agreement or the Clinical Investigation, the Trust shall be entitled, acting reasonably, in addition to any other remedy available, to terminate this Agreement with immediate effect, taking into consideration the potential effects of termination on the health of the Clinical Investigation Subjects. If the Sponsor or any of his employees, Agents or sub-contractors, or any person acting on their behalf, commits any offence under the Bribery Act 2010, in relation to any other agreement with the Trust or an authority that is a health service body within the meaning given by Section 9(4) of the National Health Service and Community Care Act 1990 and S 65 (1) of the National Health Service Act 2006, the Trust shall be entitled, acting reasonably, in addition to any other remedy available, to terminate this Agreement with immediate effect, provided that before so doing, the Trust shall have considered all of the circumstances of the case in consultation with the Sponsor and shall, in particular, have considered the potential effects of termination on the health of the Clinical Investigation Subjects.

3.6 Should there be any inconsistency between the Clinical Investigation Plan and the other terms of this Agreement, or any other document incorporated therein, including the Sponsor's Standard Operating Procedures, the terms of the Clinical Investigation Plan shall prevail to the extent of such inconsistency except as if the inconsistency relates to clauses 5, 6, 8 and/or 9 of this Agreement.

4. OBLIGATIONS OF THE PARTIES AND THE INVESTIGATOR

4.1 The Trust shall procure that the Investigator obtain and maintain all favourable opinions from the relevant research ethics committee where required for the conduct of the Clinical Investigation and that he keep the Sponsor and the R&D Office fully apprised of the progress of any ethics committee submissions and shall upon request provide the Sponsor and the R&D Office with all correspondence relating to such submissions. No change in the Clinical Investigation Plan requested by a relevant ethics committee without the prior written consent of the Sponsor shall have any force or effect whether consented to by the Trust, the Investigator, or any other person.

4.2 Subject to clause 4.3, to satisfy public interest in the open registration of information concerning Clinical Investigations involving NHS patients and facilities, the Sponsor shall submit the Clinical Investigation for listing in a free, publicly accessible clinical trial registry within 21 days of initiation of patient enrolment.

4.3 Deferred registration

If, having considered all the circumstances, the Sponsor is of the view that the public interest benefits of registering the Clinical Investigation on the timescale specified in clause 4.2 are outweighed by the harm that registration at that time might do to the commercial value of the Investigational Medical Device or the commercial interests of the Sponsor, registration of the Clinical Investigation may
be deferred as follows:

4.3.1 Regulated Clinical Investigation

The Sponsor may defer registration until 30 days after the date that the Investigational Medical Device is CE Marked for the intended purpose being investigated. In the event that the Sponsor decides not to CE Mark the Investigational Medical Device for the intended purpose being investigated, the Sponsor may defer registration for up to 24 months after the Completion Date. The Clinical Investigation shall also be registered within 21 days of a decision to close the Clinical Investigation on safety grounds. In any event, the Sponsor shall register the Clinical Investigation within 36 months of the date scheduled for resolution of all CRF queries set out in Appendix 2.

4.3.2 Non-regulated Clinical Investigation

In the case of a Non-regulated Clinical Investigation, the Sponsor may defer registration for up to 12 months after the Clinical Investigation Completion Date. In any event, the Sponsor shall register the Clinical Investigation within 18 months of the date scheduled for resolution of all CRF queries set out in Appendix 2.

4.4 In addition to any publications in learned journals relating to the Clinical Investigation, as set out at clause 8 below, to satisfy public interest in the results of Clinical Investigations involving NHS patients and facilities, the Sponsor shall ensure that the analysis of the results of the Clinical Investigation are published on a free, publicly accessible clinical trial results database as follows:

4.4.1 Regulated Clinical Investigation

The Sponsor shall publish the analysis of the results within 30 days of CE Marking for the intended purpose being investigated. In respect of a Clinical Investigation that is under review by peer-reviewed journals that prohibit disclosure of results pre-publication, the analysis of the results shall be posted at the time of publication.

Following analysis of data from the Clinical Investigation, in the event that the Sponsor decides not to CE Mark the Investigational Medical Device for the intended purpose being investigated, the Sponsor shall publish the analysis of the results within 24 months of the Clinical Investigation Completion Date. In the case of Clinical Investigations closed on safety grounds, the Sponsor shall publish the analysis of the results within 12 months of the date of closure. In any event, the analysis of the results of the Clinical Investigation shall be posted within 36 months of the date scheduled for resolution of all CRF queries set out in Appendix 2.

4.4.2 Non-regulated Clinical Investigation

The Sponsor shall publish the analysis of the results of the Clinical Investigation within 12 months of the Clinical Investigation Completion Date. In any event, Sponsor shall publish the analysis of the results of the Clinical Investigation within 18 months of the date scheduled for resolution of all CRF queries set out in Appendix 2.

4.5 The Trust shall not, and shall procure that the Investigator shall not, register
either the Clinical Investigation or the results on any publicly accessible clinical trial registry or results database.

4.6 The Parties shall conduct the Clinical Investigation in accordance with:

4.6.1 the Clinical Investigation Plan, a copy of which is attached at Appendix 1 to this Agreement;

4.6.2 the manufacturer’s recommended Instructions for Use for the Investigational Medical Device;

4.6.3 in the case of a Non-regulated Clinical Investigation, the intended purpose for which the Investigational Medical Device has been CE Marked as detailed in the Instructions for Use;

4.6.4 the Letter of No Objection to the Clinical Investigation issued by the Medicines and Healthcare products Regulatory Agency for a Regulated Clinical Investigation;

4.6.5 the terms and conditions of the favourable opinion of the relevant South West - Exeter Research Ethics Committee where an opinion is required under National Research Ethics Service (NRES) guidance on medical device studies, copies of which the Trust shall supply to the Sponsor on request.

4.7 For Regulated Clinical Investigations, until the Sponsor has obtained all required documentation from the Regulatory Authority (where necessary) and a favourable opinion from the Research Ethics Committee, it shall not supply the Investigational Medical Devices to the Trust. For Regulated Clinical Investigations, the Trust shall ensure that neither administration of the Investigational Medical Device to any Clinical Investigation Subject nor any other clinical intervention mandated by the Clinical Investigation Plan takes place in relation to any such Clinical Investigation Subject until it is satisfied that all relevant regulatory approvals and a favourable opinion from the research ethics committee have been obtained.

4.8 For Non-regulated Clinical Investigations, the Trust shall ensure that neither administration of the Investigational Medical Device to any Clinical Investigation Subject nor any other clinical intervention mandated by the Clinical Investigation Plan takes place in relation to any such Clinical Investigation Subject until it is satisfied that where necessary, a favourable opinion from the research ethics committee has been obtained.

4.9 In the event of any Substantial Amendments being made to the Clinical Investigation Plan, the Trust shall procure that the amendments be signed by the Investigator and be implemented by the Investigation Site Team Members as required by the Sponsor. The Sponsor shall initiate simultaneously the change control procedures set out in clause 14 below.

4.10 The Sponsor shall make available to the Investigator copies of the documentation referred to in sub-paragraph 4.6.1 and 4.6.2 and evidence of grant of the authorisation listed in 4.6.4 above and the Trust shall procure that the Investigator include such documents together with the favourable opinion of the research ethics committee in the Site File, where this was required under NRES Guidance mentioned at sub-paragraph 4.6.5.

4.11 The Trust shall procure that the Investigator make any necessary disclosures of
financial interests and arrangements as specified by the Sponsor and for the purposes of these obligations the Sponsor shall advise the Investigator in writing of the date the Clinical Investigation has been completed.

4.12 The Trust shall not, and shall procure that the Investigator shall not, permit a non-CE marked Investigational Medical Device to be used for any purpose other than the conduct of the Clinical Investigation. Upon termination or expiration of this Agreement, the disposal or return of Investigational Medical Devices supplied by the Sponsor for the Clinical Investigation shall be managed in accordance with the Clinical Investigation Plan or the Sponsor’s written instructions.

4.13 The Trust shall use its best endeavours to ensure that the Investigator recruits a minimum of 30 Clinical Investigation Subjects to participate in the Clinical Investigation and the Parties shall conduct the Clinical Investigation in accordance with the Timelines.

4.14 In the event that the Clinical Investigation is part of a multi-centre clinical investigation (which for the purposes of this Agreement shall mean that at least one other institution is taking part) the Sponsor may amend the number of Clinical Investigation Subjects to be recruited pursuant to clause 4.13 above as follows:

4.14.1 if in the reasonable opinion of the Sponsor recruitment of Clinical Investigation Subjects is proceeding at a rate below that required to enable the relevant Timeline to be met the Sponsor may by notice to the Trust require recruitment at the Investigation Site to cease and the terms of the Agreement shall relate thereafter to the number of Clinical Investigation Subjects who have been enrolled in the Clinical Investigation at the date of such notice; or

4.14.2 if recruitment of Clinical Investigation Subjects is proceeding at a rate above that required to meet the relevant Timeline the Sponsor may with the agreement of the Trust increase the number of Clinical Investigation Subjects to be recruited.

4.15 The following provisions relate to access, research misconduct and Regulatory Authorities:

4.15.1 The Trust shall permit the Investigation Monitor, the Sponsor’s appointed representatives and any Auditor or Inspector access to all relevant clinical data of Clinical Investigation Subjects for monitoring, source data verification and adverse event reporting or investigation, such access to be arranged at mutually convenient times and on reasonable notice. Such monitoring may take such form as the Sponsor reasonably thinks appropriate including the right to inspect any facility being used for the conduct of the Clinical Investigation, reasonable access to Investigation Site Team Members and to examine any procedures or records relating to the Clinical Investigation, in accordance with the provisions of clause 6.2 of this Agreement. The Sponsor shall alert the R&D Office of the Trust promptly to significant issues (in the opinion of the Sponsor) relating to the conduct of the Clinical Investigation.

4.15.2 In the event that the Sponsor reasonably believes there has been any research misconduct in relation to the Clinical Investigation, the Trust shall, and shall procure that the Investigator shall, provide all reasonable assistance to any investigation into any alleged research misconduct
undertaken by or on behalf of the Sponsor, the results of which the Party on whose behalf the investigation was undertaken shall, subject to any obligations of confidentiality, communicate to the Trust. In the event that the Trust reasonably believes there has been any research misconduct in relation to the Clinical Investigation, the Sponsor shall provide all reasonable assistance to any investigation into any alleged research misconduct undertaken by or on behalf of the Trust, the results of which shall, subject to any obligations of confidentiality, be communicated to the Sponsor.

4.15.3 The Trust shall promptly inform the Sponsor of any intended or actual inspection, written enquiry and/or visit to the Investigation Site by any Regulatory Authority in connection with the Clinical Investigation and forward to the Sponsor copies of any correspondence from any such Regulatory Authority relating to the Clinical Investigation. The Trust will use all reasonable endeavours to procure that the Sponsor may have a representative present during any such visit.

4.15.4 The Trust shall permit the Sponsor to examine the conduct of the Clinical Investigation and the Investigation Site upon reasonable advance notice during regular business hours to determine that the Clinical Investigation is being conducted in accordance with the Clinical Investigation Plan, EN ISO 14155 or ICH GCP and the applicable regulatory requirements.

4.15.5 The Trust shall, and shall procure that the Investigator shall, co-operate with the Sponsor in the investigation and reporting of any unanticipated adverse events and incidents to the relevant Regulatory Authority.

4.15.6 The Sponsor shall provide, and the Trust shall permit the Investigator and Investigation Site Team Members to participate in, product training as necessary, investigation-related training, EN ISO 14155 or ICH GCP training as appropriate, and investigator meetings organised by the Sponsor.

4.16 The Trust shall ensure that any clinical biological samples required to be tested by the Trust during the course of the Clinical Investigation are tested in accordance with the Clinical Investigation Plan and at a laboratory approved by the Sponsor.

4.17 Upon completion of the Clinical Investigation (whether prematurely or otherwise) the Trust shall procure that the Investigator co-operate with the Sponsor in producing a report of the Clinical Investigation detailing the methodology, results and containing an analysis of the results and drawing appropriate conclusions.

4.18 Subject to the Trust’s and the Investigator’s overriding obligations in relation to Clinical Investigation Subjects and individual patient care, the Trust shall not and shall procure that the Investigator and the Investigation Site Team Members shall not during the term of this Agreement conduct any other investigation or trial which might hinder the Trust’s or the Investigator’s ability to recruit and study the required cohort of Clinical Investigation Subjects.

5. LIABILITIES AND INDEMNITY

5.1 In the event of any claim or proceeding in respect of personal injury made or brought against the Trust by a Clinical Investigation Subject, the Sponsor shall indemnify the Trust, its servants, agents and employees in accordance with the
terms of the indemnity set out at Appendix 4 hereto.

5.2 Nothing in this clause 5 shall operate so as to restrict or exclude the liability of any Party in relation to death or personal injury caused by the negligence of that Party or its servants, Agents or employees or to restrict or exclude any other liability of either Party which cannot be so restricted or excluded in law.

5.3 In no circumstances shall either Party be liable to the other Party in contract, tort (including negligence or breach of statutory duty) or otherwise however arising or whatever the cause thereof, for any loss of profit, business, reputation, contracts, revenues or anticipated savings or any special, indirect or consequential damage of any nature, which arises directly or indirectly from any default on the part of any other Party.

5.4 Subject to clauses 5.2 and 5.5, the Trust’s liability to the Sponsor arising out of or in connection with any breach of this Agreement or any act or omission of the Trust in connection with the performance of the Clinical Investigation shall in no event exceed the amount of fees payable by the Sponsor to the Trust under this Agreement. In the case of equipment loaned to the Trust for the purposes of the Clinical Investigation, the Trust’s liability arising from its negligence shall exclude fair wear and tear and shall not exceed the value of the equipment.

5.5 In respect of any willful and/or deliberate breach by the Trust, or any breach of clauses 6, 8 and/or 9, the Trust’s liability to the Sponsor arising out of or in connection with the breach shall not exceed twice the value of the contract.

5.6 Subject to clauses 5.1 and 5.2, the Sponsor’s aggregate liability to the Trust whether arising in contract, tort, negligence, breach of statutory duty or otherwise shall not exceed the sum of £5,000,000 (five million pounds).

5.7 The Sponsor shall take out appropriate insurance cover or shall provide an indemnity satisfactory to the Trust in respect of its potential liability under clause 5.1 above and such cover shall be for a minimum of GBP 5,000,000 (five million pounds). The Sponsor shall produce to the Trust, on request, copies of insurance certificates, together with evidence that the policies to which they refer remain in full force and effect, or other evidence concerning the indemnity. The terms of any insurance or the amount of cover shall not relieve the Sponsor of any liabilities under this Agreement.

6. CONFIDENTIALITY, DATA PROTECTION AND FREEDOM OF INFORMATION

6.1 Medical Confidentiality, Data Protection and Freedom of Information

The Parties agree to adhere to the principles of medical confidentiality in relation to Clinical Investigation Subjects involved in the Clinical Investigation. Personal data (as defined in the Data Protection Act 1998) shall not be disclosed to the Sponsor by the Trust save where this is required to satisfy the requirements of the Clinical Investigation Plan or for the purpose of monitoring, auditing or adverse event reporting or investigation, or in relation to a claim or proceeding brought by the Clinical Investigation Subject in connection with the Clinical Investigation. The Sponsor shall not disclose the identity of Clinical Investigation Subjects to third parties without prior written consent of the Clinical Investigation Subject, except in accordance with the provisions of the Data Protection Act 1998 and the principles set out in the NHS Confidentiality Code of Practice (November
2003), unless in relation to a claim or proceeding brought by the Clinical Investigation Subject in connection with the Clinical Investigation.

6.2 Each Party shall comply with the Data Protection Act 1998 ("the 1998 Act") and any other applicable data protection legislation. In particular where either Party is acting as the data processor of the other Party ("data controller"), the Party processing data on behalf of the other agrees to comply with the obligations placed on the data controller by the seventh data protection principle ("the Seventh Principle") set out in the 1998 Act, namely:

6.2.1 to maintain technical and organisational security measures sufficient to comply at least with the obligations imposed on the data controller by the Seventh Principle;

6.2.2 only to process Personal Data for and on behalf of the data controller, in accordance with the instructions of the data controller and for the purpose of the Clinical Investigation and to ensure the data controller’s compliance with the 1998 Act;

6.2.3 to allow the data controller to audit the processing party’s compliance with the requirements of this clause on reasonable notice and/or to provide the data controller with evidence of its compliance with the obligations set out in this clause 6.2.

6.2.4 the processing party shall obtain prior agreement of the data controller to store or process Personal Data at sites outside the European Economic Area (comprising the countries of the European Community, Norway, Iceland and Liechtenstein).

6.2.5 both parties agree to use all reasonable efforts to assist each other to comply with the 1998 Act. For the avoidance of doubt, this includes providing the other with reasonable assistance in complying with subject access requests served under Section 7 of the 1998 Act and consulting with the other prior to the disclosure of any Personal Data created in connection with the conduct or performance of the Clinical Investigation in relation to such requests.

6.2.6 Freedom of Information

The Sponsor acknowledges that the Trust is subject to the Freedom of Information Act 2000 ("FOIA") and the Codes of Practice issued under the FOIA as may be amended, updated or replaced from time to time.

6.2.7 If the Trust receives a request under the FOIA to disclose any information that belongs to the Sponsor or its Affiliates, it shall notify the Sponsor in accordance with Clause 16 as soon as is reasonably practicable, in any event, not later than five (5) working days after receiving the request and shall consult with the Sponsor in accordance with all applicable guidance.

6.2.8 The Sponsor acknowledges and agrees that:

(a) subject to clause 6.2.8(b), the decision on whether any exemption applies to a request for disclosure of recorded information under the FOIA is a decision solely for the Trust;

(b) where the Trust is managing a request as referred to in clause
6.2.7, the Sponsor shall co-operate with the Trust and shall use its reasonable endeavours to respond within eight (8) working days of the Trust’s request for assistance in determining whether or not an exemption to the FOIA applies.

6.2.9 Where the Trust determines that it will disclose the Confidential Information, notwithstanding any objections from the Sponsor, it shall notify the Sponsor in writing, giving at least four (4) working days notice of its intended disclosure.

6.3 Confidential Information

6.3.1 The Sponsor and the Trust shall ensure that only those of its officers, Agents and employees (and in the case of the Sponsor those of its Affiliates) directly concerned with the carrying out of this Agreement have access to the Confidential Information of the other Party. Each Party undertakes to treat as strictly confidential and not to disclose to any third party any Confidential Information of the other Party, save where disclosure is required by a Regulatory Authority or by law (including any disclosure required to ensure compliance by the Trust with the FOIA, in accordance with clauses 6.2.6, 6.2.7 and 6.2.8 above). The Party required to make the disclosure shall inform the other within a reasonable time prior to being required to make the disclosure (and, where appropriate in accordance with clause 6.2.7), of the requirement to disclose and the information required to be disclosed. Each Party undertakes not to make use of any Confidential Information of the other Party, other than in accordance with this Agreement, without the prior written consent of the other Party.

6.3.2 The obligations of confidentiality set out in this clause 6.3 shall not apply to Confidential Information which is (i) published or becomes generally available to the public other than as a result of a breach of the undertakings hereunder by the receiving Party, (ii) in the possession of the receiving Party prior to its receipt from the disclosing Party, as evidenced by contemporaneous written evidence, and is not subject to a duty of confidentiality, (iii) independently developed by the receiving Party and is not subject to a duty of confidentiality, (iv) obtained by the receiving Party from a third party not subject to a duty of confidentiality.

6.3.3 In the event of a Party visiting the establishment of the other Party, the visiting Party undertakes that any further Confidential Information which may come to the visiting Party’s knowledge as a result of any such visit shall be treated as Confidential Information in accordance with this sub-clause 6.3.

6.3.4 This clause shall remain in force without limit in time in respect of Confidential Information which comprises Personal Data or which relates to a patient, his or her treatment and/or medical records. Save as aforesaid and unless otherwise expressly set out in this Agreement, this clause shall remain in force for a period of 10 years after the termination or expiry of this Agreement.

7. PUBLICITY

7.1 The Sponsor shall not use the name of the Trust, nor of any member of the Trust’s staff, in any publicity, advertising or news release without the prior written
approval of an authorised representative of the Trust, such approval not to be unreasonably withheld. The Trust shall not, and shall procure that the Investigator and Investigation Site Team Members do not, use the name of the Sponsor or Affiliate or of any of its employees, nor the name of the Clinical Investigation, nor the name of the Investigational Medical Device, in any publicity, advertising or news release without the prior written approval of the Sponsor, such approval not to be unreasonably withheld.

7.2 Neither the NHS Trust nor the Investigator shall issue any information or statement to the press or public, including but not limited to advertisements for the enrolment of Clinical Investigation Subjects, without, where appropriate, its review and the delivery of a favourable opinion by the research ethics committee and the prior written permission of the Sponsor.

8. PUBLICATION

8.1 The Sponsor recognises that the Trust and the Investigator have a responsibility under the Research Governance Framework for Health and Social Care to ensure that results of scientific interest arising from the Clinical Investigation are appropriately published and disseminated. The Sponsor agrees that employees of the Trust and the Investigator shall be permitted to present at symposia, national or regional professional meetings, and to publish in journals, theses or dissertations, or otherwise of their own choosing, methods and results of the Clinical Investigation, subject to this clause 8 and any publication policy described in the Clinical Investigation Plan. If the Clinical Investigation is multi-centred (as defined in clause 4.12 above), any publication based on the results obtained at the Investigation Site (or a group of sites) shall not be made before the first multi-centre publication. If a publication concerns the analyses of subsets of data from a multi-centred Clinical Investigation the publication shall make reference to the relevant multi-centre publication(s).

8.2 Upon completion of the Clinical Investigation, and any prior publication of multi-centre data, or when the Clinical Investigation data are adequate (in Sponsor's reasonable judgement), the Trust and/or the Investigator may prepare the data derived from the Clinical Investigation for publication. Such data shall be submitted to the Sponsor for review and comment prior to publication. In order to ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination shall be submitted to the Sponsor for review at least sixty (60) days (or the time limit specified in the Clinical Investigation Plan if longer) prior to submission for publication, public dissemination, or review by a publication committee.

8.3 The Trust agrees, and shall ensure that the Investigator agrees, that all reasonable comments made by the Sponsor in relation to a proposed publication by the Trust and/or the Investigator shall be incorporated by the Trust and/or the Investigator into the publication.

8.4 The Trust acknowledges that the Sponsor may present at symposia, national or regional professional meetings, and publish in journals, theses or dissertations, or otherwise of their own choosing, methods and results of the Clinical Investigation and in particular, but without limiting the foregoing, post a summary of study results in on-line clinical trials register(s) before or after publication by any other method. In the event the Sponsor coordinates a multi-centre publication, the participation of the Investigator or other representatives of the Trust as a named author shall be determined in accordance with the Sponsor’s policy and generally accepted standards for authorship. If the Investigator or
other representative of the Trust is a named author of the multi-centre publication, such person shall have access to the Clinical Investigation data from all Clinical Investigation sites as necessary to participate fully in the development of the multi-centre publication.

8.5 During the period for review of a proposed publication referred to in clause 8.2 above and subject to the provisions of clause 4.4, the Sponsor shall be entitled to make a reasoned request to the Trust that publication be delayed for a period of up to six (6) months from the date of first submission to the Sponsor in order to enable the Sponsor to take steps to protect its proprietary information and/or Intellectual Property Rights and Know How and the Trust shall not unreasonably withhold or delay its consent to such a request. The Trust shall not unreasonably withhold or delay its consent to a request from the Sponsor for an exceptional additional delay if, in the reasonable opinion of the Sponsor, the Sponsor's proprietary information and/or Intellectual Property Rights and Know How might otherwise be compromised or lost.

9. INTELLECTUAL PROPERTY

9.1 All Intellectual Property Rights and Know How owned by or licensed to the Sponsor prior to and after the date of this Agreement other than any Intellectual Property Rights and Know How arising from the Clinical Investigation Plan are and shall remain the property of the Sponsor.

9.2 All Intellectual Property Rights and Know How owned by or licensed to the Trust prior to and after the date of this Agreement other than any Intellectual Property Rights and Know How arising from the Clinical Investigation Plan are and shall remain the property of the Trust.

9.3 All Intellectual Property Rights and Know How arising from and relating to the Clinical Investigation Plan or the Investigational Medical Device (including but not limited to its design and use alone or in combination with other medical devices or medicinal products), and including the results of the Clinical Investigation, but excluding any clinical procedure and improvements thereto that are clinical procedures of the Trust, shall vest in the Sponsor in accordance with clauses 9.4 and 9.5 below.

9.4 In accordance with clause 9.3 above, the Trust hereby assigns, and shall procure that the Investigator assigns, its rights in relation to all Intellectual Property Rights and in all Know How, falling within 9.3 above, to the Sponsor and at the request and expense of the Sponsor, the Trust shall execute, and shall procure that the Investigator executes, all such documents and do all such other acts as the Sponsor may reasonably require in order to vest fully and effectively all such Intellectual Property Rights and Know How in the Sponsor or its nominee.

9.5 The Trust and the Investigator shall promptly disclose to the Sponsor any Know How generated pursuant to this Agreement and falling within clause 9.3 above and undertake not to use or disclose such Know How other than for the purposes of this Agreement.

9.6 Nothing in this clause 9 shall be construed so as to prevent or hinder the Trust from using Know How gained during the performance of the Clinical Investigation in the furtherance of its normal business activities, to the extent such use does not result in the disclosure or misuse of Confidential Information or the infringement of any Intellectual Property Right of the Sponsor.
10. **FINANCIAL ARRANGEMENTS**

10.1 Arrangements relating to the financing of this Clinical Investigation by the Sponsor are set out in Appendix 5 hereto.

10.2 In the event that amendments to the Clinical Investigation Plan require changes to the investigation financing arrangements, an amended financial schedule shall be signed by the Parties pursuant to clause 14.2 below and attached as a supplement at Appendix 5 of this Agreement.

10.3 All payments shall be made according to the schedule contained in Appendix 5 on presentation of a VAT invoice to the Sponsor by the Trust.

10.4 The Sponsor shall promptly respond to any reasonable request for invoicing data received from the Trust within 60 days of the close-out of the Investigation Site. The Trust shall send its final invoice, (or, as the case may be, issue a credit note and make repayment of any monies previously paid for work not completed), to the Sponsor as soon as possible and, in any event, within 45 days of receipt of the said data where such a request has been made, or within 45 days of study close-out in all other circumstances unless there is a written agreement between the Trust and the Sponsor to extend these periods.

10.5 The Sponsor shall make payment within sixty (60) days of the date of receipt of the invoice mentioned in Clause 10.3 above.

10.6 Any delay in the payment of the payee invoices by the Sponsor shall incur an interest charge on any amounts overdue of 4 per cent (4%) per annum above the National Westminster Bank plc base rate prevailing on the date the payment is due.

11. **TERM**

This Agreement shall remain in effect until completion of the Clinical Investigation, close-out of the Investigation Site and completion of the obligations of the Parties under this Agreement or earlier termination in accordance with this Agreement.

12. **EARLY TERMINATION**

12.1 Either the Sponsor or the Trust (the Terminating Party) may terminate this Agreement with immediate effect at any time if the other Party or the Investigator (the Defaulting Party) is:

12.1.1 in breach of any of the Defaulting Party's obligations hereunder (including a failure without just cause to meet a Timeline) and fails to remedy such breach where it is capable of remedy within twenty eight (28) days of a written notice from the Terminating Party specifying the breach and requiring its remedy;

12.1.2 declared insolvent or has an administrator or receiver appointed over all or any part of its assets or ceases or threatens to cease to carry on its business or, in the case of the Trust, if it is a foundation trust authorised pursuant to the National Health Service Act 2006 and following such authorisation any step or proceedings is taken against the Trust by the Independent Regulator under Sections 52 to 55 of that Act; or if not and the Secretary of State makes an order under Sections 66 to 68 or 70 of
that Act.

12.2 A Party may terminate this Agreement on notice to the other Party with immediate effect if it is reasonably of the opinion that the Clinical Investigation should cease in the interests of the health of Clinical Investigation Subjects involved in the Clinical Investigation.

12.3 The Sponsor may terminate this Agreement on notice to the Trust if the Investigator is no longer able (for whatever reason) to act as Investigator and no replacement mutually acceptable to the Trust and the Sponsor can be found.

12.4 The Sponsor may terminate this Agreement immediately upon notice in writing to the Trust for reasons not falling within clauses 12.1.1, 12.2 or 12.3 above. In all such circumstances the Sponsor shall confer with the Investigator and use its reasonable endeavours to minimise any inconvenience or harm to Clinical Investigation Subjects caused by the premature termination of the Clinical Investigation.

12.5 In the event of early termination of this Agreement by the Sponsor, pursuant to clauses 12.2, 12.3 and 12.4 and subject to an obligation on the Trust and the Investigator to mitigate any loss, the Sponsor shall pay all costs incurred and falling due for payment up to the date of termination, and also all expenditure falling due for payment after the date of termination which arises from commitments reasonably and necessarily incurred by the Trust for the performance of the Clinical Investigation prior to the date of termination, and agreed with the Sponsor.

12.6 In the event of early termination, if payment (whether for salaries or otherwise) has been made by the Sponsor to the Trust in advance for work not completed, such monies shall be applied to termination related costs and the Trust shall issue a credit note and repay the remainder of the monies within 45 days of receipt of written notice from the Sponsor.

12.7 At close-out of the Investigation Site following termination or expiration of this Agreement the Trust shall immediately deliver, and shall make sure that the Investigator delivers to the Sponsor and at the Sponsor’s expense, all Confidential Information and any other unused materials and/or equipment provided to the Trust and/or the Investigator pursuant to this Agreement.

12.8 Termination of this Agreement shall be without prejudice to the accrued rights and liabilities of the Parties under this Agreement.

13. RELATIONSHIP BETWEEN THE PARTIES

13.1 Neither Party may assign its rights under this Agreement or any part thereof without the prior written consent of the other Party, such consent not to be unreasonably withheld or delayed, and neither Party may sub-contract the performance of all or any of its obligations under this Agreement without the prior written consent of the other Party, such consent not to be unreasonably withheld or delayed. Any party who so sub-contracts shall be responsible for the acts and omissions of its sub-contractors as though they were its own.

13.2 Nothing shall be construed as creating a joint venture, partnership, contract of employment or relationship of principal and agent between the Parties.

13.3 Notwithstanding clause 13.1, the Sponsor may assign, novate, or otherwise transfer any of its rights and/or obligations under this Agreement to an Affiliate.
14. AGREEMENT AND MODIFICATION

14.1 Any change in the terms of this Agreement shall be valid only if the change is made in writing, agreed and signed by the Parties.

14.2 Any amendment to the Clinical Investigation Plan pursuant to clause 4.9 ("Clinical Investigation Plan Amendment") shall be managed by means of the change control procedure set out in this clause 14.2.

14.2.1 For the purposes of this Agreement a “change request” is a request to change the obligations of the Parties arising from a Clinical Investigation Plan Amendment.

14.2.2 Where the Sponsor originates a change request, the Trust shall provide the Sponsor, within thirty five (35) days of receiving the change request, details of the impact which the proposed Clinical Investigation Plan Amendment will have upon the costs of carrying out the Clinical Investigation and the other terms of this Agreement.

14.2.3 A change request shall become a “change order” when the requirements of the change control procedure have been satisfied and any necessary change to this Agreement is signed by the authorised representatives of both Parties.

14.2.4 An amended financial schedule shall be signed and appended to this Agreement according to clause 10.2 above.

14.3 This Agreement including its Appendices contains the entire understanding between the Parties and supersedes all other agreements, negotiations, representations and undertakings, whether written or oral of prior date between the Parties relating to the Clinical Investigation, which is the subject of this Agreement. Nothing in this Agreement shall, however, operate to limit or exclude any liability for fraud.

15. FORCE MAJEURE

Neither Party shall be liable to the other Party or shall be in default of its obligations hereunder if such default is the result of war, hostilities, terrorist activity, revolution, civil commotion, strike, epidemic, accident, fire, wind, flood or because of any act of God or other cause beyond the reasonable control of the Party affected. The Party affected by such circumstances shall promptly notify the other Party in writing when such circumstances cause a delay or failure in performance ("a Delay") and where they cease to do so. In the event of a Delay lasting for four (4) weeks or more the non-affected Party shall have the right to terminate this Agreement immediately by notice in writing to the other Party.

16. NOTICES

Any notices under this Agreement shall be in writing, signed by the relevant Party to this Agreement and delivered personally, by courier or by recorded delivery post.

Notices to the Sponsor shall be addressed to:

Clinical Manager
International Group
17. RIGHTS OF THIRD PARTIES

Nothing in this Agreement is intended to confer on any person any right to enforce any term of this Agreement which that person would not have had but for the Contracts (Rights of Third Parties) Act 1999 ("Third Party Rights Act"). Any right or remedy of a third party which existed or is available apart from the Third Party Right Act is not affected; in particular, without limitation, any right of any Clinical Investigation Subject to claim compensation in accordance with the Clinical Investigation Compensation Guidelines referred to in Appendix 3.

18. WAIVER

No failure, delay, relaxation or indulgence by any Party in exercising any right conferred on such Party by this Agreement shall operate as a waiver of such right, nor shall any single or partial exercise of any such right nor any single failure to do so, preclude any other or future exercise of it, or the exercise of any other right under this Agreement.

19. DISPUTE RESOLUTION

19.1 In the event of a dispute arising under this Agreement, authorised representatives of the Parties shall discuss and meet as appropriate to try to resolve the dispute within seven (7) days of being requested in writing by any Party to do so. If the dispute remains unresolved, it shall then be referred to a senior manager from each of the Parties who shall use all reasonable endeavours to resolve the dispute within a further fourteen (14) days.

19.2 In the event of failure to resolve the dispute through the steps set out in clause 19.1 the Parties agree to attempt to settle it by mediation in accordance with the Centre for Effective Dispute Resolution Model Mediation Procedure.

19.2.1 To initiate mediation, either Party shall give notice in writing (ADR Notice) to the other Party requesting mediation in accordance with this clause 19.2. The Parties shall seek to agree the nomination of the mediator, but in the absence of agreement he shall be nominated by the President for the time being of the British Medical Association. The
mediation shall start no later than twenty (20) days after date of the ADR Notice.

19.3 If the dispute is not resolved within thirty (30) days of the ADR Notice, either Party shall be entitled to submit to the exclusive jurisdiction of the courts of England and Wales.

19.4 Nothing in this Agreement shall prevent either Party from seeking an interim injunction in respect of a breach of this Agreement. For the avoidance of doubt nothing in this clause shall amount to an agreement that either of the Parties is entitled to an interim injunction.

20. SURVIVAL OF CLAUSES

The following clauses shall survive the termination or expiry of this Agreement:-

1.1 Definitions
3.2 to 3.6 (inclusive) Clinical Investigation Governance
4.3, 4.4, 4.5, 4.15, Obligations of the Parties and the Investigator
5 Liabilities and Indemnity
6 Medical Confidentiality, Data Protection and Freedom of Information
7 Publicity
8 Publication
9 Intellectual Property
12.5 to 12.8 (inclusive) Early Termination
13 to 21 (inclusive) Miscellaneous provisions

Subject to clause 6.3.4, clause 6.3 (Confidential Information) shall survive the termination or expiry of this Agreement for a period of ten (10) years commencing on the date of such termination or expiry.

21. GOVERNING LAW

This Agreement shall be governed and construed in accordance with the laws of England and Wales and the Parties submit to the exclusive jurisdiction of the English Courts in respect of any dispute or claim arising out of or in connection with it.
Signed on behalf of the:

SPONSOR: ..........................................................

.......................................................... Date:

..........................................................
(Print name and position of authorised signatory)

Signed on behalf of the:

TRUST: ..........................................................

.......................................................... Date:

..........................................................
(Print name and position of authorised signatory)

Authorised signatory (Chief Executive, Director of R&D, or Finance Director)
APPENDIX 1

The Clinical Investigation Plan
# APPENDIX 2

## TIMELINES FOR PARTIES

<table>
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<tr>
<th>Milestone</th>
<th>Sponsor responsibility</th>
<th>Site responsibility</th>
<th>Target date</th>
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</thead>
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<td>X</td>
<td>X</td>
<td>January 2012</td>
</tr>
<tr>
<td>Ethics Committee submission</td>
<td>[X]</td>
<td>X</td>
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<tr>
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<td>X</td>
<td>June 2012</td>
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<tr>
<td>Last Clinical Investigation Subject recruited</td>
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<tr>
<td>All CRF queries submitted</td>
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<tr>
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APPENDIX 3

CLINICAL INVESTIGATION COMPENSATION GUIDELINES

Preamble

The Association of British Healthcare Industries favours a simple and expeditious procedure in relation to the provision of compensation for injury caused by a participation in clinical investigations. The Association therefore recommends that a member company sponsoring a clinical investigation should provide without legal commitment a written assurance to the investigator - and through him to the relevant research ethics committee - that the following Guidelines will be adhered to in the event of injury caused to a patient attributable to participation in the investigation in question.

1. Basic Principles

1.1 Notwithstanding the absence of legal commitment, the company should pay compensation to patient-volunteers suffering bodily injury (including death) in accordance with these Guidelines.

1.2 Compensation should be paid when, on the balance of probabilities, the injury was attributable to the use of a medical device under investigation or any clinical intervention or procedure provided for by the clinical investigation plan that would not have occurred but for the inclusion of the patient in the investigation.

1.3 Compensation should be paid to a child injured in utero though the participation of the subject’s mother in a clinical investigation as if the child were a patient-volunteer with the full benefit of these Guidelines.

1.4 Compensation should only be paid for the more serious injury of an enduring and disabling character (including exacerbation of an existing condition) and not for temporary pain or discomfort or less serious curable complaints.

1.5 Where there is an adverse event caused by a medical device under investigation and injury caused by a procedure adopted to deal with that adverse event, compensation should be paid for such injury as if it were caused directly by the medical device under investigation.

1.6 Neither the fact that the adverse event causing the injury was foreseeable or predictable, nor the fact that the patient has freely consented (whether in writing or otherwise) to participate in the investigation should exclude a patient from consideration for compensation under these Guidelines, although compensation may be abated or excluded in the light of the factors described in paragraph 4.2 below.

1.7 For the avoidance of doubt, compensation should be paid regardless of whether the patient is able to prove that the company has been negligent in relation to research or development of the medical device under investigation or that the product is defective and therefore, as the producer, the company is subject to strict liability in respect of injuries caused by it.
2. Type of Clinical Research Covered

2.1 These Guidelines apply to injury caused to patients involved in clinical investigations, that is to say, patients under treatment and surveillance (usually in hospital) which the use of the medical device under investigation is intended to assist but where the device does not bear “CE” marking in relation to the aspect(s) under investigation.

2.2 These Guidelines do not apply to injuries arising from clinical investigations on medical devices bearing “CE” marking, denoting compliance with Directives 90/385/EEC or 93/42/EEC, except to the extent that the injury is caused to a patient as a direct result of procedures undertaken in accordance with the clinical investigation plan (but not any product administered or used) to which the patient would not have been exposed had treatment been other than in the course of the investigation.

2.3 These Guidelines do not apply to clinical investigations which have not been initiated or directly sponsored by the company providing the product for research. Where investigations of products are initiated independently by doctors or third parties, responsibility for the health and welfare of patients rests with that doctor (or third party) alone (see also paragraph 5.2 below).

3. Limitations

3.1 No compensation should be paid for the failure of a medical device to have its intended effect or to provide any other benefit to the patient.

3.2 No compensation should be paid for injury caused by any other “CE” marked medical device or product used on the patient for the purpose of comparison with the medical device under investigation.

3.3 No compensation should be paid to patients receiving placebo in consideration of its failure to provide a therapeutic benefit.

3.4 No compensation should be paid (or it should be abated as the case may be) to the extent that the injury has arisen:

3.4.1 through a significant departure from the agreed clinical investigation plan;

3.4.2 through the wrongful act or default of a third party, including a doctor’s failure to deal adequately with an adverse event; or

3.4.3 through contributory negligence by the patient.

4. Assessment of Compensation

4.1 The amount of compensation paid should be appropriate to the nature, severity and persistence of the injury and should in general terms be consistent with the quantum of damages commonly awarded for similar injuries by an English Court in cases where legal liability is admitted.

4.2 Compensation may be abated, or in certain circumstances excluded, in the light of the following factors (on which will depend the level of risk the patient
can reasonably be expected to accept):

4.2.1 the seriousness of the disease being treated, the degree of probability that adverse events will occur and their seriousness, any warnings and precautions given; or

4.2.2 the risk and benefits of established treatments relative to those known or suspected of the medical device.

This reflects the fact that flexibility is required given the particular patient’s circumstances. As an extreme example, there may be a patient suffering from a serious or life-threatening disease who is warned of a certain defined risk of an adverse event. Participation in the investigation is then based on an expectation that the risk/benefit ratio associated with participation may be better than that associated with alternative treatment. It is, therefore reasonable that the patient accepts the high risk and should not expect compensation for the occurrence of the adverse incident of which he or she was told.

4.3 In any case where the company concedes that a payment should be made to a patient but there exists a difference of opinion between company and patient as to the appropriate level of compensation, it is recommended that the company agrees to seek at its own cost (and make available to the patient) the opinion of a mutually acceptable independent expert, and that his opinion should be given substantial weight by the company in reaching its decision on the appropriate payment to be made.

5. Miscellaneous

5.1 Claims pursuant to the Guidelines should be made by the patient to the company, preferably via the investigator, setting out details of the nature and background of the claim and, subject to the patient providing on request and authority for the company to review any medical records relevant to the claim, the company should consider the claim expeditiously.

5.2 The undertaking given by a company extends to injury arising (at whatever time) from all administrations, clinical interventions or procedures occurring during the course of the investigation but not to treatment extended beyond the end of the investigation at the instigation of the investigator. The use of products not bearing CE marking beyond the investigation period is wholly the responsibility of the investigator.

5.3 The fact that a company has agreed to abide by these Guidelines in respect of an investigation does not affect the right of a patient to pursue a legal remedy in respect of injury alleged to have been suffered as a result of participation. Nevertheless, patients will normally be asked to accept that any payment made under the Guidelines will be in full settlement of their claims.

5.4 A company sponsoring an investigation should encourage the investigator to make clear to participating patients that the investigation is being conducted subject to these Guidelines relating to compensation for injury arising in the course of clinical investigations and have available copies of the Guidelines should they be requested.
APPENDIX 4

FORM OF INDEMNITY

1. The Sponsor indemnifies and holds harmless the Trust and its employees and Agents against all claims and proceedings (to include any settlements or ex gratia payments made with the consent of the Parties hereo and reasonable legal and expert costs and expenses) made or brought (whether successfully or otherwise):

1.1 by or on behalf of Clinical Investigation Subjects and (or their dependants) against the Trust or any of its employees or agents for personal injury (including death) to Clinical Investigation Subjects arising out of or relating to the administration of the Investigational Medical Devices under investigation or any clinical intervention or procedure provided for or required by the Clinical Investigation Plan to which the Clinical Investigation Subjects would not have been exposed but for their participation in the Clinical Investigation;

1.2 by the Trust, its employees or Agents or by or on behalf of a Clinical Investigation Subject for a declaration concerning the treatment of a Clinical Investigation Subject who has suffered such personal injury.

2. The above indemnity by the Sponsor shall not apply to any such claim or proceeding:

2.1 to the extent that such personal injury (including death) is caused by the negligent or wrongful acts or omissions or breach of statutory duty of the Trust, its employees or Agents;

2.2 to the extent that such personal injury (including death) is caused by the failure of the Trust, its employees, or Agents to conduct the Clinical Investigation in accordance with the Clinical Investigation Plan;

2.3 unless as soon as reasonably practicable following receipt of notice of such claim or proceeding, the Trust shall have notified the Sponsor in writing of it and shall, upon the Sponsor’s request, and at the Sponsor’s cost, have permitted the Sponsor to have full care and control of the claim or proceeding using legal representation of its own choosing;

2.4 if the Trust, its employees, or Agents shall have made any admission in respect of such claim or proceeding or taken any action relating to such claim or proceeding prejudicial to the defence of it without the written consent of the Sponsor such consent not to be unreasonably withheld provided that this condition shall not be treated as breached by any statement properly made by the Trust, its employees or Agents in connection with the operation of the Trust’s internal complaint procedures, accident reporting procedures or disciplinary procedures or where such a statement is required by law.

3. The Sponsor shall keep the Trust and its legal advisors fully informed of the progress of any such claim or proceeding, will consult fully with the Trust on the nature of any defence to be advanced and will not settle any such claim or proceeding without the written approval of the Trust (such approval not to be unreasonably withheld).

4. Without prejudice to the provisions of paragraph 2.3 above, the Trust shall use its best endeavours to inform the Sponsor promptly of any circumstances reasonably thought
likely to give rise to any such claim or proceeding of which it is directly aware and shall keep the Sponsor reasonably informed of developments in relation to any such claim or proceeding even where the Trust decides not to make a claim under this indemnity. Likewise, the Sponsor shall use its reasonable endeavours to inform the Trust of any circumstances and shall keep the Trust reasonably informed of developments in relation to any such claim or proceeding made or brought against the Sponsor alone.

5. The Trust and the Sponsor shall each give to the other such help as may reasonably be required for the efficient conduct and prompt handling of any claim or proceeding by or on behalf of Clinical Investigation Subjects (or their dependants) or concerning such a declaration as is referred to in paragraph 1.2 above.

6. Without prejudice to the foregoing if injury is suffered by a Clinical Investigation Subject while participating in the Clinical Investigation, the Sponsor agrees to operate in good faith the guidelines published in 1995 by The Association of the British Healthcare Industries and entitled “Clinical Investigation Compensation Guidelines” and shall request the Investigator to make clear to the Clinical Investigation Subjects that the Clinical Investigation is being conducted subject to the Association Guidelines.

7. For the purpose of this indemnity, the expression “Agents” shall be deemed to include without limitation any nurse or other health professional providing services to the Trust under a contract for services or otherwise and any person carrying out work for the Trust under such a contract connected with such of the Trust’s facilities and equipment as are made available for the Clinical Investigation.

8. For the avoidance of doubt, this Appendix 4 is subject to the provisions of clause 5 of the Agreement.
APPENDIX 5

FINANCIAL ARRANGEMENTS

Philips and the investigator have a shared goal to investigate the application of Non-Invasive Ventilation during Pulmonary Rehabilitation in patients with Chronic Obstructive Pulmonary Disease (COPD). To achieve this goal, Philips shall support the study with [Redacted] GBP and pay R&D setup fees as follows:

Philips will pay the full amount due and R&D setup fees upon signature of this agreement and receipt of an invoice issued by the Institution.

Philips will also provide 3 Trilogy100, which will be loaned for the term of this agreement, upon signature of this agreement.

Payment will be made to the Institution’s Bank:

[Redacted]

When the Trust is not the investigator’s principal employer, this should include, after the schedule of payments, the statement that:

It shall be the responsibility of the Trust to make the appropriate agreed pass-through payments to the investigator’s principal employer, as indicated above.

All Invoices should be addressed to:

[Redacted]
Clinical Manager
International Group
Philips Home Healthcare Solutions
Chichester Business Park
City Fields Way
Tangmere
Chichester
West Sussex
PO20 2FT
APPENDIX 6
CONDITIONS APPLICABLE TO THE INVESTIGATOR

(a) he is free to participate in the Clinical Investigation and there are no rights which may be exercised by or obligations owed to any third party which might prevent or restrict his performance of the obligations detailed in this Agreement.

(b) where the Trust is not the Investigator’s principal employer, he has notified his principal employer of his proposed participation in the Clinical Investigation and, where relevant, his supervision of Investigation Site Team Members. He has obtained all necessary consents from his principal employer relating to this.

(c) he is not involved in any regulatory or misconduct litigation or investigation by the Food and Drug Administration, the Medicines and Healthcare products Regulatory Agency, the European Medicines Agency, the General Medical Council or other regulatory authorities. No data produced by him in any previous clinical study has been rejected because of concerns as to its accuracy or because it was generated by fraud.

(d) he has considered, and is satisfied that, facilities appropriate to the Clinical Investigation are available to him at the Investigation Site and that he is supported, and will continue to be supported, by medical and other staff of sufficient number and experience to enable the Trust to perform the Clinical Investigation efficiently and in accordance with its obligations under the Agreement.

(f) he is employed by, or has a contract for services (commonly known as an honorary contract) with, the Trust, which is a member of the Clinical Negligence Scheme for Trusts (CNST), or the Welsh Risk Pooling Scheme for Trusts (WRPST) or the Clinical Negligence and Other Risk Indemnity Scheme (CNORIS), as appropriate.

(g) during the Clinical Investigation, he will not serve as an investigator or other significant participant in any clinical investigation or trial for another sponsor if such activity might adversely affect his ability to perform his obligations under this Agreement.
### Appendix 7 Philips-Respironics Trilogy 100 specification

#### Specifications

<table>
<thead>
<tr>
<th>Specification</th>
<th>Details</th>
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</thead>
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<tr>
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<tr>
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<tr>
<td><strong>Ventilation types</strong></td>
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<td>AC, SIMV (w/PS), CV</td>
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<tr>
<td><strong>Pressure modes</strong></td>
<td>CPAP, S, S/T, T, PC-SIMV (w/PS)</td>
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<tr>
<td><strong>EPAP</strong></td>
<td>4 – 20 cm H₂O</td>
</tr>
<tr>
<td><strong>Pressure Support</strong></td>
<td>4 – 20 cm H₂O</td>
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</table>
This is the data download from the Trilogy 100 ventilator to demonstrate the data of the CPET. It presents wave forms of respiratory data over the time of the exercise. The ventilator flow rate was maintained throughout the exercise test. This can be seen on the top wave form graph. The second graph demonstrates the RR, third graph the PS used, fourth graph inspiration to expiration ratio and final graph is $V_E$. 
This graph demonstrates the numerical average of the ventilator data. The average minute ventilation of the exercise test (top graph) was 39.22L/min. The average RR was 17 breaths per minute (third graph). The average IPAP was
19.44cmH₂O and EPAP 3.51cmH₂O (sixth graph). The average mask leak was 61.89L/min (bottom graph).

This image demonstrates the time and date of use.
Appendix 9 Letter to GP

Dear Doctor

Re: -

The above named patient has consented to participate in a research study titled –

A randomized control trial of non-invasive ventilation (NIV) during an exercise programme following acute acidic exacerbation of COPD in hospital and follow-up use at home: feasibility of using the Trilogy Ventilator.

This study involves each patient being randomly allocated to one of three groups –

1. Standard Care: - care as currently prescribed for each patient following an acute exacerbation of COPD
2. Standard Care plus NIV in hospital: - As Group 1, but having undergone an exercise programme within hospital using NIV as part of that programme
3. Standard care + NIV in hospital + NIV at home: - As Group 2, but your patient has been provided with an NIV device for use at home during an exercise programme

Your patient has been allocated to GROUP .......

Each group will be monitored for 3 months from the date of discharge and has been asked to complete a diary of use of medical services and a number of questionnaires.

We have informed your local Pulmonary Rehabilitation service that we have discharged your patient from hospital and asked them to allocate a slot to their programme after completion of the study in 3 months. Your patient has consented to this delay.

If you would like any further information, then please contact us as above

Yours faithfully

Letter to General Practitioner; v1a: 25/06/2012
Appendix 10 Trial inclusion and exclusion document

Inclusion/Exclusion form

**Patient Identification Number for this trial:**

**Date of assessment:**

**Title of Project:** A randomized control trial of non-invasive ventilation (NIV) during an exercise programme following acute acidotic exacerbation of COPD in hospital and follow-up use at home: feasibility of using the Trilogy Ventilator.

**Inclusion Criteria**

Does the patient have a diagnosis of a COPD exacerbation resulting in a hospital admission for respiratory acidosis and type II respiratory failure, requiring treatment with NIV during this hospital admission, for any length of time. Yes ☐ No ☐

**Exclusion criteria**

Primary diagnosis not COPD. Yes ☐ No ☐

Not had a respiratory acidosis diagnosed through arterial blood gas (ABG) analysis. Yes ☐ No ☐

Not had NIV treatment. Yes ☐ No ☐

Under 25 years of age. Yes ☐ No ☐

Unable to follow commands or unable to consent. Yes ☐ No ☐

Known contraindication to NIV (Royal College of Physicians, 2008). Yes ☐ No ☐

Unable to tolerate acute hospital NIV. Yes ☐ No ☐

Unable to or refused to comply with physiotherapy. Yes ☐ No ☐

Had an additional pathology that limited ability to mobilise. Yes ☐ No ☐

Dying or receiving end of life care and not expected to survive this hospital admission. Yes ☐ No ☐

**Eligible for study: Yes ☐ No ☐**

Inclusion and exclusion form-- NIV Study; v1: 11/11/2012
## Appendix 11 Participant Diary

### Symptom Diary Card

#### Instructions for Use

Please complete for each day of the week in the evening.

Please use the following scales when scoring your symptoms:

<table>
<thead>
<tr>
<th>Q1 - Breathlessness</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better than usual</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal/usual</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Worse than usual</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Much worse than usual</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q2 – Sputum Volume</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than teaspoonful</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teaspoonful</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egg cupful</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than an egg cupful</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Q3 – Sputum Colour</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cream</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dark Cream</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pale Green</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q4 – How well today</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better than usual</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal/Usual</td>
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<tr>
<td>Worse than usual</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Much worse than usual</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q6 – Daily Activities</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>No difference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A little difficulty</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some difficulty</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A lot of difficulty</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q7 – Physical Activities</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
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<tr>
<td>A little difficulty</td>
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<tr>
<td>Some difficulty</td>
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<tr>
<td>A lot of difficulty</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Q8 – Social Activities</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
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<tr>
<td>A little difficulty</td>
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<tr>
<td>Some difficulty</td>
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<tr>
<td>A lot of difficulty</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Q9 – Work/Usual Activities</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half Day</td>
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</tr>
<tr>
<td>Full Day</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Q10 - Sleep</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better than usual</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Normal/Usual</td>
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<td></td>
</tr>
<tr>
<td>Worse than usual</td>
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<td></td>
</tr>
<tr>
<td>Much worse than usual</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q11 – Wake Up in Night</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 - 2</td>
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<tr>
<td>3 - 5</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>More than 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week Beginning:</td>
<td>Monday</td>
<td>Tuesday</td>
<td>Wednesday</td>
<td>Thursday</td>
<td>Friday</td>
</tr>
<tr>
<td>----------------</td>
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<td>--------</td>
</tr>
<tr>
<td>Q1</td>
<td>How breathless have you been today? <strong>Score 1 to 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td>How much sputum have you produced today? <strong>Score 1 to 5</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3</td>
<td>What colour was your sputum today? <strong>Score 1 to 5</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4</td>
<td>How well were you today? <strong>Score 1 to 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Due to increased chest problems, have you -</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Q5</td>
<td>Found it difficult to perform normal activities of daily living – dressing, washing etc.? <strong>Score 1 - 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q6</td>
<td>Found it difficult to perform physical activity you are usually capable of – hurrying, walking upstairs? <strong>Score 1 - 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q7</td>
<td>Found it difficult to perform social activity you are usually capable of – visiting friends, going-out with friends? <strong>Score 1 - 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q8</td>
<td>Missed time from work or usual activities? <strong>Score 1 – 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q9</td>
<td>How well did you sleep last night? <strong>Score 1 – 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q10</td>
<td>How many times did you wake up in the night? <strong>Score 1 - 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please Tick (✓) if the answer is Yes to the following questions

| Q11            | Have you had any other symptoms – nasal discharge or congestion, wheeze, sore throat, cough? |         |           |          |        |          |        |
| Q12            | Have you taken more medication than normal today? |         |           |          |        |          |        |
| Q13            | Have you contacted your GP/GP Nurse today? |         |           |          |        |          |        |
| Q14            | Have you been your GP surgery today due to your chest problems? |         |           |          |        |          |        |
| Q15            | Have you been to hospital today because of chest problems? |         |           |          |        |          |        |
| Q16            | Are you taking a course of antibiotics for chest problems today? |         |           |          |        |          |        |
| Q17            | Are you taking a course of steroid tablets for chest problems today? |         |           |          |        |          |        |
| Q18            | Have had any changes in your normal medication today? |         |           |          |        |          |        |
Appendix 12 SOP Exercise plan

<table>
<thead>
<tr>
<th>Issuing an exercise plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Check patients observations are stable</td>
</tr>
<tr>
<td>2 Set the most important core element of lower limb endurance from the 6 MWT Equation: (distance walked/6 x 10 minutes) x 80% = .... For example if the patient walked 456 m in 6 minutes the total distance to be walked in 10 minutes is 608 m (this equates to 20.2 laps of a 30 m track in 10 minutes) Aim to increase to 20 minutes 3 x week</td>
</tr>
<tr>
<td>3 Set an alternative lower limb endurance exercise for static cycling: 5 minutes cycling at a BORG score of 3-4 Aim to increase to 15 minutes 3 x week (alternative to walking)</td>
</tr>
<tr>
<td>4 Endurance training lower limbs: 1-3 sets of 8-15 reps 2-3 days/week, with loads equivalent to 40-60% load of 1 rep max (the maximum load moved only once over the full ROM without compensatory movement) General rule: Low weight/high repetitions/slow rhythm Aim BORG score: 2-3 Use leg weights</td>
</tr>
<tr>
<td>5 Endurance training upper limbs: 1-3 sets of 8-15 reps 2-3 days/week, with loads equivalent to 40-60% load of 1 rep max (the maximum load moved only once over the full ROM without compensatory movement) 1-2 minutes rest between sets General rule: Low weight/high repetitions/slow rhythm Aim BORG score: 2-3 Use dumbbells</td>
</tr>
</tbody>
</table>
6 Strengthening exercises lower limbs:
1-5 reps x 70-80% load of 1 rep max (the maximum load moved only once over the full ROM without compensatory movement)
4-7 sets with 2-6 minutes rest between sets
General rule: High weight x lower number of repetitions/quick rhythm
Use leg weights
Other adaptable for hospital/home use: sit-stand, SLR, Step up’s, squats

7 Strengthening exercises upper limbs:
1-5 reps x 70-80% load of 1 rep max (the maximum load moved only once over the full ROM without compensatory movement)
4-7 sets with 2-6 minutes rest between sets
General rule: High weight x lower number of repetitions/quick rhythm
Use dumbbells

8 Ensure patients are aware to report any new symptoms and side effects during or following the exercise to medics and researcher

15 Ensure that the patient has the contact details of the researcher

Email: Katy.buchan@UHBrstol.nhs.uk
Tel:
Bleep:

**You need to state that it is to do with the NIV study otherwise the switchboard will not contact us**
## STANDARD OPERATING PROCEDURE

### Issuing the Trilogy Ventilator

<table>
<thead>
<tr>
<th>Step</th>
<th>Instruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Check the recent chest X-ray: ensure no pneumothorax/extensive bullous disease.</td>
</tr>
<tr>
<td>2</td>
<td>Check patient observations are stable</td>
</tr>
<tr>
<td>3</td>
<td>Ensure equipment is clean, has a new filter, is working well and has a clear memo asset sticker on the device</td>
</tr>
</tbody>
</table>
| 4    | Set up Trilogy device.  
    | Follow below settings:  
    | Mode = Standard Timed  
    | Trigger = Auto-Track  
    | Back up rate = 10  
    | Timed inspiration = 1.0  
    | Initial starting pressures = 12 cmH\textsubscript{2}O Inspiratory Positive Airways Pressure & 4 cmH\textsubscript{2}O Expiratory Positive Airways Pressure  
<pre><code>| Increase to optimum settings: Aiming for a Pressure Support (PS) of 20 cmH\textsubscript{2}O. |
</code></pre>
<p>| 5    | Ensure external battery is in-situ and power cord |
| 6    | Ensure SD card is in-situ |
| 7    | Complete Case Record Form to ensure patient ID number is linked to the Ventilator serial number and memo asset number |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>If SPO₂ &lt;90% and patient is requiring Oxygen, entrain Oxygen into the back port of the Trilogy device</td>
</tr>
<tr>
<td>9</td>
<td>Ensure device locked on limited view when optimum settings achieved</td>
</tr>
</tbody>
</table>
| 10 | Assess the patient for a mask, fit for full face initially only trial nasal/pillows if the patient is unable to tolerate this style  
              Demonstrate to the patient how to put on/undo mask  
              Demonstrate to the patient the expiratory port on the mask  
              Demonstrate to the patient how the mask connects to the hose and hose to the ventilator  
              Demonstrate to the patient how to clean the mask |
| 11 | Explain ventilator controls to the patient and attach labels on/off, reset, Yes/No and alarm silence to assist with usage. Explain connection of oxygen if the patient is having additional entrained oxygen. If using additional Oxygen explain to the patient to turn on the ventilator first before adding the Oxygen and to remove the Oxygen first before turning off the ventilator to avoid gas trapping in the ventilator. |
| 12 | Issue patient with Respironics patient user guide for Trilogy |
| 13 | Begin with exercise training of patient (see exercise plan SOP)  
              The settings and Oxygen may need to be increased to ensure patient's ventilation is supported fully during exercise |
| 14 | Ensure the patient is aware of all possible side-effects and knows to inform the a medic and the researcher if they are feeling unwell |
| 15 | If the patient is allocated to group 3 issue a spare hose/mask for duration of the project |
| 16 | If the patient is allocated to Group 3 ensure Oxygen is prescribed for home if the patient is needing this for ambulation  
              Ensure green Oxygen tubing goes home with patient |
<table>
<thead>
<tr>
<th></th>
<th>Ensure patient knows how to connect the Ventilator to the concentrator</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>If the patient is allocated to group 3 ensure the patient has a travel ventilator bag</td>
</tr>
<tr>
<td></td>
<td>Ensure that the ventilator goes home with the patient</td>
</tr>
<tr>
<td>18</td>
<td>Ensure that the patient has the contact details of the researcher</td>
</tr>
</tbody>
</table>

**QUERIES**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Email:</td>
<td><a href="mailto:Katy.buchan@UHBristol.nhs.uk">Katy.buchan@UHBristol.nhs.uk</a></td>
</tr>
<tr>
<td>Tel:</td>
<td></td>
</tr>
<tr>
<td>Bleep:</td>
<td></td>
</tr>
<tr>
<td>Emergency:</td>
<td>You need to state that it is to do with the NIV study otherwise the switchboard will not contact us</td>
</tr>
</tbody>
</table>
29 October 2012

To Whom It May Concern:

This is to confirm that St George’s University of London (St George’s Hospital Medical School) has given permission for Kathryn Buchan and Adrian Kendrick, Sleep and NIV Service, Bristol Royal Infirmary to use the St George’s Respiratory Questionnaire (SGRQ) in a project entitled “NIV on exercise in COPD patients”.

Professor Paul Jones, PhD FRCP
Professor of Respiratory Medicine
ST. GEORGE’S RESPIRATORY QUESTIONNAIRE
ORIGINAL ENGLISH VERSION

ST. GEORGE’S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please tick in one box to show how you describe your current health:

Very good  Good  Fair  Poor  Very poor

---

Copyright reserved
P.W. Jones, PhD, FRCR
Professor of Respiratory Medicine,
St. George’s University of London,
Jenner Wing,
Cranmer Terrace,
London SW17 ORE, UK.
Tel. +44 (0) 20 8725 5371
Fax +44 (0) 20 8725 5965

UK/English (original) version

continued...
St. George’s Respiratory Questionnaire
PART 1

Questions about how much chest trouble you have had over the past 4 weeks.

Please tick (✓) one box for each question:

<table>
<thead>
<tr>
<th>Question</th>
<th>most days a week</th>
<th>several days a week</th>
<th>a few days a month</th>
<th>only with chest infections</th>
<th>not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Over the past 4 weeks, I have coughed:</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2. Over the past 4 weeks, I have brought up phlegm (sputum):</td>
<td></td>
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</tr>
<tr>
<td>3. Over the past 4 weeks, I have had shortness of breath:</td>
<td></td>
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</tr>
<tr>
<td>4. Over the past 4 weeks, I have had attacks of wheezing:</td>
<td></td>
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</tr>
<tr>
<td>5. During the past 4 weeks, how many severe or very unpleasant attacks of chest trouble have you had?</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
   Please tick (✓) one:                                                   |                  |                     |                    |                             |            |
   more than 3 attacks                                                     |                  |                     |                    |                             |            |
   3 attacks                                                               |                  |                     |                    |                             |            |
   2 attacks                                                               |                  |                     |                    |                             |            |
   1 attack                                                               |                  |                     |                    |                             |            |
   no attacks                                                             |                  |                     |                    |                             |            |
| 6. How long did the worst attack of chest trouble last?                  |                  |                     |                    |                             |            |
   (Go to question 7 if you had no severe attacks)                        |                  |                     |                    |                             |            |
   Please tick (✓) one:                                                   |                  |                     |                    |                             |            |
   a week or more                                                         |                  |                     |                    |                             |            |
   3 or more days                                                         |                  |                     |                    |                             |            |
   1 or 2 days                                                            |                  |                     |                    |                             |            |
   less than a day                                                        |                  |                     |                    |                             |            |
| 7. Over the past 4 weeks, in an average week, how many good days (with little chest trouble) have you had? |
   Please tick (✓) one:                                                   |                  |                     |                    |                             |            |
   No good days                                                           |                  |                     |                    |                             |            |
   1 or 2 good days                                                      |                  |                     |                    |                             |            |
   3 or 4 good days                                                       |                  |                     |                    |                             |            |
   nearly every day is good                                               |                  |                     |                    |                             |            |
   every day is good                                                      |                  |                     |                    |                             |            |
| 8. If you have a wheeze, is it worse in the morning?                     |                  |                     |                    |                             |            |
   Please tick (✓) one:                                                   |                  |                     |                    |                             |            |
   No                                                                     |                  |                     |                    |                             |            |
   Yes                                                                    |                  |                     |                    |                             |            |

UK/ English (original) version 2

continued...
St. George’s Respiratory Questionnaire
PART 2

Section 1
How would you describe your chest condition? Please tick (✓) one:
The most important problem I have ☐
Causes me quite a lot of problems ☐
Causes me a few problems ☐
Causes no problem ☐

If you have ever had paid employment. Please tick (✓) one:
My chest trouble made me stop work altogether ☐
My chest trouble interferes with my work or made me change my work ☐
My chest trouble does not affect my work ☐

Section 2
Questions about what activities usually make you feel breathless these days.
Please tick (✓) in each box that applies to you these days:

<table>
<thead>
<tr>
<th>Activity</th>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting or lying still</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Getting washed or dressed</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Walking around the home</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Walking outside on the level</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Walking up a flight of stairs</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Walking up hills</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Playing sports or games</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
### Section 3

**Some more questions about your cough and breathlessness these days.**

<table>
<thead>
<tr>
<th></th>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>My cough hurts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>My cough makes me tired</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am breathless when I talk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am breathless when I bend over</td>
<td></td>
<td></td>
</tr>
<tr>
<td>My cough or breathing disturbs my sleep</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I get exhausted easily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Section 4

**Questions about other effects that your chest trouble may have on you these days.**

<table>
<thead>
<tr>
<th></th>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>My cough or breathing is embarrassing in public</td>
<td></td>
<td></td>
</tr>
<tr>
<td>My chest trouble is a nuisance to my family, friends or neighbours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I get afraid or panic when I cannot get my breath</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel that I am not in control of my chest problem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I do not expect my chest to get any better</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I have become frail or an invalid because of my chest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise is not safe for me</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everything seems too much of an effort</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Section 5

**Questions about your medication, if you are receiving no medication go straight to section 6.**

<table>
<thead>
<tr>
<th></th>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>My medication does not help me very much</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I get embarrassed using my medication in public</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I have unpleasant side effects from my medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>My medication interferes with my life a lot</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
St. George’s Respiratory Questionnaire
PART 2

Section 6
These are questions about how your activities might be affected by your breathing.

Please tick (✓) in each box that applies to you because of your breathing:

<table>
<thead>
<tr>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>I take a long time to get washed or dressed</td>
<td></td>
</tr>
<tr>
<td>I cannot take a bath or shower, or I take a long time</td>
<td></td>
</tr>
<tr>
<td>I walk slower than other people, or I stop for rests</td>
<td></td>
</tr>
<tr>
<td>Jobs such as housework take a long time, or I have to stop for rests</td>
<td></td>
</tr>
<tr>
<td>If I walk up one flight of stairs, I have to go slowly or stop</td>
<td></td>
</tr>
<tr>
<td>If I hurry or walk fast, I have to stop or slow down</td>
<td></td>
</tr>
<tr>
<td>My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf</td>
<td></td>
</tr>
<tr>
<td>My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim</td>
<td></td>
</tr>
<tr>
<td>My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports</td>
<td></td>
</tr>
</tbody>
</table>

Section 7
We would like to know how your chest usually affects your daily life.

Please tick (✓) in each box that applies to you because of your chest trouble:

<table>
<thead>
<tr>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>I cannot play sports or games</td>
<td></td>
</tr>
<tr>
<td>I cannot go out for entertainment or recreation</td>
<td></td>
</tr>
<tr>
<td>I cannot go out of the house to do the shopping</td>
<td></td>
</tr>
<tr>
<td>I cannot do housework</td>
<td></td>
</tr>
<tr>
<td>I cannot move far from my bed or chair</td>
<td></td>
</tr>
</tbody>
</table>
St. George's Respiratory Questionnaire

Here is a list of other activities that your chest trouble may prevent you doing. (You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect you):

- Going for walks or walking the dog
- Doing things at home or in the garden
- Sexual intercourse
- Going out to church, pub, club or place of entertainment
- Going out in bad weather or into smoky rooms
- Visiting family or friends or playing with children

Please write in any other important activities that your chest trouble may stop you doing:

--------------------------------------------------------------------------------------------------------
--------------------------------------------------------------------------------------------------------

Now would you tick in the box (one only) which you think best describes how your chest affects you:

- It does not stop me doing anything I would like to do
- It stops me doing one or two things I would like to do
- It stops me doing most of the things I would like to do
- It stops me doing everything I would like to do

Thank you for filling in this questionnaire. Before you finish would you please check to see that you have answered all the questions.
Appendix 15 LCADL Questionnaire

LONDON CHEST ACTIVITIES OF DAILY LIVING QUESTIONNAIRE

Study Number:

Do you live alone? ( ) Yes ( ) No

Please score each of the following using the scale -

0) I do not perform this activity (because I have never needed to or it is irrelevant).
1) I do not experience shortness of breath while performing this activity.
2) I experience mild shortness of breath while performing this activity.
3) I experience severe shortness of breath while performing this activity.
4) Due to shortness of breath, I cannot perform this activity anymore, and I do not have anyone to do it for me.
5) Due to shortness of breath, I cannot perform this activity anymore, and I need someone to help me or to do it for me.
<table>
<thead>
<tr>
<th>Question</th>
<th>Question</th>
<th>Your Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal Care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Drying yourself after the shower</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Clothing the upper part of your body (T-shirt, coat)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Putting on shoes/socks</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Washing your hair</td>
<td></td>
</tr>
<tr>
<td>Household Activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Making your bed</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Changing the sheets</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Washing windows/curtains</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Dusting</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Doing the dishes</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Vacuum cleaning/sweeping</td>
<td></td>
</tr>
<tr>
<td>Physical Activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Climbing stairs</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Bending over</td>
<td></td>
</tr>
<tr>
<td>Leisure Activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Walking in the home</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Going out</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Speaking/talking</td>
<td></td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>How much does shortness of breath affect your performance of activities of daily living?</td>
<td>Quite a bit, Slightly, Not at all</td>
</tr>
</tbody>
</table>
Appendix 16 Modified Borg dyspnoea scale

0 Nothing at all
0.5 Very, very slight (just noticeable)
1 Very slight
2 Slight
3 Moderate
4 Somewhat severe
5 Severe
6
7 Very severe
8
9 Very, very severe (almost maximal)
10 Maximal
Appendix 17 MMRC Dyspnoea scale

Modified Medical Research Council
Dyspnoea Scale

Grade

0  “I only get breathless with strenuous exercise”

1  “I get short of breath when hurrying on the level or walking up a slight hill”

2  “I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level”

3  “I stop for breath after walking about 100 yards or after a few minutes on the level”

4  “I am too breathless to leave the house” or “I am breathless when dressing”

NB: This is the modified MRC scale that uses the same descriptors as the original MRC scale in which the descriptors are numbered 1-5. The modified MRC scale (0-4) is used for calculation of BODE index.

The Pulmonary Rehabilitation Toolkit: An Initiative of The Australian Lung Foundation and Australian Physiotherapy Association
## Research Standard Operating Procedure (SOP) for Exercising on NIV: 6 Minute Walk Test

**SETTING**  
Bristol Royal Infirmary and Home

**FOR STAFF**  
Exercise on NIV research team: Assessing the 6MWT

**PATIENTS**  
Only to be used for COPD patients who have consented to be participants in the above research.

### STANDARD OPERATING PROCEDURE

<table>
<thead>
<tr>
<th>Carrying out the 6MWT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Check the patient observations are stable</td>
</tr>
<tr>
<td>2 Absolute Contraindications:</td>
</tr>
<tr>
<td>Unstable Angina during the previous month and</td>
</tr>
<tr>
<td>Myocardial infarction during the previous month</td>
</tr>
<tr>
<td>Relative Contraindications:</td>
</tr>
<tr>
<td>Resting Heart rate of &gt;120</td>
</tr>
<tr>
<td>Systolic blood pressure of &gt;160 mmHg</td>
</tr>
<tr>
<td>Diastolic blood pressure of &gt; 100 mmHg</td>
</tr>
<tr>
<td>3 If patient has stable exertional angina ensure that the test is performed after</td>
</tr>
<tr>
<td>anti-angina medication is taken, and rescue nitrate medication should be readily</td>
</tr>
<tr>
<td>available.</td>
</tr>
<tr>
<td>4 Testing to be performed in a location near to a crash trolley on the ward</td>
</tr>
<tr>
<td>At home: Near to telephone to call for an ambulance at home/ researcher to have mobile</td>
</tr>
<tr>
<td>phone available to call for an ambulance in an emergency situation (check signal in</td>
</tr>
<tr>
<td>rural areas prior to initiating test)</td>
</tr>
<tr>
<td>5 Ensure that supplies are available if taken by the patient of: Oxygen, sublingual</td>
</tr>
<tr>
<td>nitroglycerine, bronchodilator inhalers/nebulizers</td>
</tr>
<tr>
<td>6 Ensure that the researcher is up-to-date with basic life support training</td>
</tr>
<tr>
<td>7 If patient uses LTOT or ambulatory Oxygen ensure that this is used by the patient</td>
</tr>
<tr>
<td>during the assessment. This must be documented on the Case Record Form (CRF) for use</td>
</tr>
<tr>
<td>and quantity. The way the Oxygen was carried must be documented. The use of Oxygen</td>
</tr>
<tr>
<td>must be identical in subsequent tests.</td>
</tr>
<tr>
<td>8 If the patient needs to ambulate using a frame, this must be documented as the</td>
</tr>
<tr>
<td>modified</td>
</tr>
</tbody>
</table>
6MWT on the CRF and subsequent tests must use the frame.

9 Reasons for stopping a test include:
   Chest pain
   Intolerable dyspnoea
   Leg cramps
   Staggering
   Diaphoresis: excessive sweating
   Pale/ashen appearance

10 The 6MWT should be performed indoors, along a long, flat, straight corridor with a hard surface that is seldom travelled.
   Home: if the weather is comfortable, the test may be performed outdoors.
   The walking course must be where feasible 30m in length, this should be measured out before the test
   The length of the course should where possible be marked at the beginning and every
   3 m, a starting line which marks the beginning and end of each 60 m lap should be
   clearly visible.
   The turnaround points should be marked, ideally with cones

11 Equipment:
   Access to telephone
   Stopwatch
   A chair that is easily moved along the walking course
   Walking frame if indicated
   Oxygen if indicated
   Markers for turning points
   Recording sheet/pen/clip board
   CRF
   BORG Scale: printed on laminated card, 11 inches high, Font size 20
12 Patient preparation

1. Comfortable clothing should be worn
2. Appropriate shoes/slippers for walking should be worn
3. Patients should use their usual walking aid for the test (documented on CRF)
4. Patient’s should continue with usual medication routine (documented on CRF, especially any medications taken immediately prior to the test)
5. Patients should not have exercised vigorously within 2 hours of beginning the test

13 Measurements

1. A practice test should ideally be performed at least 1 hour before a re-test and the results recorded on the CRF
2. Repeat testing should be performed about the same time of day to minimize intraday variability, time and date of test should be recorded on CRF
3. The patient should sit and rest in a chair at the starting position for 10 minutes prior to the test. Check for observations, contraindications, suitable clothing and footwear
4. Record pulse oximetry: baseline SpO2 and HR
5. Patient stands and rates their baseline dyspnoea and overall fatigue using the Borg scale. Ask the patient:
   “please rate your level of shortness of breath using this scale”
   “please rate your level of fatigue using this scale”
6. Set the timer to 6 minutes, assemble all equipment and documentation
7. Instruct the patient:
   “The object of the test is to walk as far as possible in 6 minutes. You will walk back and forth in this hallway (along this marked course). Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall whilst resting, but resume walking as soon as you are able.”
   “You will be walking back and forth around the markers. You should turn quickly around the cones and continue back the other way without hesitation. Now I am
going to show you. Please watch the way I turn without hesitation.”

8. Demonstrate by walking one lap yourself

9. Ask the patient “if they are ready to begin?”

10. Explain to the patient you are “keeping track of the lap’s you complete”

11. Remind the patient “remember that the object is to walk as far as possible for 6 minutes, but don’t run or jog. Start now, or whenever you are ready”

12. Do not walk with the patient, as soon as the patient starts to walk, start the timer

13. Do not talk to anyone during the walk, watch the patient, do not get distracted, each time the participant returns to the start line, mark a lap on the record sheet. Let the participant see you do this, exaggerate the pen stroke. Ensure all rests are recorded in detail.

14. After the first minute, tell the patient, in an even voice tone

“You are doing well. You have 5 minutes to go”

15. When the timer has 4 minutes remaining, say in an even voice tone

“Keep up the good work, you have 4 minutes to go”

16. When the timer has 3 minutes remaining, say in an even voice tone

“You are doing well. You are halfway done”

17. When the timer has 2 minutes remaining, say in an even voice tone

“Keep up the good work you have only 2 minutes left”

18. When the timer has 1 minutes remaining, say in an even voice tone

“You are doing well you have only 1 minute to go”

19. Do not use other words of encouragement or body language to speed up the patient

20. If the patient stops before the 6 minutes is up and needs a rest say “you can lean against the wall if you would like, then continue walking whenever you feel able”, if the patient decides to stop or you decide for them to stop, let the patient sit down and discontinue the walk, note the time, distance and reason for stopping prematurely.

21. When the timer is 15 seconds from completion, say this:

“In a moment I’m going to tell you to stop. When I do, just stop right where you are and I will come to you”

22. When the timer buzzes, say this
23. “Stop. I will bring the chair to you”

24. Post-test:
   Record BORG score Dyspnœa and fatigue scores
   Ask “what if anything, kept you from walking further”
   Record SpO₂ and HR
   Record the number of laps
   Record any additional metres covered, calculate the total distance walked, rounding to the nearest metre, and record it on the worksheet

25. Congratulate the patient on good effort and offer a drink of water

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Ensure the patient is aware of all possible side-effects and knows to inform the medic and the researcher if they are feeling unwell</td>
</tr>
<tr>
<td>15</td>
<td>If the patient is allocated to group 3 issue a spare hose/mask for duration of the project</td>
</tr>
</tbody>
</table>
| 16 | If the patient is allocated to Group 3 ensure Oxygen is prescribed for home if the patient is needing this for ambulation  
   Ensure green Oxygen tubing goes home with patient  
   Ensure patient knows how to connect the Ventilator to the concentrator |
| 17 | If the patient is allocated to group 3 ensure the patient has a travel ventilator bag  
   Ensure that the ventilator goes home with the patient |
| 18 | Ensure that the patient has the contact details of the researcher |

**QUERIES**  
Email: Katy.buchan@UHBristol.nhs.uk
<table>
<thead>
<tr>
<th>Tel:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleep:</td>
<td></td>
</tr>
<tr>
<td>Emergency:</td>
<td></td>
</tr>
</tbody>
</table>

You need to state that it is to do with the NIV study otherwise the switchboard will not contact us
Appendix 19 Interview Guide

Introduction questions

1. Can you give me a snap shot of your experience in using the equipment for the last three months?
2. How would you describe using the equipment to someone who has never seen the equipment?
3. Has the ventilator influenced your life?

Using the equipment

4. Overall has the ventilator been a positive or a negative experience for you?
5. Did you find it easy exercising on the ventilator?
6. Were there any difficulties of exercising on the ventilator?
7. Were there times when you chose not to use the equipment?
8. Is there anything you would change about the design of the equipment used?

Experience

9. Have you experienced any physical changes over the last 3 months?
10. Have you experienced any other changes?
11. What do your family and friends think of the equipment?
12. Did anything surprise you about the study?
13. Did anything surprise you about the equipment?

Advice

14. Do you have any advice for a person who is about to take part in the research?
15. Do you have any advice for health professionals who set patients up on this equipment?
16. Do you have any advice for health professionals carrying out this type of research?

Extra information

17. Is there anything you would like to add about your experience of using the equipment?
18. Is there anything else you would like to add about your experience of the study?
Appendix 20 Interview transcriptions

Interview 1: Vanessa
Tuesday 18th June Interview: 3.30pm in the kitchen of the home of NIV1:3 on stool and interviewer sitting opposite by window, can hear gentle chug of oxygen concentrator and birds singing outside the open window, faint smell of cigarettes is present. The participant asked for lots of prompts and breaks for breathlessness.

Interviewer: “Alright…ok…so first question you said on more than one occasion that you dread my visits can you tell me about this?”

Vanessa: “erm…erm…well… obviously it’s I don’t dread you coming so much as the purpose of your visit that’s what I dread really… erm… I suppose it’s the thought of having to do the exercise erm… use the mask erm… and the worst bit is taking the mask off afterwards and getting my breath back.”

Interviewer: “yeah but I have the knowledge that you rarely cancelled a visit why was this?”

Vanessa: “erm…crumbs this is really off putting can we have a break”

Interviewer: “let’s have a break for a minute (turned off recorder at patients request)”

Vanessa: “what was the question again?”

Interviewer: “so even though you dreaded my visits “

Vanessa: “oh I haven’t cancelled”

Interviewer: “you rarely cancelled an attendance, why was this?”

Vanessa: “because I know that what I dread well it isn’t as bad as the sessions gonna be and I don’t want to let you down erm and I know that some good’ll probably come of it the session afterwards anyway”

Interviewer: “probably?”

Vanessa: “probably erm yeah”

Interviewer: “what good?”

Vanessa: “erm that the exercise will probably do some good physically and yeah probably be helpful in the long run “

Interviewer: “ok… could you give me a snapshot of your experiences of using the equipment over the last 3 months?”

Vanessa: “(pause) I suppose my main feeling is that I haven’t really been physically up to it that I haven’t had such as much benefit from.. from the sessions as I could have had because of being unable to erm do any exercises on my own in the daytime when you haven’t called”

Interviewer: “why was that do you think?”
Vanessa: “mainly because I think I’m struggling too much just to get through each day erm doing the main things I need to do you know like eating and clearing up and things like that”

Interviewer: “How would you describe using the equipment to someone whose never seen it?”

Vanessa: “what the machine? You mean erm laughs I don’t know what I’d say laughs”

Interviewer: “ok how would you describe how it feels?”

Vanessa: “erm when you’ve actually got it on it can feel quite relaxing”

Interviewer: “mm”

Vanessa: “I feel it actually gives me dry mouth which I don’t I don’t like very much and I don’t like taking it off because of you know the transition back to you know the normal oxygen machine”

Interviewer: “has the ventilator influenced your life, do you think?”

Vanessa: “erm I do like the idea of having access to it even though I haven’t used it on my own if I didn’t have so many other things stressing me out (laughs) then I’d probably put more effort into having a go and using it on its own cause I think that.. I think it would help me… with some of the erm daily problems I’ve had”

Interviewer: “can you give me some examples of what you think it might help with?”

Vanessa: “things like the breathing problem and although you tell me my levels are fine for some reason they don’t feel fine and the confusion I’ve had and the light headedness and things like that “

Interviewer: “overall has the ventilator been a positive or negative experience for you?”

Vanessa: “erm I’ll say positive overall (laughing) even though I hate to admit that (laughing)”

Interviewer: “why do you hate to admit that?”

Vanessa: “because my attitude doesn’t suggest that….sorry I need a rest now”

Interviewer: “yes let’s have a rest (recorder turned off)”

Interviewer: “ok so we are starting the tape again I’m just going to check that he’s working which he is…Ok did you find it easy exercising on the ventilator?”

Vanessa: “erm...yeah I suppose yeah”

Interviewer: “were there any difficulties in exercising?”

Vanessa: “difficulties in exercising?”

Vanessa: “no not especially I suppose the main thing was… was how easily tired it made me erm yeah my limbs erm”
Interviewer: “did it feel any different to when you have exercised without the ventilator?”

Vanessa: “erm Oh I don’t know…I can’t remember particularly I don’t think so”

Interviewer: “can you remind me of the time, when the exercise plan we were going to do was changed because your arms were aching because you’d been brushing your hair? You felt unable to do the weights”

Vanessa: “erm that was to in order to do my hair I had to have my arms lifted up above my head for quite a few minutes it took me about twenty minutes to half an hour to do my hair and that was quite tiring on my arms and my shoulders so by the time I’d finished doing my hair yeah my arms and shoulders were quite tired and sore”

Interviewer: “can you remember and explain some of the reasons why you did cancel a few of the sessions?”

Vanessa: “erm ones I cancelled oh what was it it’s hard for me to remember what it was it was see this is the (tut) memory problem I’ve got”

Interviewer: “it’s ok you’re fine.. your’e fine.. was one to do with not feeling well?”

Vanessa: “yeah”

Interviewer: “tiredness?”

Vanessa: “oh there’s that but wasn’t there one where I’d hurt my leg or something or”

Interviewer: “ there was one where your leg was aching but that was after we’d done an exercise session and I think one may have been when the council was telephoning or coming to visit to sort out your heating”

Vanessa: “(shrugs) yeah”

Interviewer: “that’s ok we can come back to that erm is there anything you would change about the design of the equipment?”

Vanessa: “erm ..(shakes head)”

Interviewer: “anything about the actual ventilator or mask or hose or the way we connect the oxygen?”

Vanessa: “no I don’t know I don’t think so although I’m quite nervous about using it and putting it on and stuff”

Interviewer: “ what are you nervous about?”

Vanessa: “about….erm connecting it up properly and you know not having…..”

Interviewer: “to the oxygen?”

Vanessa: “yeah to the oxygen and not being able to sort the oxygen quick enough if I’m not getting it right”
Interviewer: “so do you think you need to be quite quick when you use it?”

Vanessa: “mmm”

Interviewer: “Anything about the size of the equipment or weight or mask?”

Vanessa: “I find the weight of the equipment heavy to lift but then that can be put in place you know it’s not to heavy for me to move I could put it in place first and then put the equipment on and stuff you know at the side of the bed erm “

Interviewer: “can you put the mask on easily?”

Vanessa: “yeah I don’t find that easy to put on plus aswell because I have to take my glasses off then I can’t see properly so that makes me nervous not being able to see properly if I am doing it on my own”

Interviewer: “rest or you ok?”

Vanessa: “yeah I could do with a rest”

(Tape recorder paused)"

Interviewer: “Ok we are starting the recorder again...yeah? Do you think you’ve experienced any physical changes over the last three months?”

Vanessa: “erm only maybe very marginally simply because I haven’t been able to make full use of you know the opportunity to do the exercises I think if I’d have managed to do it more times in the week then I think I would have benefitted quite significantly”

Interviewer: “ok just describe how you think you have marginally changed?”

Vanessa: “erm small amount of additional strength in my limbs especially my legs er you know where which is what we worked on mainly.”

Interviewer: “Did you experience any other changes?”

Vanessa: “erm actually confidence that my breathing is better than I realised by having the machine the little thing showing me every time you came that my Sat’s levels were good and stuff”

Interviewer: “any other experiences sort of your emotions or stress levels....”

Vanessa: “laughs erm yeah I suppose my stress levels improved mainly because you were as good as your word that I didn’t feel pressured that I had to do anything I didn’t want to do”

Interviewer: “On a couple of visits you did admit to feeling slightly better having done the exercise the next couple of days can you tell me about that?”

Vanessa: “I was lying laughs erm oh did I do that laughs I don’t know what to say erm well yeah it did seem to have a good effect on my mood and my feeling physically even though I was a bit tired afterwards and needed a little sleep or nap erm generally speaking I did feel better”

Interviewer: “what do your family or friends think of the equipment?”
Vanessa: “erm Burt (son) and Ernie (nephew) think it’s great they think that erm I should make more use of it and they are happy to help me use it if I want to.”

Interviewer: “cause initially you did say to me erm that they thought it was a waste of money could you elaborate on that?”

Vanessa: “Oh Burt’s attitude, that’s my son, his attitude very much is that most of what’s happened to me I deserve because I haven’t completely given up smoking so he tends to fluctuate between feeling that there’s no point in having any treatment at all while I still smoke and making use of treatment that will help and that if it helps enough maybe it will help me give up smoking if you understand that”

Interviewer: “I do”

Vanessa: “so I need to rest”

Interviewer: “yes you’ve done really well”

(Tape recorder paused)”

Interviewer: “right restarting the recorder. Did anything surprise you about the study?”

Vanessa: “erm in what way?”

Interviewer: “was there anything you weren’t expecting”

Vanessa: “erm I don’t know I don’t think so I didn’t really know what to expect”

Interviewer: “Did anything surprise you about the equipment?”

Vanessa: “erm”

Interviewer: “cause you’ve used hospital NIV how did it compare to this”

Vanessa: “well I didn’t really use it myself did I at the hospital it was always a nurse you know to operate things so I suppose I suppose I was surprised at just how much I lacked confidence in using it erm yeah”

Interviewer: “ok do you have any advice for person about to take part in the research study “

Vanessa: “erm well just basically to go for it that it’s not as bad as you think it’s gonna be (laughing)”

Interviewer: “Have you got any advice for health professionals setting up patients on this equipment?”

Vanessa: “erm no not really I’m happy with the way its been used on me and yeah”

Interviewer: “Is there anything else you’d like to add about your experience of using the equipment?”

Vanessa: “erm…..”

Interviewer: “Anything you hated anything you loved?”
Vanessa: “erm no I just wish that I wasn’t so that my condition wasn’t so poor to start with a year or two ago I’d have probably benefited much more than this than I am doing now “

Interviewer: “So you think that you may have liked to have a go of exercising on the ventilator sooner?”

Vanessa: “yeah”

Interviewer: “What about, anything else you want to add about the whole experience of being involved in the research? And all the outcome measures things like the walking test the questionnaires “

Vanessa: “laughs”

Interviewer: “the diary”

Vanessa: “well diaries and questionnaires I absolutely hate in any form for anything so erm that’s something that I would have struggled to do you know anyway erm “

Interviewer: “How about the walking test?”

Vanessa: “yeah the walking test I found quite good because it gave ma an idea of just how far I can walk unaided sort of thing so”

Interviewer: “what about the actical, did that feel alright?”

Vanessa: “the what?”

Interviewer: “the device on your wrist”

Vanessa: “oh yeah that’s been fine that’s still there”

Interviewer: “was there anything else you would have liked to have done… different exercises? Or…”

Vanessa: “like I say I just wish I could have done more exercises longer… more in the week”

Interviewer: “Is there anything I could have changed to make you feel more confident to use the machine on your own”

Vanessa: “no”

Interviewer: “or to exercise more?”

Vanessa: “no I think you did everything you could against my lack of confidence”

Interviewer: “Is there anything else you’d like to add”

Vanessa: “no not really (laughs)”

Interviewer: “That’s great”

(Interview time 1hour, actual talking time 25 minutes due to dyspnoea)
Interview 2: Neil
In lounge participant sitting next to researcher on couch in lounge of the ground floor flat. Kitten is playing on the floor with the tubing of the ventilator.

Interviewer: “So yep we are recording. Can you give me a snapshot of your experience of the study over the last 3 months?”

Neil: “Erm...a snapshot erm……”

Interviewer: “Your experience…?”

Neil: “Erm I don't really know I just thought erm I mean it has been helpful obviously in the fact that you know erm that somebody is I presume is you know is coming round to monitor you and erm discuss your medication and discuss your ongoing health I suppose”

Interviewer: “Ok how would you describe the equipment to somebody who has never seen the equipment?”

Neil: “erm a little bit daunting initially (laughs) but once you use it and you experience it you get very much used to it and erm it is no problem at all really so you know you find it well the whole equipment and so forth you find useful really”

Interviewer: “How would you describe how it feels?”

Neil: “Erm... initially quite erm you might find it a little bit as I did err a little bit claustrophobic erm which I have done with using masks erm recently in the last six months I’ve found very very claustrophobic but err certainly you get used to and obviously it is there to to help you”

Interviewer: “Did it differ from the machine you used at the hospital?”

Neil: “Erm...not really only in the shape of the mask I think was the only difference that I can remember”

Interviewer: “Has the ventilator influenced your life?”

Neil: “Has it influenced my life erm probably not (laughs)I don’t know not personally it hasn’t sort of changed my life (laughs)you know (laughs) it’s not like having children or marriage you know (laughs)”

Interviewer: “Overall has the ventilator been a positive or negative experience for you?”

Neil: “I expect it has been a positive experience yes…”

Interviewer: “Why is that?”

Neil: “Well it does I think it does help you with your exercise erm I think that’s the positive thing because I realised pretty early on that I erm that you need to do some sort of exercise to stabilise your condition and erm help you in future years....”

Interviewer: “Did you find it easy exercising on the ventilator?”

Neil: “Err initially not no erm it took several goes actually when I say several probably about two to three err goes before erm I got used to it really…”

Interviewer: “Why was that?”
Neil: “Erm again I think it’s the claustrophobic aspect to it and also I don’t know which brought on a little bit of a what we discussed just now a little bit of a panic err to so you know so you were probably breathing more heavily which you know is not natural.”

Interviewer: “Were there any difficulties when you exercised on the ventilator?”

Neil: “No none what so ever no”

Interviewer: “You only used the equipment on the days I visited could”

Neil: “I have used them no I have used it on other occasions sat over there and erm used it there as well…”

Interviewer: “How did you find that?”

Neil: “Ok the only thing that I did find difficult at times was putting the mask on to be quite honest with you and then I’d try try and try sometimes I have used it a couple of times erm and then you think oh blow it I’ll just do the exercises without using the equipment so that’s the only down side I mean I would have used it if I could you know fit it on better”

Interviewer: “Ummhmm is there anything you regret about the study?”

Neil: “No none whatsoever”

Interviewer: “Is there anything you were expecting or hoping the study would do that hasn’t happened?”

Neil: “No as far as I was aware I would think that this is doing a cross section as to you you to erm I presume help people in in the future really that’s the way I read it”

Interviewer: “Is there anything you would change about the design of the equipment used?”

Neil: “Yeah the mouthpiece (laughs) obviously because I’ve stated (laughs) “

Interviewer: “Ok... Have you experienced any physical changes over the last three months?”

Neil: “Erm I think in the last three months I I think before I was struggling to to perhaps go to the shops that type of thing and stopping off I just presumed that type of condition but since I have exercised and so forth erm you know I was able to walk to my shops and back without stopping”

Interviewer: “Ok have you experienced any other changes?”

Neil: “erm…”

Interviewer: “feelings or emotions or changes to your mental health?”

Neil: “No not really no”

Interviewer: “What do your family and friends think of the equipment and neighbours?”
Neil: “Erm I don’t think any of them have particularly seen it erm no I mean the only people that see and the neighbours do see is the nebulizers and that doesn’t worry me at all so”

Interviewer: “Did anything surprise you about the equipment or study?”

Neil: “Erm no not really erm I don’t think no”

Interviewer: “Have you got any advice for a person who is about to take part in the research study?”

Neil: “Err I think the only thing is erm erm I think is the keep up what you are being told by the nurse erm because it will only help you really you know I think that the advice the advice that you’re given really you’ve got to take on board because the stronger you are the more exercise is going to help your condition and help prolong your life which is what it’s all about really I suppose”

Interviewer: “Do you have any advice for health professionals who set patients up on this equipment?”

Neil: “Erm no I think my only concern erm is is the design of the mask really that that really is and I think you know because I’m still working and I’m still reasonably active you know I think for anybody that’s older and a little bit more not so perhaps as able as I am I would think they’d find that very very quite difficult to actually implement and use really”

Interviewer: “Do you think there was enough time in hospital to get used to the equipment before you went home?”

Neil: “Yes Yes Yes”

Interviewer: “Do you have any advice for health professionals carrying out this type of research?”

Neil: “Erm not really no”

Interviewer: “Did you find the walk tests, the questionnaires and the diaries?”

Neil: “Yeah I I the diaries are useful erm the walk tests erm I did find difficulty with them sometimes because I would out quite a lot into it erm and obviously the nurse would monitor me erm how I was and so forth but when doing a full exercise and then you know going to work I did find it it did take quite a lot out of me err not that I was thinking it would take a lot out of me but erm it I did actually find that it did a little bit”

Interviewer: “Did you find that on the days that when we exercised on the machine as well?”

Neil: “Erm yes that as well especially the leg exercise“

Interviewer: “Anything you would like to add about your experience of using the equipment? You have said to me you thought it helped”

Neil: “Yep”

Interviewer: “And that you thought it helped you walk further to the shops in what way di the ventilator help with the exercise?”
Neil: “Erm... to be quite honest with you I didn’t see a lot of difference from using the ventilator to erm there were a couple of times where we didn’t use it and erm I didn’t see any difference between actually using it and erm doing it without the erm ventilator”

Interviewer: “Ok Anything else you would like to add?”

Neil: “no not really erm I feel that I should you know which we discussed earlier that I should keep up some of the exercises which I think are important I think that is really about it.”

Interview 3: Gert

Took place 18/11/12 at 11am in the living room (the walls are stark as the wallpaper has been stripped off some time ago but not replaced), participant is sitting on the sofa in her tracksuit with the oxygen on via nasal specs and researcher is sitting on the opposite sofa, participants husband and daughter wandering in/out. There is a faint smell of cigarette smoke present, the audible chug of the oxygen concentrator can be heard and the television initially blaring out on 24 hour Christmas films channel.

Interviewer: “Ok so I’m starting the tape recorder…lovely he’s recording….and now on with the questions”

Gert: “I ain’t no good at talking and this sort of thing you know that...”

Interviewer: “So tell me about your hospital admission just before you started this research programme?”

Gert: “It was alright actually...I gotta be…the BRI…they do treat you well I gotta say they they did everything for me in there without them I wouldn’t be here I don’t think ….but they are good……”

Interviewer: “And how were your general activity levels and health, before you came in, do you think?”

Gert: “Before I went in to hospital? “

Interviewer: (Nods)

Gert: “Bad...Breathing...Bad it was all bad…but then you don’t realise how bad you are til you go in there do you? I always concentrated on the breathing but it’s not always that is it so it’s just as well I did go in when I did.”

(Husband enters lounge and takes remote control to turn up television…)

Interviewer: “Hi Roger...we are just doing the interview at the moments that’s why the Telly’s turned down...ok...”

Roger: “Oh right...” (Laughs)

(Roger sits down at the table)

Interviewer: “So when we are talking about the study can you tell me your experience of using the equipment for the last three months?”
Gert: “Well I gotta say…I don’t… I didn’t like using it I gotta say and the thing that goes in your nose…I don’t like that sort of thing…but in general… yeah…I think it’s a good thing actually…I think it’s a good thing…I just didn’t like that part (looks at Roger)”

Roger: “No? What the thing up your nose…”

Gert: “Yeah…I tell you Roger I don’t like it up your nose…it’s the air going through your nose… because if it’s too high obviously it covers your breathing and it reminds me of that I had in hospital of the mask that’s what it reminds me of and I didn’t like that either (laughs) but no in general I think it’s a good thing to come round like this…I never knew people would come round like this but yeah…”

Interviewer: “So was it the actual pillows that you…”

Gert: “Yeah…yes…yeah well if you got to use it you got to use it haven’t you but in general it was alright…."

Interviewer: “What about the pressure?”

Gert: “I didn’t like the pressure on it either… no…I didn’t …no”

Interviewer: “Was there anything worse about it at the beginning or…?”

Gert: “It’s the beginning that’s the worse once you’ve got it on you are alright cause you’ve got to get used to it…..but it is the beginning puts you right off….but once you’ve got it on you’re alright”

Interviewer: “Did it change over the 3 months or you didn’t enjoy…?”

Gert: “I didn’t enjoy any of it…no, no”

Interviewer: “How would you describe using the equipment to someone who has not used it before?”

Gert: “Very difficult (laughs) cause I didn’t like using it without you being here mind…cause I was frightened that I was going to break it or I was gonna do something that’s why I never ever used it but erm once.. I think once they you’ve shown them properly a couple of times they should be alright shouldn’t they…”

Interviewer: “How would you describe it to them?”

Gert: “Oh (laughs) I don’t know, I don’t know how to describe it…but then I’m not that sort of person so…..”

Interviewer: “What would you say it feels like?”

Gert: “What doing it yourself?...No…I didn’t like it at all I gotta admit……..”

Interviewer: “Was it similar to anything you could describe or felt…?”

Gert: “No…No I haven’t ever felt it so I don’t know”

Interviewer: “Or could you describe it to someone?”

Gert: “No…no …I haven’t ever felt it so I don’t know……”

Interviewer: “So would you say overall the ventilator has been a positive or a negative experience for you?”
Gert: “Well it’s obviously a positive thing otherwise I wouldn’t be using it would I? So it is obviously positive but err… some things you get used to and some things you don’t do you? And that I didn’t get used to”

Interviewer: “What did you get used to? Was there anything we did that you got used to?”

Gert: “I mean the exercising that’s alright I don’t mind things like that…it was just that...(looking at the ventilator) but other than that yeah it was alright………..”

Interviewer: “Did you find it easy exercising on the ventilator?”

Gert: “Yeah I did yeah I did find it easy…yeah”

Interviewer: “In comparison to when you did it without did you find any differences?”

Gert: “What without it……..Oh yeah you don’t get the same benefit do you? If you haven’t got it on you don’t get the same benefit…so…yeah having it on did make a lot of difference…”

Interviewer: “In what way?”

Gert: “Well it helped you didn’t it when you did your exercises…it does help you…..so”

Interviewer: “I’m going to push you…in what way?”

Gert: “I don’t know…………don’t ask me that…”

Interviewer: “So you said it was better using the machine…how did it do that?”

Gert: “It helps you breathe a little bit better with it on it does…when you’re exercising….otherwise you’re out of breath so bloody quick that did help… but other than that …no”

Interviewer: “Did it help during or after for recovery or both?”

Gert: “No… during…………”

Interviewer: “So what was the hardest bit about it?”

Gert: “Erm…”

Interviewer: “The mask….the”

Gert: “It is the mask…yeah…”

Interviewer: “And I know you said you used it when I was here but you didn’t use it when I?”

Gert: “Once…I used it once when you weren’t here…”

Interviewer: “And how did you find that?”

Gert: “I couldn’t get on with it…cause it was only the once…and it was the pressure…I couldn’t get the pressure right…the thing is if you’re not using it all the time you don’t know do you so…that is why I never used it again without you being here…cause I couldn’t get it right….”

Interviewer: “The mask fit or?”
Gert: “No the mask fitted...no it did fit...it was just getting the pressures right on it...”

Interviewer: “The pressures?”

(Silence)

Interviewer: “Ok was everything else ok...the hose...etc.”

Gert: “Yes everything was fine...everything was fine”

Interviewer: “Is there anything you’d change about the design of the equipment?”

Gert: “Yeah the whole lot (laughs)...nah... it’s alright if you...I mean if you’ve gotta use it you’ve got to use it haven’t you the designs alright in it...it’s just a matter of putting it on the floor really so yeah that’s alright.. I mean you wouldn’t have it any other way really are you cause that’s about right”

Interviewer: “So you’ve said to me you don’t like the mask...what would you change about that?”

Gert: “It’s at... the nose really...it’s the pressure...but then that gotta be there...so”

Interviewer: “So do you think it would be better if the machine started with a lower...?”

Gert: “Yes definitely lower...put it on low...let it increase and then you get used to that...”

Interviewer: “Is that what was hard about doing it on your own was you couldn’t get the pressure right?”

Gert: “Yes because I couldn’t get the pressure right...Yeah...otherwise I would have used it...”.

(Silence)

Interviewer: “Erm do you think you’ve experienced any physical changes over the last 3 months?”

Gert: “No”

Interviewer: “No?”

(Silence)

Interviewer: “Have you experienced any benefit from using it?”

Gert: “No I can’t say I have I gotta be honest...no I haven’t”

Interviewer: “Were there any negatives of using it?”

Gert: “No not really...no”

(Silence)

Interviewer: “What do your family and friends think about it?”

Gert: “They haven’t seen it...I don’t get a lot of people up here...so...it’s just as well really there aren’t a lot of people that come up here...so”
Interviewer: “What does your husband think about it?”
Gert: “He’s alright with it...in’t it Roger...”
Roger: “Yeah”
Gert: “That machine”
Roger: “Umhmm”
Gert: “He thought it was good”
(Silence)
Interviewer: “Did anything surprise you about doing the study or using the equipment?”
Gert: “No not really...no”
(Silence)
Interviewer: “Have you got any advice for a person who’s about to take part in it?”
Gert: “Don’t bother (laughs) don’t bother no it is a good thing when you it is... if you...you know it is if you need something like that it is a good thing for people to use”
Interviewer: “Why do you think it’s a good thing?”
Gert: “Well it ain’t no good to me I... I didn’t use it but it would help with your breathing I suppose wouldn’t it…”
Interviewer: “Do you think you got any benefit from the sought of twice a week sessions you did with me?”
Gert: “No I just enjoyed somebody coming to be honest... It was just somebody turning up......and... cause I don’t get nobody up here anyway...so company as well as you know…..”
Interviewer: “Do you think it had any impact on your walking or?”
Gert: “I could walk alright with it”
Interviewer: “Or your weight …?”
Gert: “The weight it didn’t but...not at the moment no ....It might have done actually cause I am losing it, I am losing it...this at the moment... I aint this is what I got but I am losing the weight I gotta admit”
Interviewer: “There were a couple of sessions where you mentioned that you thought your tummy had ...?”
Gert: “Gone...Yeah it went down but…this is different (pointing at stomach) this will go in a couple of days”
Interviewer: “What about sort of getting out and about?”
Gert: “I do get out and about yeah I do get out and about...I ain’t saying I walk that far but I don’t but I do get out and about”
Interviewer: “Can you see any difference in how you were before you went in to hospital to how you are now?”

Gert: “Oh yeah definitely Oh yeah I can walk a little bit better than what I did...and I do feel a little bit better I gotta say...cause before then I was just I was miserable...I gotta admit...and things was worrying me as well but at the moment now I’m fine...I’m much better now I do say so”

Interviewer: “So before your admission you were feeling anxious and down?”

Gert: “Yeah I was really down and yeah I was but at the moment no I’m alright”

Interviewer: “Good...Have you got any advice for a health professional setting up patients on this equipment?”

Gert: “No not really cause I ain’t no good at that sort of thing...so...I ain’t no good at speaking to people anyway...so...”

Interviewer: “Well you have given me advice...you’ve said how you would start the pressure on low then turn it up”

Gert: “Oh yeah...you gotta do that...yeah...but it is a good thing for anybody to use”

Interviewer: “How about the mask?... how could we make that better... how could we change it?”

Gert: “You can’t really can you...the mask is the mask in it”

Interviewer: “All right erm did you think that the exercising each week on the ventilator might have...might have erm...”

Gert: “Helped?...yeah It did help yeah it did I get in and out a little bit more I’ve got to say...whereas I used to sit in the chair and let him (nodding at husband) do everything but not now I do’s get up...and do washing and that sort of thing so...”

Interviewer: “Do you think it was worth it?”

Gert: “Yeah I think so...yeah yeah it was worth it”

Interviewer: “Anything else that you want to add?”

Gert: (Groans)

Interviewer: “About the exercising...the ventilator...anything you found hard?”

Gert: “Well I didn’t find anything hard really...I mean that sort of thing would be alright for old people as well wouldn’t it...because it’s light...”

Interviewer: “Yep...did you find it easy exercising in your home?”

Gert: “Yeah I did yeah...I did but we’ll after Christmas start back at the school (local gym group)”

Interviewer: “That’s good to hear...Anything else you want to add?”

Gert: “No”

Interviewer: “Feel happy?”

Gert: “Yep”
Interviewer: “Thank you…I know it’s difficult and you didn’t like doing it but you did really well”

Gert: “I hate doing things like that”

(Recorder turned off)

Interview 4: Elsie

Took place in Elsie’s council flat, faint smell of cigarettes, lots of cats present and chug of oxygen concentrator present.

Interviewer: “So I’ll just check the recorder is working...testing...lovely. Alright...so...I’ll sit this side so you can see me facing you...Ok so this is just to recap of it all really where am I best to sit here so I’m facing you?”

Elsie: “no you’re fine there”

Interviewer: “It’s a recap of the whole project and you using the ventilator and your experiences. So just a few general questions that I’ll ask you and then some more specific ones...but it’s more for you to do most of the chatting to me which I know you like talking so...(laughs)...that’s always good”

Elsie: (Laughs)

Interviewer: “So to start with if you just tell me a little bit about the run up to the project and how it’s been the actual experience of having COPD?”

Elsie: “It’s a horrible thing to have because it does stop you from doing a lot of things...erm…”

Interviewer: “Like what….?”

Elsie: “Things you used to be able to do like a lot of cleaning things which I’ve managed to overcome which I do erm but not in a fast speed I just started slowing down on everything”

Interviewer: “Anything else it’s stopped you doing?”

Elsie: “No… not… well I’m not as active as I used to be but I try to keep it at a level”

Interviewer: “So prior to coming into hospital what were your main symptoms would you say?”

Elsie: “What this time...or...?”

Interviewer: Nods

Elsie: “Erm... just couldn’t breathe very well”

Interviewer: “Anything else?”

Elsie: “I don’t know If I did I can’t remember if I did have a cough … I just didn’t feel well..”

Interviewer: “And was it a gradual thing…or did you...something that happened suddenly?”
Elsie: “About three or four days it start...sort of built up but then I mean I was only on one Litre of oxygen I mean when I went into hospital they put it up to 3 and my sats and everything went up”

Interviewer: “And how had your health been the year before coming into hospital?”

Elsie: “I was fine for a year... yep... cause I’d been in hospital the year before and everything was fine but it was that Christmas sort of when you’re rushing around everywhere cause it always seem like Christmas time that I go down...sighs”

Interviewer: “Ok...and tell me a bit about sort of...how you came to come into hospital?”

Elsie: “Erm... I was feeling unwell and the doctor... came out and he said to me that he would get some nurses in every day...every evening they would come and look at me and monitor me and everything...erm. they done it for about two or three days and the third day things weren’t changing so they rang and spoke to the doctor and the doctor said arrange for an ambulance...me sats just wouldn’t come up”

Interviewer: “And how did you feel at that moment coming into hospital?”

Elsie: “Erm... sighs well...there was no other choice really because I just want to get better...sighs”

Interviewer: “And what were your symptoms coming in to hospital?”

Elsie: “Erm the breathing as I said I don’t think I did have a cough...I just felt tired and my breathing”

Interviewer: “And what was your activity levels just prior to coming in?”

Elsie: “Erm all over the Christmas I was fine it was like a couple of days after Christmas I started to sort of feel worn out...it was like I couldn’t bring myself back up I was just going down and down”

Interviewer: “Had you been able to leave the house?”

Elsie: “I was out Christmas time but I don’t think I went out after that”

Interviewer: “Ok erm... can you tell me a bit about your hospital experience and how that was?”

Elsie: “Erm... a bit frightening in the beginning...erm...”

Interviewer: “What was frightening about it?”

Elsie: “Cause I was sort of had to wear a mask...erm...”

Interviewer: “Tell me about that, what did that feel like?”

Elsie: “Well I’m a bit claustrophobic and I sort of can’t stand anything around my head...erm...but if it got me better then obviously you know erm...but I didn’t stay in bed which I never do if I’m ill I’m I want to get out of bed and sit in the chair and I was glad when you came along and took me for walks and talking to me”
Interviewer: “Ok great...so how much better did you feel sort of the day you left hospital from coming in?”

Elsie: “From going in erm I feel about 70% better but now as the time has gone on now it’s escalated”

Interviewer: “Great”

Elsie: “So I was still a bit shaky when I came home weren’t I”

Interviewer: “Shaky in what way...weak?”

Elsie: “Nervous”

Interviewer: “What were you nervous about?”

Elsie: “Erm I think it was everything like you said I was weak erm unsteady on my feet aswell erm”

Interviewer: “That’s fine...ok so tell me about your experience of exercising on the ventilator if you think about it from the beginning to now?”

Elsie: “It’s really helped...”

Interviewer: “Ok in what way?”

Elsie: “It’s improved on my breathing erm it doesn’t make me want to stop and overall it is a good thing for like people in my condition to use”

Interviewer: “Did it feel very different to using the ventilator in hospital?”

Elsie: “Yeah a lot different”

Interviewer: “I’m going to push you as to why...?”

Elsie: “It wasn’t so overpowering on the face and the mask didn’t feel half as bad........”

Interviewer: “Do you think it helped that you’d experienced it acutely sort of in hospital?”

Elsie: “Yeah...yeah...”

Interviewer: “So if I’d come to you before and said I’m going to try the ventilator on...?”

Elsie: “It would have frightened me”

Interviewer: “It would have frightened you?”

Elsie: “Yeah...yeah...yeah”

Interviewer: “Cause it did frighten you a little bit in the beginning when I came to talk to you?”

Elsie: “Yeah I was thinking about the other one laughs...yeah...Alright in the beginning with the other one I was scared...erm and I...”

Interviewer: “What made you scared? Was it how unwell you were?”
Elsie: “No I think it was just having that over my face and it was very hard to get to sleep with it because it was the way it was going and I think I must have just given in and just laid down to it and that was it...but it seemed to be like I was fighting it for some reason but I started going through the night then with with it ok”

Interviewer: “Did you see the ventilator and maybe you didn’t? But as deterioration is that why you were anxious about it?”

Elsie: “Yeah…”

Interviewer: “So like with home oxygen that was another step?”

Elsie: “Yeah…yeah…cause I thought I was gonna be on it all the time...I think it was when you came round talking to me and told me it was just when I needed it at night and whatever”

Interviewer: “Was it was it a different way of introducing the mask that helped so obviously when you were in hospital it’s put on in a different way obviously it’s quite urgent because you’re poorly?”

Elsie: “Yeah”

Interviewer: “Did it seem different…?”

Elsie: “What this one here”

“Yeah yeah very much different it was slowly introduced “

Interviewer: “Yep”

Elsie: “And… erm… its as I said it’s not because the thing is you breathe with that one the other one does the breathing for you”

Interviewer: “So the claustrophobia you got with the machine in hospital you didn’t seem to get with this one?”

Elsie: “I did but not as bad…yeah”

Interviewer: “More to begin with is it something that got better?”

Elsie: “Yeah…it got better as time went on…yeah”

Interviewer: “Ok good and erm how does it feel this ventilator when you’re using it how would you describe it to someone that’s not seen it before?”

Elsie: “Don’t know…erm…what the use of it?”

Interviewer: “Yeah what does it feel like?”

Elsie: “Erm… helpful in the way that you don’t seem to get out of breath like you do if you do one without it”

Interviewer: “So you spoke about the hospital one being a timing thing and fighting with it why doesn’t this one feel like that, did this one ever feel like that in the beginning?”

Elsie: “No I was just scared in the beginning…yeah…………..”
Interviewer: “How does it feel…would you be able to describe the sensation to anyone…what it feels like…the pressure?”

Elsie: “Erm…if… if…you don’t work with it you get all the noise the bubbling…it’s just concentrating on using it and using it the right way…………”

Interviewer: “Sort of how long do you think it took you to get used to it?”

Elsie: “Couple of days”

Interviewer: “Were you anxious about using it on the days I wasn’t here?”

Elsie: “No…No cause you’d already talked me through it erm as I said if you don’t use it in the right sequence it doesn’t work properly does it your blowing back into it so you are breathing it in as it is giving it to you and then out again”

Interviewer: “Did you find there was anything tricky about setting it up?”

Elsie: “No…no”

Interviewer: “No problems with connecting the oxygen…or?”

Elsie: “I did did once erm and the masks quite easy…what I did was I kept it as it was…I didn’t undo any of it……”

Interviewer: “Did you find it quite easy exercising with the ventilator?”

Elsie: “Yeah…yep…I mean I can do it with or without I could do it with or without it but as I was supposed to be using it I carried on using it”

Interviewer: “Did it make you feel more confident to do exercise without it then as well?”

Elsie: “Yeah…very much so…”

Interviewer: “Why do you think that was?”

Elsie: “I don’t know because you talked to me about it I’ll be honest with you it seems to give you the will to try things erm you know you sort of done it with that and then you think let me try it without it and its surprising..”

Interviewer: “In a good way?”

Elsie: “Yeah because you haven’t got that you know when like you’re up and down you haven’t got that going with you even if you don’t do the full amount like you were doing on that at least you are doing something and that is the way I looked at it as well I did try as much as I could but obviously I done more with that”

Interviewer: “Did you find it took much power and it was expensive to run?”

Elsie: “No because I charge it once since I’ve come out of hospital”

Interviewer: “Right…..now I’m just going to remember a few things you have said about it and one negative was you couldn’t wear your glasses with it?”

Elsie: “No”

Interviewer: “Was that an issue?”
Elsie: “Well if I was sort of on it most of the time I don’t think I would have liked it because obviously the glasses and it’s not very nice...this one’s ok but the bipap with false teeth”

Interviewer: “Right ok...so this one was fine with your dentures...?”

Elsie: “Yeah...yeah”

Interviewer: “But the one in the hospital was not?”

Elsie: “Yeah”

Interviewer: “Was that the shape of the mask in hospital or?”

Elsie: “I think what it was was crunching your teeth what with them being loose and they were sort of going out”

Interviewer: “Ok but you never experienced that with this…”

Elsie: “No No”

Interviewer: “Interesting…and how was it when you were trying to walk on it?”

Elsie: “I didn’t like that”

Interviewer: “Interesting…Ok why not?”

Elsie: “Don’t know…”

Interviewer: “Because you couldn’t see?”

Elsie: “Yeah it it as I said to you in hospital it sort of throws you off and I wasn’t actually walking in a line I was whether it was cause as you said the vision sort of thing it was sort of blocking vision”

Interviewer: “But all the other exercise were easy to do on it?”

Elsie: “Yeah”

Interviewer: “Did you find it heavy to move around?”

Elsie: “No”

Interviewer: “Quite light?”

Elsie: “Nods”

Interviewer: “Did it pack up alright?”

Elsie: “Yeah”

Interviewer: “Clean alright”

Elsie: “Yeah...everything’s in there anyway so”

Interviewer: “Great...so...erm… how was it being involved on the research?”

Elsie: “It was very helpful...you were very understanding...and you were very helpful”

Interviewer: “Is it something you have done before?”

Elsie: “No”
Interviewer: “Is it something you would do again?”

Elsie: “Yeah”

Interviewer: “That’s good why do you say that?”

Elsie: “Because it er well there’s always changes and you’ve probably come up with and another person’s probably come up with something that would be more helpful as well I really really appreciated what you have done…”

Interviewer: “Thankyou…I’m going to check through my list…is there anything else you want to add before I go through some more specific questions?”

Elsie: “No…no…it seems …how many weeks have we done this now..”

Interviewer: “So twelve”

Elsie: “Yeah that’s surprising isn’t it”

Interviewer: “Gone quick?”

Elsie: “Yeah…the only …well…the only thing that upset me in the beginning…was the weather and not being able to go out…and I think I was getting very depressed…because it was four walls and that was the only thing I feel was a let-down the whole three months…we were talking about six weeks weren’t we when I never went out..”

Interviewer: “Cause of winter?”

Elsie: “mmm…and I think since the weather has changed…alright it’s not very nice today but I think since the weather changed it has brightened me up as well”

Interviewer: “Do you think if you hadn’t have had this you would have done any of the exercises?”

Elsie: “I would have done some because I can remember…but not it’s more advance what you’ve done now with this”

Interviewer: “So sort of having severe lung disease…did you feel there was much more that could be done for you?”

Elsie: “No…No and this is where you come in (tearful)…I really appreciate it………..”

Interviewer: “Did you feel forgotten?”

Elsie: “Yeah…yeah cause once well obviously once you’re discharged from the hospital from the doctor you know you just report back to your doctor if you’re not well but again that worries me if I went to the doctors with a chest infection will it automatically mean back in hospital cause I mean is he going to give you a chance to see if you come out of it…and that is one thing that worries me or don’t worry me I think about I mean..”

Interviewer: “Do you worry about coming back into hospital?”

Elsie: “No I don’t worry it’s just the fact that is it every time I’ve got a cold I got to go in? Cause I can’t see that I mean you can probably answer that?”
Interviewer: “So you are worried…I’m not sure I’m understanding what you are worried about?”

Elsie: “No not worried I just think about…Is it every time I get a cold will I end up in hospital…yeah…I mean I’ve got my tablets…”

Interviewer: “Your antibiotics and steroids”

Elsie: “Yeah yep and I have been told the steroids for a cough now I was always told the antibiotics”

Interviewer: “The antibiotics if it is a productive cough”

Elsie: “Mmm”

Interviewer: “No not necessarily…I guess because you were so unwell they are not going to mess around it might be that you only need to come in for twenty hours…what it doesn’t mean is that you are ultimately going to have the machine on and I think that’s the important thing to reassure you…what they will do is take a blood test quickly to decide and that’s the thing because it’s better that you go in and are sorted out quickly and you might only need to stay a couple of days as opposed to a week”

Elsie: “Yeah…mm…yeah”

“I and I know when we’ve talked about stuff and general health and wellbeing you did say that the past year you’d been doing less than previously?”

Elsie: “No for eleven months “

Interviewer: “So really it was the last month?”

Elsie: “It was like in the December after Christmas I’d been well from Christmas to the new year New Year’s eve I started to feel unwell”

Interviewer: “And had you had any contact with the hospital in that last year?”

Elsie: “No I’d had a letter to go but that was cancelled by the hospital cause it was snow then the next one I had my aunty had died and it was her funeral so I rang and then I had another letter saying that cause I hadn’t been to 5 appointments which wasn’t true it was 2 appointments they closed the book on me and they were going to write to my doctor and if anything my doctor would have to refer me back”

Interviewer: “Do you find it difficult to get to appointments?”

Elsie: “What the hospital…no…no over there its brilliant BRI it’s a bit different but that’s handy over there yeah and my GP’s just down the road”

Interviewer: “How would you describe using the equipment to someone that’s not used it before?”

Elsie: “Go ahead and use it…don’t be afraid because it will help”

Interviewer: “Any advice top tips?”

Elsie: “Do as you’re told (laughs) and push on through…”

Interviewer: “So how has it influenced your life would you say?”

536
Elsie: “It’s been a good teacher…very good teacher…”

Interviewer: “Do you mean in terms of pacing?”

Elsie: “Yeah…erm… you…you obviously you’ve got to work with the machine you’ve got to work with the machine but you’ve got to concentrate on what you are doing as well otherwise it would just be a waste of time…am I answering all your questions alright?”

Interviewer: “Yes it’s good I want to hear from you so its fine I’d rather you just chat on…

Erm so would you overall say it’s been a positive or negative experience?”

Elsie: “Positive”

Interviewer: “Was there anything challenging about it?...I guess the claustrophobia in the beginning was?”

Elsie: “Erm it was just getting used to it and I as you know I didn’t really walk with it it was only with you that I walked with it erm but it was………”

Interviewer: “Was all the instructions on it easy? The ons…offs …the connections?”

Elsie: “Yeah, yeah”

Interviewer: “And did it feel like an extra burden having another piece of kit in your house…not just that but the exercise equipment as well taking up more room?”

Elsie: “No… No… No”

Interviewer: “It didn’t make you feel like you’d progressed a bit or changed?”

Elsie: “Well no because probably you probably had all this equipment before but nobody had sort of only you have come out…I don’t know I mean is it new to you?”

Interviewer: “Erm…it’s not new to me in that I’ve worked with it for a long time but this obviously using it for exercise is quite a new idea particularly in people that sort of have more advanced COPD that have come into hospital and been unwell…yeah that’s a new thing…erm were there times when you chose not to use it or not to exercise?”

Elsie: “Only…my back today…”

Interviewer: “That’s fine…but was there at time when you couldn’t be bothered or?”

Elsie: “No I done it and I done the stairs and I done the steps”

Interviewer: “Was it an effort to do it on some days?”

Elsie: “No…because I that can be a lot easier than to do it without it”

Interviewer: “So you can achieve more with it?”

Elsie: “Yeah…yeah…”
Interviewer: “If you did do an exercise session did that mean you could still do your daily tasks?”

Elsie: “Yes...yeah”

Interviewer: “Would you change anything about the design of the equipment?”

Elsie: “No...because it’s compact...very compact... and I mean everything’s in the bag so you haven’t got to oh where I put that and where is that...it’s all there”

Interviewer: “So I know you’ve used nebulisers before and you’ve used oxygen concentrators how does it compare to that in terms of set up...?”

Elsie: “About the same, it’s only like the fact that you unplug this put it in the side...you put the tube in for your mask and you’ve got your switches”

Interviewer: “Are you going to miss it?”

Elsie: “Probably will...yeah...yeah but as I said I want to go forward and say well I’ve done this on my own or I done that on my own”

Interviewer: “So have you experienced any physical changes over the past few months?”

Elsie: “I’ve got stronger a lot stronger…”

Interviewer: “Are we talking emotional strength…or physical strength?”

Elsie: “Everything...everything it has opened my eyes more knowing that there is something else out there that will help…”

Interviewer: “Any other physical changes?”

Elsie: “I don’t know I……”

Interviewer: “Do you think you’ve lost weight?”

Elsie: “About the same...well I’m a little bit lower than I was about 4 to 5lb lower but it is keeping active really does help cause I think probably by now I’d of probably have put more on…”

Interviewer: “Because of being at home?”

Elsie: “Yep....”

Interviewer: “Have you experienced any other changes? So sort of feelings...emotions... or mental health?”

Elsie: “Well I’m not as depressed as I was because I’ve got something to occupy me as you said when I’m not using it and I’m sat there I get up every ten to fifteen minutes and I walk into the kitchen or walk the hallway and I come back in I don’t stay in one place “

Interviewer: “So it’s changed your…”

Elsie: “Attitude towards exercise”

Interviewer: “And being sedentary?”

Elsie: “Yes”
Interviewer: “That’s great to hear…what do any friends who have seen you use it…what do they think about it?”

Elsie: “I’ve only one friend see me…but I have had lots of comments about how well I look…”

Interviewer: “That’s good…and what did they think about the equipment?”

Elsie: “My friend said it’s amazing…what they can do for people now…”

Interviewer: “Did anything surprise you about the study?”

Elsie: “No because if it helps other people I don’t really mind because I done one for breast cancer on the tablet and it wasn’t until the end of the five year survey that you knew what you were taking in fact I didn’t know for about ten years and it turned out I was taking tempazepam…not temazepam…tamoxifin…and not placebo…but that was only because they rang me to ask me to do another trial and I said well no not really because I didn’t have the results of the last one and then the next day they rang to say I was on tamoxifen…”

Interviewer: “Has it been time consuming for you?”

Elsie: “No...No...I mean you are not here every day so you know you’ve helped me...so what I’ve done every day is like a pattern every day right eleven O’clock it’s time to do this and I got myself into that (laughs) I mean you gotta have a timetable or a you know obviously if I had doctors or anything...but I still done it not said oh well I’m going to the doctors so I won’t...or I can’t be bothered with that today...I done it”

Interviewer: “That’s great. Did you have any side effects from using it? Did you notice?”

Elsie: “Aching limbs ((laughs)) yeah but that could have been the stairs as well though mind”

Interviewer: “Anything from a respiratory point of view...did you get a dry mouth?”

Elsie: “That does dry your mouth out but as soon as you take it off you are alright...but erm...the exercise did...it’s like you said if you are not used to it you will you will feel it (laughs)”

Interviewer: “Erm do you have any advice for people who set this up on people...so particularly the people who do the acute hospital stuff...if they had put it on you differently would it have changed your perception of it?”

Elsie: “And talked more about it as well...cause they don’t really tell you what they are actually doing all they say is that we’ve got to put a mask on you and that’s it...”

Interviewer: “So you don’t think they explained properly what it was?”

Elsie: “No...no”

Interviewer: “Did you know about it before?”

Elsie: “Yeah”

Interviewer: “Had you had it before?”
Elsie: “No”

Interviewer: “What was your understanding of it before you had it?”

Elsie: “Erm that it did help to take out some of the enzymes in your body and that is what it does isn’t it…”

Interviewer: “Had you seen any one use it before?”

Elsie: “I’ve seen quite a few people…my sister had it…I think…but she wasn’t on it all the time and they wouldn’t let her have it..”

Interviewer: “Did that influence what you thought about it?”

Elsie: “No…No cause I saw the difference in her look”

Interviewer: “Have you got any advice for someone like me who sets this up on patients at home…anything I could change?”

Elsie: “No because you explained everything …you explained to me in hospital and then when we got together the first time you showed me and you explained all that it does and you said like you can turn it up you can adjust it an everything which is good”

Interviewer: “That’s good to hear. So is there anything else about using the equipment or the study that you would like to talk about or add?”

Elsie: “Well I’d just like other people to take part it would make a lot of difference for yourselves and it would help the people cause I’ve seen what it done to me…”

Interviewer: “Just give me an idea of what you can do now…what you couldn’t do before?”

Elsie: “Erm I can walk round the shops, I go up and down the stairs, I walk out to the front with the oxygen obviously erm I’ve been out a few times…been to the hospital…been to the doctors…been to my cousins…went out for a meal which is something I haven’t done for a long long time.. I mean I couldn’t tell you well it was probably about eight months ago that I walked around the supermarket with a trolley…cause a lot of people… even this morning said oh where’s your scooter”

Interviewer: “That’s great and you’re back doing stairs”

Elsie: “Yep…”

Interviewer: “Is that something you hadn’t done?…”

Elsie: “Yep…Erm I haven’t done it today obviously but I done it the last few days but I will make up for it honestly… I will do it”

Interviewer: “But it’s something you haven’t been able to do for a while? You’d been getting the lift?”

Elsie: “Hmm… I mean I won’t go down all the flights of stairs…but I must admit I went over there this morning and if I didn’t have the trolley before  I would have had to have stayed on the bike…scooter”

Interviewer: “The next stage is to go on to pulmonary rehab which is fantastic”

Elsie: “Ummhmm”
Interviewer: “Was that something you would have thought about before?”
Elsie: “I turned it down quite a few times”
Interviewer: “Why was that?”
Elsie: “Because people had told me they are very pushy”
Interviewer: “In what way?”
Elsie: “Force you to do things…but I’ve learnt now you shouldn’t listen to other people (coughs)”
Interviewer: “And is that the only reason that you turned it down?”
Elsie: “Yeah”
Interviewer: “Did anyone explain to you that this might not be the case?”
Elsie: “I read it this time in a booklet from the hospital I came away with the other day…they won’t force you to do anything you don’t want to do (laughs)”
Interviewer: “So now you’ve finished this research…are you feeling a bit more positive about life?”
Elsie: “(tearful) very much…very much (laughs) but I’ll tell you why I’m laughing I’ll tell you soon”
Interviewer: “Ok…and do you feel a bit more positive about your condition?”
Elsie: “Yeah…yeah”
Interviewer: “And obviously you still get breathless do you feel in control of it now?”
Elsie: “Yeah yep and I’ll be honest with you Kate I know like with the oxygen…erm I said to you about cold sores…if you know anyone that is the best thing (pointing to lip salve)not Vaseline…they are gone
Erm what was the question you asked me”
Interviewer: “Erm do you fell more in control?”
Elsie: “Yeah…yeah… and another help has been me getting a sats machine as well because I can monitor the doctor…but they are expensive for some people that was £24 “
Interviewer: “So self monitoring is important to you?”
Elsie: “Yeah…when I saw them a while ago they were sixty nine pounds and when the doctor took hers out last week it’s exactly the same as the one I got (laughs)cause I said to her I bought one and she said very good idea”
Interviewer: “Why is it important for you to know what your oxygen levels are?”
Elsie: “Because if my sats go don then I know that there’s something wrong and then it’s not advancing more”
Interviewer: “And how did you feel doing the monitoring stuff…so the questionnaires and walk tests”
Elsie: “Brilliant because it’s all a kick up the bum (Laughs)"

Interviewer: “So you never resented it…”

Elsie: “No”

Interviewer: “And the walk tests because I know that’s something you had talked about disliking before”

Elsie: “I did pretty well”

Interviewer: “Amazing”

Elsie: “Yeah I think over the weeks it starts to build up more and more and more...the last time was twenty seven times weren’t it... I mean I couldn’t believe I done that many and then we done steps you know I think it’s progression you done that and then you think oh I’ll achieve this or that the next time I just go for it…”

Interviewer: “What do you think the worst thing about COPD is?”

Elsie: “Breathlessness…frustration of not being able to alright I don’t hoover I use the little hand held erm I do everything...I clean windows and everything but in moderation I don’t go berserk with it I cooked a lovely dinner yesterday...I washed up...everything...but it’s just that as I’ve said to you before I am one that used to walk fast do everything pretty fast and it’s the learning to slow down and it does help...you still get breathless but not as bad”

Interviewer: “So you have had to completely change…”

Elsie: “Your way of life...yeah”

Interviewer: “Do you feel...I mean I know you get out and about now but Would you say it was quite lonely having COPD?”

Elsie: “Erm... it can be I mean I’ve got loads of friends but I just don’t see them now... I mean I had a friend we used to go out in the car and we used to go shopping and everything together but I don’t even ask now and she doesn’t ask me sometimes you can feel very cut off I mean the girls I used to work with before at work you know in a job you keep in touch for a while and then everything wears off and you don’t hear anything for a while...a couple of people on Facebook....that I used to work with and all that...but you can get very lonely...very very lonely…”

Interviewer: “Do you think there is much support for people with COPD?”

Elsie: “There probably is Kate if you look around but who do you contact..... I know there is a phone number for the British Lung foundation and all that but there’s nothing is there now really… (Sighs and yawns)”

Interviewer: “So let’s finish the interview on a positive…so my understanding of what you have told me is the research has been a very good experience for you?”

Elsie: “Very very good”

Interviewer: “It has changed your perception of the ventilator?”

Elsie: “Yeah”

Interviewer: “Its changed your perception of exercise?”
Elsie: “Yep”

Interviewer: “And you are able to do a lot more than you were?”

Elsie: “Yeah”

Interviewer: “You are not afraid of exercise?”

Elsie: “No”

Interviewer: “And it has also improved your feeling down/depression?”

Elsie: “Yeah”

Interviewer: “Would you say there is anything else or is it all?”

Elsie: “Captured...I mean there’s nothing else really... I could kick myself now for having this (Elsie injured her back loading the washing machine) but it doesn’t stop me walking a slow pace but not too far... I don’t say to myself I can’t do that so every 10 to 15 minutes even if it’s only out there and come back in at my own pace I done it cause the worse thing you can do is just sit there as with this illness and with what I got wrong with me now,”

Interviewer: “Anything else you want to add?”

Elsie: “No so is there any contacts?”

Interviewer: “There is the breathe easy groups so the BLF have the contacts for your nearest group...now there used to be one in Whitchurch but that had shut for a bit the BLF will be able to update you...they meet monthly and all stages of disease go and they do social activities...bingo...etc...the one I have attended is in North Bristol...that would be my preference...but also when you go to Pulmonary rehabilitation they do a follow up group so they do a maintenance group so once you’ve completed the 6 week course you can still continue...if there isn’t a breathe easy group they need someone like you to start one up”

Elsie: “Yeah...yeah...”

(Stopped recorder)

(Post interview Elsie said the other main change she wanted to thank me for was increasing her confidence and making her feel like the old Elsie again...making her feel human. But she didn’t want to say this on tape because she knew she would get upset but was happy for me to document this.)
## Appendix 21 Baseline severity data

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## Appendix 2 6MWT Raw data

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### Raw data for the 6MWT (m): Exercise on NIV in hospital group.

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### Raw data for the 6MWT (m): Exercise on NIV in hospital and home group.

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Appendix 23 SGRQ Raw data

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The raw data for SGRQ: Total scores for Exercise on NIV in hospital group.

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The raw data for SGRQ: Total scores for Exercise on NIV in hospital and home group.

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The raw data for SGRQ: Symptom scores for Standard care group.

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Appendix 24 LCADL Raw data

Raw data for the LCADL: Standard care group.

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Raw data for the LCADL: NIV on exercise in hospital group.

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Raw data for the LCADL: NIV on exercise in hospital and home group.

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**Appendix 25 MMRC Dyspnoea score**

**MMRC Raw data: Standard care group.**

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**MMRC Raw data: Exercise on NIV in hospital group.**

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**MMRC Raw data: Exercise on NIV in hospital and home group.**

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Appendix 26 MBORG Raw data

**MBORG raw data: Standard care group.**

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**MBORG raw data: Exercise on NIV in hospital group.**

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**MBORG raw data: Exercise on NIV in hospital and home group.**

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Appendix 27 EQ-5D-5L: Raw data

EQ-5D-5L utility score raw data: Standard care group.

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EQ-5D-5L utility score raw data: Exercise on NIV hospital group.

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EQ-5D-5L utility score raw data: Exercise on NIV hospital and home group.

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### EQ-5D-5L VAS raw data: Standard care group.

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### EQ-5D-5L VAS raw data: Exercise on NIV in hospital group.

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### EQ-5D-5L VAS raw data: Exercise on NIV in hospital and home group.

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