

# The effect of domiciliary non-invasive ventilation (NIV) on clinical outcomes in stable and recently hospitalized patients with severe obstructive pulmonary disease (COPD)

Dretzke, Janine; Moore, David; Dave, Chirag; Mukherjee, Rahul; Price, Malcolm; Bayliss, Susan; Jordan, Rachel; Turner, Alice

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1 **The effect of domiciliary non-invasive ventilation (NIV) on clinical outcomes in stable**  
2 **and recently hospitalized patients with severe obstructive pulmonary disease (COPD):**  
3 **a systematic review and meta-analysis**

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Janine Dretzke<sup>1</sup>, David Moore<sup>1\*</sup>, Chirag Dave<sup>2</sup>, Rahul Mukherjee<sup>2</sup>, Malcolm Price<sup>1</sup>, Sue Bayliss<sup>1</sup>, Xiaoying Wu<sup>1</sup>, Rachel Jordan<sup>1</sup>, Alice M Turner<sup>2,3</sup>

8 <sup>1</sup> Institute of Applied Health Research, College of Medical and Dental Sciences, University of  
9 Birmingham, Edgbaston, Birmingham, B15 2TT, UK

10 <sup>2</sup>Heart of England NHS Foundation Trust, Heartlands Hospital, Birmingham B9 5SS, UK

11 <sup>3</sup>Queen Elizabeth Hospital Research Laboratories, University of Birmingham, Edgbaston,  
12 Birmingham B15 2TT, UK

13

14 \*Corresponding author (Dr David Moore, Institute of Applied Health Research, College of  
15 Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT,  
16 UK, [d.j.moore@bham.ac.uk](mailto:d.j.moore@bham.ac.uk); 44 121 4147449)

17

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19 hospitalization, systematic review, meta-analysis

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## 29 **ABSTRACT**

### 30 **Introduction**

31 Non-invasive ventilation (NIV) improves survival among patients with hypercapnic respiratory  
32 failure in hospital but evidence for its use in domiciliary settings is limited. A patient's  
33 underlying risk of having an exacerbation may affect any potential benefit that can be gained  
34 from domiciliary NIV. This is the first comprehensive systematic review to stratify patients  
35 based on a proxy for exacerbation risk: patients in a stable state and those immediately  
36 post-exacerbation hospitalization.

37

### 38 **Methods**

39 Systematic review of randomized (RCTs) and non-randomized controlled trials comparing  
40 the relative effectiveness of different types of NIV with each other and usual care on hospital  
41 admissions, mortality and health-related quality of life (HRQoL). Standard systematic review  
42 methods were used for identifying studies (to September 2014), quality appraisal and  
43 synthesis. Data were presented in Forest plots and pooled where appropriate using random-  
44 effects meta-analysis.

45

### 46 **Results**

47 31 studies were included. For stable patients there was no evidence of a survival benefit  
48 from NIV (RR 0.88 (0.55, 1.43),  $I^2=60.4%$ ,  $n=7$  RCTs), but there was a possible trend  
49 towards fewer hospitalisations (WMD -0.46 (-1.02, 0.09),  $I^2=59.2%$ ,  $n=5$  RCTs) and  
50 improved HRQoL. For post-hospital patients, survival benefit could not be demonstrated  
51 within the 3 RCTs (RR 0.89 (0.53, 1.49),  $I^2=25.1%$ ) although there was evidence of benefit  
52 from 4 non-RCTs (RR 0.45 (0.32, 0.65),  $I^2=0%$ ). Effects on hospitalizations were  
53 inconsistent. Post-hoc analyses suggested that NIV-related improvements in hypercapnia  
54 were associated with reduced hospital admissions across both populations. Little data were  
55 available comparing different types of NIV.

56

57 **Conclusion**

58 The effectiveness of domiciliary NIV remains uncertain, however some patients may benefit.

59 Further research is required to identify these patients and to explore the relevance of

60 improvements in hypercapnia in influencing clinical outcomes. Optimum time-points for

61 commencing domiciliary NIV and equipment settings need to be established.

62

63

64

## 65 INTRODUCTION

66 Chronic obstructive pulmonary disease (COPD) is a chronic progressive lung disease,  
67 characterized by non-reversible airflow obstruction and intermittent exacerbations.<sup>1</sup>  
68 Treatment for COPD is based on pharmacotherapy, pulmonary rehabilitation and, in some  
69 cases, long-term oxygen therapy (LTOT). Exacerbations are a key cause of increased  
70 morbidity, mortality and poor health status, and place a considerable burden on the  
71 healthcare system.<sup>2</sup> Approximately 15% of COPD patients per year have exacerbations  
72 necessitating hospital admission;<sup>3;4</sup> between 10-25% of patients admitted with hypercapnic  
73 respiratory failure due to COPD die in hospital.<sup>5</sup> Reduced exacerbation frequency is  
74 therefore an important therapeutic target.

75

76 Non-invasive ventilation (NIV) is a method of providing ventilatory support via a mask and  
77 is effective in improving survival among patients with acute or acute-on-chronic hypercapnic  
78 respiratory failure in hospital<sup>6;7</sup>. Evidence for domiciliary use of NIV in non-acute COPD  
79 patients is more limited despite a number of systematic reviews.<sup>8-11</sup> As patients immediately  
80 post-hospitalization are at greater risk of recurrence of exacerbation than those more  
81 stable<sup>12</sup>, this difference could influence the effectiveness of NIV in preventing or reducing the  
82 impact of these events. This is the first systematic review to stratify data by these two patient  
83 groups and it is the most comprehensive review to date, including evidence from RCTs, non-  
84 randomized controlled studies and RCTs comparing different NIV settings, and considering  
85 mortality, hospitalizations and quality of life (QOL) as outcomes. Finally, this is the first  
86 systematic review to attempt an analysis, albeit exploratory, of the relationship between  
87 hypercapnia and clinical outcomes.

88

## 89 METHODS

90 A protocol detailing the methodology was registered with PROSPERO  
91 (CRD42012003286).<sup>13;14</sup> A summary of the methods is presented here. Search strategies

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92 incorporated a combination of text words and index terms relating to NIV and COPD.  
93 Bibliographic databases (MEDLINE, MEDLINE In Process, EMBASE, Cochrane CENTRAL,  
94 CINAHL and Science Citation Index Expanded (ISI)), the British Library's ZETOC and ISI  
95 Conference Proceedings Citation Index (CPCI) and clinical trials registers were searched  
96 from 1980 to Sept 2014. No study design or language restrictions were imposed. Citation  
97 checking of included studies was undertaken, and experts in the field consulted to identify  
98 further studies. The search strategy for MEDLINE is shown in the supplementary file.

99

100 Studies were eligible for inclusion if they met the criteria shown in Table 1.

101 Primary outcomes of interest were mortality, hospitalizations, exacerbations and QOL.

102 Secondary outcomes included lung function and blood gases. Study selection was  
103 performed by two reviewers independently. Disagreements were resolved through  
104 discussion and/or referral to a third reviewer.

105

106 Risk of bias was assessed based on the Cochrane collaboration risk of bias tool (for RCTs  
107 and non-randomized controlled studies), with additional criteria considered for crossover  
108 trials (ie whether there was a carry-over effect; whether only first period data were available;  
109 whether analysis was appropriate to cross-over trials; and comparability of results with those  
110 from parallel-group trials).<sup>15</sup>

111

112 Data extraction was performed by one reviewer using a standardized, piloted data extraction  
113 form, with numerical data checked by a second reviewer. Study selection and data extraction  
114 of non-English language papers was performed by native speakers of the respective  
115 languages with guidance from the reviewers.

116

117 Studies were grouped according to average proximity of patients to their most recent  
118 exacerbation that required hospitalization. If patients had not been hospitalized within 4

119 weeks to 3 months at commencement of the study or were described as “stable”, they were  
120 classed as the stable population. Where there was clear evidence that treatment with NIV in  
121 a study commenced after an episode of hospitalization (due to an exacerbation), these  
122 patients were classed as the post-hospital population, with the assumption that on average  
123 this population were at greater risk of a subsequent exacerbation.

124

125 Separate analyses were performed for each study design (RCT, controlled studies) and  
126 primary outcome (survival and hospitalizations). Where there was clinical and  
127 methodological homogeneity between studies reporting the same outcome and using the  
128 same outcome statistic (reported or calculable), random effects meta-analysis was  
129 undertaken in STATA (Stata Statistical Software: Release 10. StataCorp LP). Results for  
130 other primary outcomes were reported narratively (exacerbations and QOL). Secondary  
131 outcome data (FEV<sub>1</sub>, FVC, PaCO<sub>2</sub>, PaO<sub>2</sub>, 6MWD) were not pooled due to between study  
132 heterogeneity, but is presented in forest plots in order to show the overall direction of effect  
133 and uncertainty.

134

135 Exploratory post-hoc analyses of study level data were performed to determine if baseline  
136 hypercapnia could predict response to NIV, or whether change in hypercapnia correlated  
137 with any effect of NIV on mortality and hospitalizations.

138

139 PRISMA reporting guidelines are adhered to.<sup>16</sup>

140

## 141 **RESULTS**

### 142 **Main study characteristics**

143 Screening of the 7,405 records identified by the searches yielded 21 RCTs (18 NIV v usual  
144 care; 3 NIV vs another form of NIV) and 10 non-randomized controlled studies (5

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145 prospective, 5 non-prospective; Figure 1). Table 2 shows the main characteristics of these  
146 studies.

147 All patients had GOLD stage III and/or IV COPD, or were described as 'severe' (where  
148 reported). Eighteen studies provided details on assessing patients for obstructive sleep  
149 apnea, to rule out overlap syndrome. Twenty studies were in stable populations, 9 in post-  
150 hospital populations and there were no details for two. For post-hospital populations there  
151 was clear evidence in all study reports that NIV treatment commenced after hospitalization  
152 due to an exacerbation. For both populations there was usually no information on the length  
153 of time before NIV was initiated, or previous exacerbation history. Varying proportions of  
154 patients were on LTOT. Most studies included hypercapnic patients, though the cut-off for  
155 classification varied. Two RCTs<sup>17;18</sup> included normocapnic patients, whilst one RCT<sup>19</sup> stated  
156 that the number of hypercapnic patients included was small.

157  
158 NIV settings, therapeutic/tolerability targets (pressure, volume or blood gases), and reporting  
159 of these varied across studies. There was some variability in usual care, with three studies  
160 considered to have more intensive approach to usual care: a 12-week multidisciplinary  
161 rehabilitation program, followed by a long-term home-based rehabilitation program<sup>20;21</sup>; a  
162 pulmonary rehabilitation program for part of the RCT<sup>18</sup> and a "home supervision program"<sup>22</sup>.

163  
164 There was a lack of reporting of some details relevant to study quality, particularly regarding  
165 loss to follow-up, handling of missing data and blinding of outcome assessors. Only three  
166 RCTs included a "sham NIV" arm, lack of which may have led to performance bias and/or  
167 bias in patient reported QOL. By definition, the non-randomized studies were more prone to  
168 bias; some retrospective studies had clear evidence of baseline imbalances between NIV  
169 and comparator groups, with the consequence of this on study findings unknown.



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170 Length of follow-up varied between 3 and 24 months (RCTs) and between 12 months and 10  
171 years (controlled studies). The longest follow-up periods (4-10 years) were in the  
172 retrospective controlled studies.

### 173 **Main findings**

#### 174 NIV compared with usual care only: stable population

175 Data from 7 RCTs<sup>19;21;23-27</sup> (pooled RR 0.88 (0.55, 1.43),  $I^2=60.4%$ ) and 4 controlled  
176 studies<sup>22;28-30</sup> (pooled RR 1.19 (0.65, 2.18),  $I^2=0%$ ) suggested no significant difference  
177 between domiciliary NIV and usual care alone in terms of survival up to 24 months (Figure  
178 2). Excluding the RCT by Casanova<sup>19</sup>, which included only few patients with hypercapnia,  
179 had little effect, changing the pooled RR to 0.85 (0.46, 1.58). Data from 5 RCTs<sup>21;23-25;27</sup> and  
180 3 controlled studies<sup>22;28;29</sup> (Figure 3) suggested a trend towards fewer hospital  
181 admissions/days in hospital with NIV, , albeit not statistically significant. Evidence on  
182 exacerbations not leading to hospitalization based on 4 RCTs<sup>17;19;21;24</sup> and one controlled  
183 study<sup>29</sup> showed no significant effect of NIV (supplementary file). For QOL, there appeared to  
184 be a trend favoring NIV, but a consistent benefit could not be demonstrated; heterogeneity in  
185 outcomes measured and time-points hampered analyses of this measure (supplementary file  
186 ). There was some evidence to suggest NIV improved blood gases (based on mainly  
187 unadjusted results; Figure 4 and 5).

188

#### 189 NIV compared with usual care only: post-hospital population

190 No survival benefit was evident from three RCTs<sup>31-33</sup> (pooled RR 0.89 (0.53, 1.49),  $I^2=$   
191 25.1%), though four non-randomized controlled studies<sup>34-37</sup>, which are potentially more prone  
192 to bias, favored NIV (pooled RR 0.45 (0.32, 0.65),  $I^2=0%$ ; Figure 2). Findings for hospital  
193 admissions were inconsistent, with one RCT<sup>33</sup> finding a statistically significant benefit of NIV,  
194 one<sup>31</sup> marginally favoring NIV and one<sup>32</sup> marginally favoring usual care (without NIV) (Figure  
195 3). Quality-of-life data was reported in only one post-hospital RCT<sup>32</sup>, and there were no

196 differences between NIV and usual care. Limited data from three trials<sup>31-33</sup> suggested a  
197 potential benefit from NIV in terms of reduction in PaCO<sub>2</sub> (Figure 5).

198

### 199 Study quality

200 None of the RCTs assessed as having a high risk of bias contributed data to meta-analyses,  
201 yet some of the non-randomized controlled studies in the meta-analyses (for both  
202 populations) did. The small number of studies precluded assessment of the potential for  
203 publication bias (eg using funnel plots) and sensitivity analyses around study quality.

204

### 205 Sub-group analysis

206 No further sub-group analysis (beyond study design and population) was possible given the  
207 small number of trials and inconsistent reporting of relevant characteristics. However, many  
208 clinicians believe the extent of hypercapnia or a change in hypercapnia status are related to  
209 the effect of NIV. In this context it is worth noting that the study by Köhnlein (2014)<sup>23</sup> had the  
210 highest hypercapnia threshold as an eligibility criterion (PaCO<sub>2</sub> ≥7kPa), and also showed a  
211 statistically significant survival benefit (and a non-significant trend towards fewer hospital  
212 admissions). Further, the study by Zhou (2008)<sup>24</sup>, which along with the Köhnlein (2014)<sup>23</sup>  
213 study had the highest mean PaCO<sub>2</sub> found a statistically significant benefit from NIV in  
214 hospital admissions. In order to explore hypercapnia level further as a potential predictor of  
215 benefit from NIV, data on mean PaCO<sub>2</sub> levels prior to initiation of NIV and change in mean  
216 PaCO<sub>2</sub> levels due to NIV from each study (where reported) were plotted against mortality  
217 and hospitalization data in order to determine if baseline PaCO<sub>2</sub> levels could predict  
218 response to NIV, and whether the effect of NIV on PaCO<sub>2</sub> levels correlates with the effect on  
219 clinical outcomes (Figure 6 a-d). These exploratory analyses suggested a trend towards a  
220 correlation between changes in hypercapnia status and hospital admissions (based on 8  
221 RCTs<sup>21;23-25;27;31-33</sup>). Such a potential correlation was not observed for mortality (based on 10  
222 RCTs<sup>19;21;23-27;31-33</sup>). Baseline hypercapnia status did not appear to predict response to NIV for

223 mortality (based on 10 RCTs<sup>19;21;23-27;31-33</sup>); the data was suggestive of a possible trend  
224 towards a correlation between baseline hypercapnia and hospital admissions (based on 8  
225 RCTs<sup>21;23-25;27;31-33</sup>). Formal sub-group analysis based on level of hypercapnia were however  
226 not deemed to be appropriate as this would have meant dichotomising trials based on an  
227 arbitrary CO<sub>2</sub> threshold. Adherence to NIV and effect of NIV settings could also not be  
228 analyzed.

### 229 Different types of NIV

230 With regard to the effectiveness of different NIV settings, three small crossover trials in  
231 stable populations were identified; two<sup>38;39</sup> comparing higher versus lower pressure NIV, and  
232 one<sup>40</sup> comparing different back-up rates. All were short-term (6-8 weeks) and did not assess  
233 mortality or hospitalizations/exacerbations. Treatment compliance was similar between arms  
234 in two studies<sup>39;40</sup>, and higher in the high pressure arm for the third<sup>38</sup> but drop-out rates were  
235 high in the pressure trials.<sup>38;39</sup> The limited QOL data precluded drawing firm conclusions. The  
236 only statistically significant result<sup>38</sup> was greater PaCO<sub>2</sub> reduction with higher pressure NIV  
237 (supplementary file ).

238

### 239 **DISCUSSION**

240 This is the first systematic review of domiciliary NIV to attempt to account for differing  
241 baseline risks of exacerbation by categorising populations into stable and post-hospital  
242 based on proximity to an in-patient stay for an exacerbation; it is also the most  
243 comprehensive to date, including evidence from RCTs, non-randomized controlled studies  
244 and RCTs comparing different NIV settings, and without restriction to English language only  
245 publications. Overall, the evidence from RCTs in a stable population could not demonstrate  
246 benefit for mortality from domiciliary NIV compared to usual care alone ( 7 RCTs<sup>19;21;23-27</sup>  
247 and 4 controlled studies<sup>22;28-30</sup>), although there was a trend towards fewer hospital  
248 admissions (5 RCTs<sup>21;23-25;27</sup> and 3 controlled studies<sup>22;28;29</sup>) and, to a lesser extent, improved  
249 QOL (7 RCTs<sup>17;18;21;23;26;27;41</sup> and 1 controlled study<sup>29</sup>) for the stable population. A survival

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250 benefit for the post-hospital population could not be shown based on three RCTs<sup>31-33</sup>, though  
251 there was some evidence of benefit based on four (potentially biased) non-randomized  
252 controlled studies<sup>34-37</sup>. Findings for hospital admissions ( 3 RCTs<sup>31-33</sup>) were inconsistent.  
253 There was too little evidence to draw any conclusions on the potential benefits of higher  
254 pressure NIV settings.

255

### 256 Exacerbation risk and domiciliary NIV

257 It was hoped that sub-group analyses based on the frequency of exacerbations prior to NIV  
258 treatment would be possible, as frequent exacerbators (patients with  $\geq 2$  exacerbations/year)  
259 are a clinically relevant subgroup<sup>42</sup>, with a generally stable exacerbation frequency on other  
260 existing therapies.<sup>43</sup> However, this was hampered by lack of reporting of this parameter.

261

262 There is evidence, however, to support the use of recent hospitalization as a proxy for a  
263 higher risk of recurring exacerbation. Prior hospital admission is recognized to be the biggest  
264 driver for a further exacerbation requiring admission<sup>12</sup>, and NIV use in hospital has also been  
265 recognized as a predictor of overall exacerbation rate.<sup>44</sup> Furthermore, recurrent type 2  
266 respiratory failure, ie respiratory failure with carbon dioxide retention, occurs in over 30%,  
267 and readmission at 1 year in 60%, of those who require NIV acutely in hospital.<sup>45</sup>

268 Consequently stratification based on NIV started at recent hospitalization was thought a  
269 justifiable surrogate marker of exacerbation risk. In reality there is likely to be much more of  
270 a continuum of risk, and it is further unknown what proportion of the post-hospital  
271 populations considered in the individual studies are COPD patients at the more severe end  
272 of the disease spectrum.

273

### 274 Which patients may benefit from domiciliary NIV?

275 The results of the review show that division of data based on potential exacerbation risk did  
276 not indicate a difference between populations in terms of mortality or hospitalizations; in fact

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277 there was no clear evidence for benefit for either population, though there was a non-  
278 significant trend towards a benefit with NIV in the stable population, for hospital admissions.  
279 The apparent similarity in hospitalization effect in our chosen subgroups is perhaps  
280 surprising given that those previously admitted are at higher risk of subsequent readmission.  
281 It is possible that the division used failed to capture other important differences within and  
282 between populations-for example the pre-treatment exacerbation rates were unknown.  
283 There was evidence of some heterogeneity between both stable and post-hospital studies,  
284 with some studies showing a significant benefit from NIV; one RCT<sup>23</sup> in a stable population  
285 showed a statistically significant benefit from NIV for mortality (Figure 2), and one RCT for  
286 stable<sup>24</sup> and two for post-hospital populations<sup>31;33</sup> showed significant benefit for hospital  
287 admissions (Figure 3). Two of these RCTs<sup>23;33</sup> used a higher hypercapnia threshold for  
288 patient inclusion ( $>7\text{PaCO}_2$ ); one RCT<sup>25</sup> had a lower inclusion criterion ( $>6\text{Pa CO}_2$ ), though  
289 means were suggestive of higher levels. There was no detail on the inclusion threshold for  
290 the third RCT.<sup>24</sup>

291  
292 Elements such as blood gases, prior admissions and social support have been identified as  
293 drivers to clinical decision making regarding domiciliary NIV in COPD<sup>46</sup>, all of which may  
294 impact NIV efficacy. The non-randomized post-hospital studies<sup>22;28-30</sup> assessing mortality  
295 (Figure 2) suggest a beneficial effect from NIV (significant pooled RR) and it is possible  
296 patient selection for NIV biased findings towards a positive response to NIV.

297  
298 Most populations included in studies were hypercapnic (see Table 2 for details), although the  
299 threshold used to define this varied. Post-hoc analyses undertaken across both stable and  
300 post-hospital populations suggested a trend towards a positive correlation between changes  
301 in hypercapnia and hospital admissions (but not for mortality nor correlation using pre-  
302 treatment  $\text{PaCO}_2$  level). As these are exploratory analyses the results should be interpreted  
303 cautiously; the analysis used aggregate -study level- data both for baseline hypercapnia,

304 change in hypercapnia and for clinical outcomes, and a patient level association cannot be  
305 inferred even if there is clear biological plausibility. Further caveats relate to the fact that not  
306 all trials contributed data to these analyses and that PaCO<sub>2</sub> change scores were mostly not  
307 adjusted for baseline differences. Nevertheless it does suggest that there should be further  
308 investigation of the association between hypercapnia and clinical outcomes, particularly with  
309 regard to the ability of the NIV to reduce PaCO<sub>2</sub> levels. Patients hypercapnic at discharge  
310 may normalize their PaCO<sub>2</sub> levels over time, although those who remain hypercapnic have  
311 higher mortality.<sup>47</sup> Thus if hypercapnia (or change in hypercapnia) were a driver of NIV  
312 response and were used to select patients for treatment after an exacerbation, subsequent  
313 reassessment may be needed to determine likelihood of ongoing benefit.

314

315 The current recommendation in the UK suggest that domiciliary NIV is considered on health  
316 economic grounds if a patient has had three hospital admissions with acute hypercapnic  
317 respiratory failure.<sup>48</sup> There may be other, as yet unconfirmed, patient characteristics which  
318 influence its effectiveness. Uncertainty also remains regarding the length of time NIV may  
319 provide benefit for; there are at least two RCTs<sup>49;50</sup> looking at the effect of discontinuing NIV,  
320 but this question was beyond the scope of this systematic review.

321

322

### 323 Strengths and limitations

324 A number of RCTs of reasonably good methodological quality were available, particularly for  
325 the stable population, and a comprehensive search strategy meant that this systematic  
326 review identified more relevant studies than previous ones, even after taking into account  
327 different search periods. No language restrictions meant that 19% of the included studies  
328 were non-English, a substantial proportion of the overall evidence base omitted by prior  
329 reviews.<sup>8-11</sup> This is also the first systematic review to examine patient –related outcomes and  
330 incorporate data from non-randomized studies. Furthermore, by calculating summary

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331 measures from raw data or converting data, the number of results that could be presented in  
332 forest plots was maximized. In contrast to some previous systematic reviews, secondary  
333 outcome data (lung function, blood gases and 6MWD) were not pooled due to a lack of  
334 results adjusted for baseline differences. This means that our analyses are likely to be more  
335 robust.

336 There were several limitations in the available data, largely due to inconsistency of reporting  
337 (particularly for hospital admissions) or measurement tools (especially for QOL). This meant  
338 that not all available evidence could contribute to the pooled estimates. Furthermore,  
339 admissions data may be skewed, thus the mean (SD) may not be an appropriate metric to  
340 use, though it was frequently reported. For primary outcomes, there was a lack of data  
341 explicitly linking the number of exacerbations to subsequent hospitalizations and survival for  
342 individual patients. This latter point has potential implications for double-counting data as  
343 these outcomes are not independent of each other. Ventilator settings may influence  
344 effectiveness, and settings have changed over time, such that earlier settings may today be  
345 considered ineffective. The small crossover trials<sup>38;3940</sup> in this analysis did not allow any  
346 conclusions to be drawn, and sub-group analysis based on the larger/parallel trials was not  
347 possible due to inconsistent reporting: studies variously reported mean, median or target  
348 settings, based either on pressure, blood gas or volume targets, with some stating only that  
349 levels were adjusted to patient comfort/tolerance. Reporting times also varied (eg at start of  
350 study or at discharge).

351

### 352 Recommendations for future research pertaining to domiciliary NIV in COPD

353 Variable quality of data reporting, lack of exacerbation data, potential bias and heterogeneity  
354 of reported outcomes were striking features of the included studies. These features are not  
355 uncommonly encountered when conducting systematic reviews. Whilst trials of medications  
356 are often required to report certain outcomes as part of the licensing process, medical device  
357 studies, such as those included in our review, have not always had to meet such standards

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358 despite also being subject to regulatory processes. More detailed reporting of exacerbations  
359 in particular would be valuable in this high risk population. It has been suggested that new  
360 RCTs could include a sham NIV arm in order to minimize potential bias, as well a higher and  
361 lower pressure NIV arm, to enable further exploration of the relationship between pressure  
362 and effectiveness; many of the earlier studies included used pressures which experts would  
363 now consider equivalent to a sham treatment (eg Casanova 2000<sup>19</sup>). However, sham NIV  
364 could lead to an overestimate of the potential benefit of NIV, due to its potential disbenefits  
365 on quality-of-life, therefore two control arms (with and without sham NIV) are more likely to  
366 be appropriate. Qualitative work in NIV users and prescribers not surprisingly suggests a  
367 focus on patient-centered measures (eg QOL, daily activity) is needed, alongside research  
368 to delineate those in whom the treatment is most effective.<sup>46</sup> Which instruments best capture  
369 QOL in this patient group and whether instruments are convertible is debatable.

370

371 There is at least one ongoing trial (the UK HOT-HMV trial, NCT00990132), which includes a  
372 population with an underlying risk of recurrent events similar to the post-hospital population  
373 described here. Findings from this trial will be important, but additional evidence from  
374 individual patient data (IPD) analyses of pooled studies may be required to determine  
375 whether specific patient characteristics or equipment settings predict benefit from NIV, and  
376 to establish optimum time-points for starting (and potentially discontinuing) NIV. A previous  
377 review<sup>8:9</sup> attempted such analyses, but based on a smaller group of studies, and without  
378 considering hospitalizations or survival.

379

### 380 Conclusions

381 The effectiveness of domiciliary NIV remains uncertain, however some patients appear to  
382 benefit. Further research is required to identify these patients and to explore the relevance of  
383 hypercapnic status or changes in hypercapnia due to NIV in influencing clinical outcomes for



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384 patients on long-term NIV; optimum time-points for starting NIV and equipment settings also  
385 need to be established.

386

387

### 388 Contributorship

389 JD was the lead systematic reviewer, wrote and edited sections of the paper, undertook  
390 study selection, data extraction and analysis, and quality assessment.

391 DM was co-Principle Investigator and methodological lead, led all aspects of the project,  
392 contributed to all aspects of the project, undertook study selection, and wrote and edited  
393 sections of the paper.

394 CD advised on clinical aspects of the project, and undertook study selection.

395 RM advised on clinical aspects of the project and undertook study selection.

396 MP advised on statistical aspects, analysed data and edited statistical methodological  
397 sections of the paper.

398 SB devised the search strategies and ran the searches in electronic databases.

399 XW translated Chinese papers, undertook data extraction and data checking.

400 RJ undertook study selection and contributed to methodological aspects of the project.

401 AT was co-Principle Investigator and clinical lead, oversaw all clinical aspects of the project,  
402 undertook study selection, and wrote and commented on sections of the paper.

403 All authors read and approved a draft of the article.

404

### 405 **Competing interests**

406 AT's clinic has been loaned sleep monitors by ResMed Inc. who also produce NIV  
407 equipment. RM has received non-financial support from ResMed Inc and Breas Medical in  
408 the form of training sessions for the NIV equipment supplied to his NIV multidisciplinary  
409 team. DM and JD acted as peer reviewers for the Cochrane systematic review by Struik et  
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413

414

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427

### 428 Table legends

429 Table 1: Study inclusion criteria

430 Table 2: Main study and intervention characteristics

### 431 Figure legends

432 Figure 1: PRISMA flow diagram (study selection process)

433 Figure 2: Mortality (Relative Risk)

434 Figure 3: Hospital admissions per patient per year (Weighted Mean Difference)

435 Figure 4: PaO<sub>2</sub> (Mean Difference)

436 Figure 5: PaCO<sub>2</sub> (Mean Difference)

437 Figure 6 a-d: Hypercapnia and clinical outcomes

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### 438 Supplementary file

439 Search strategy for MEDLINE; Exacerbations results; Quality- of-Life results; Results of  
440 RCTs comparing different types of NIV

441

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