Supplementary Online Content

Murphy PB, Rehal S, Arbane G, et al. Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2017.4451

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

Recruitment centers

Fifteen UK home ventilation centers participated in the study and had the trial protocol accepted by local research and development committees. However, for logistical reasons, 2 centers neither screened nor recruited patients into the study.

Patient screening and identification

Home non-invasive ventilation was performed at specialist centers. Patients were identified when admitted to local hospitals with an acute exacerbation of COPD and decompensated respiratory failure. The patients' acute management was consistent with local protocols. Following resolution of the respiratory acidemia and clinical stabilization, patients were referred from the local hospital to the home ventilation center for assessment which was scheduled for 2-4 weeks after resolution of the exacerbation. To remain consistent with established local protocols patients were admitted for screening at the home ventilation center either directly from the referring hospital or from home within the designated time window. Local management was independent of the trial protocol and NIV may have been weaned to cessation following resolution of acidemia or to nocturnal only use. Patients maintained on nocturnal NIV at the local hospital were assessed for clinical and physiological stability and had baseline assessments performed on oxygen without NIV. If transferred from another hospital the patients could not have required NIV for more than 6 hours per night or during the day in the 2-4 week period in order to maintain clinical stability.

Screening for obstructive sleep apnea

Patients with clinically significant obstructive sleep apnea (OSA) syndrome were excluded from the study. Full polysomnography was not mandated in the trial protocol but individual centers used established pathways for screening following clinical assessment. Therefore each patient underwent a clinical assessment by an experienced clinician specializing in the management of patients with sleep disordered breathing and respiratory failure. Patients in whom there was a clinical suspicion of OSA syndrome based on clinical review or overnight oximetry underwent further testing with limited respiratory polygraphy. At the lead trial site (Guys & St Thomas' NHS Foundation Trust) all recruited patients had screening respiratory polygraphy performed to assess the efficacy of the clinical assessment strategy.

Titration of non-invasive ventilation

Patients were admitted for inpatient titration of non-invasive ventilation (NIV). NIV interface (nasal, oro-nasal or total face) was selected according to patient comfort and fitted to minimize air leak. NIV device was pre-specified by center as either the

Harmony 2 (Philips-Respironics, Murrysville, Pa, USA) or VPAP IIISTa (ResMed, Bella Vista, Australia). Devices were set in the pressure support mode with recommended initial titration settings (inspiratory positive airway pressure; IPAP 18 cmH_2O, expiratory positive airway pressure; EPAP 4 cmH_2O, backup rate 14-16 bpm). Patients were acclimatized to NIV at initial titration pressures during wakefulness, if required reduced pressures were used initially to facilitate comfort. Oxygen was entrained into the NIV circuit at usual daytime flow rates. Patients underwent overnight sleep studies with oximetry-capnometry monitoring. NIV settings and oxygen flow rate were titrated to control hypoventilation and hypoxemia aiming to maintain SpO_2 >88% and to reduce $tcCO_2$ by at least 4 mmHg (*Appendix 1*). The aim was to reach a target IPAP of ≥ 25 cmH_2O, if tolerated by the patient. If required, repeat sleep studies were performed on consecutive nights to further titrate pressure support to achieve control of hypoventilation and acclimatization to therapy. Patients underwent NIV training from skilled teams at the home ventilation centers and were assessed to ensure ability to apply NIV interface and operate NIV device prior to discharge. When appropriate the patient's care provider was trained on NIV application and operation to enable support for home use of NIV.

Addition of home non-invasive ventilation to patients allocated to home oxygen therapy alone

Patients allocated to home oxygen therapy alone could have home non-invasive ventilation added to their treatment if, following readmission with acute respiratory failure, they had:

- Persistent respiratory acidosis (pH<7.30) at 2 weeks after admission
- Decompensated respiratory failure (pH<7.30) following withdrawal of acute NIV
- Failure to wean from NIV during acute episode
- Needed invasive mechanical ventilation and or tracheostomy ventilation during acute admission

Exacerbation definitions

Acute COPD exacerbations were pre-defined according to the following criteria using both event-based and symptom-based definitions in a hierarchical fashion.[1]

- COPD-related hospital admission - worsening respiratory symptoms (cough, wheeze, increased sputum production, increased volume of sputum and/or increased breathlessness) with senior physician assessment and treatment for an acute exacerbation of COPD started on admission to hospital
- Physician-assessed exacerbation - worsening respiratory symptoms (cough, wheeze, increased sputum production, increased volume of sputum and/or increased breathlessness) with physician assessment and COPD treatment escalated (increased beta-agonist use as inhaled or nebulized therapy and/or oral corticosteroids and/or oral antibiotics) by physician WITHOUT admission to hospital

- Self-treated exacerbation - worsening respiratory symptoms (cough, wheeze, increased sputum production, increased volume of sputum and/or increased breathlessness) WITHOUT physician assessment but patient self-initiated treatment for an acute exacerbation of COPD (use of rescue pack of oral corticosteroids and/or oral antibiotics)
- Untreated exacerbation – worsening of respiratory symptoms demonstrated on the diary card (*Appendix 2 and 3*), but neither patient nor physician initiated escalation of treatment for an acute exacerbation of COPD

Exacerbation frequency was calculated as an annualized rate ((exacerbation number / days in trial) * 365.25) for all patients with available data.

eResults

Time to readmission or death (primary outcome)

Adjusting for center in addition to the other minimization criteria did not significantly alter the estimation of treatment effect [HR of 0.47 (95%CI 0.30 to 0.76); p=0.002], furthermore events were balanced between centers. These results were consistent with our post hoc analysis with center included as a random effect [adjusted HR 0.43 (95%CI 0.26 to 0.70); P=0.001)] and were also consistent when center was included as a fixed effect.

The per-protocol analysis was consistent with the intention-to-treat analysis. 5 patients from home oxygen therapy (1 treatment switching, 4 withdrawal) and 15 patient from home NIV (1 treatment switching, 14 non-compliance) were excluded from the per-protocol analysis. Median time to death or readmission was 2.9 months in HOT-HMV and 1.1 months in HOT, unadjusted HR 0.58 (95%CI 0.36 to 0.95), p=0.03 and adjusted HR 0.52 (95%CI 0.31 to 0.85), p=0.01.

Sensitivity analyses

Both sensitivity analyses support our results. The worst case scenario, assuming all withdrawn patients were admitted or died, showed patients randomized to home NIV had a 55% lower risk of being readmitted to hospital or death; adjusted HR 0.45 (95%CI 0.29 to 0.69); p<0.001 (*eTable 6*). The best case scenario, assuming all withdrawn patients survived with no admissions, showed a 40% lower risk of being readmitted to hospital or death for patients randomized to home NIV; adjusted HR 0.60 (95%CI 0.38 to 0.95); p=0.03. Therefore, even in the most extreme cases, home NIV and home oxygen therapy performed better than home oxygen therapy alone.

Prevalence of sleep disordered breathing

76 patients (4%) of the screening population were excluded due to clinically significant OSA. Of the 116 patients randomized into the trial, 44 had respiratory polygraphy and displayed similar clinical characteristics to the remaining 72 patients (*eTable 7*). In particular, there were no significant differences in anthropometrics, severity of airflow obstruction or hypercapnia indicating the likely cause of respiratory failure was due to similar clinical reasons.

eDiscussion

Assessment of sleep disordered breathing

Patients underwent a full clinical assessment and overnight oximetry-capnometry to assess severity of sleep disordered breathing. When indicated by either clinical suspicion or oximetry-capnometry results, patients had further investigations to assess for possible OSA syndrome. The decision to not perform full polysomnography studies on all patients was taken on practical and pragmatic grounds to facilitate patient recruitment without undue delay pending diagnostic testing in this unwell cohort of patients. Furthermore, the treatment response in OSA is linked to patient symptoms, strongly supporting this assessment strategy.[2,3] In addition to focused screening for OSA syndrome, all patients with significant obesity (body mass index >35 kg/m^2) were excluded and patients recruited into the study all demonstrated severe obstructive airways disease as evidence by the very low FEV_1 (home NIV group 0.6 ± 0.2 L vs. oxygen group 0.6 ± 0.2 L). These data indicate that the likelihood of inclusion of patients with COPD-OSA overlap syndrome was low.

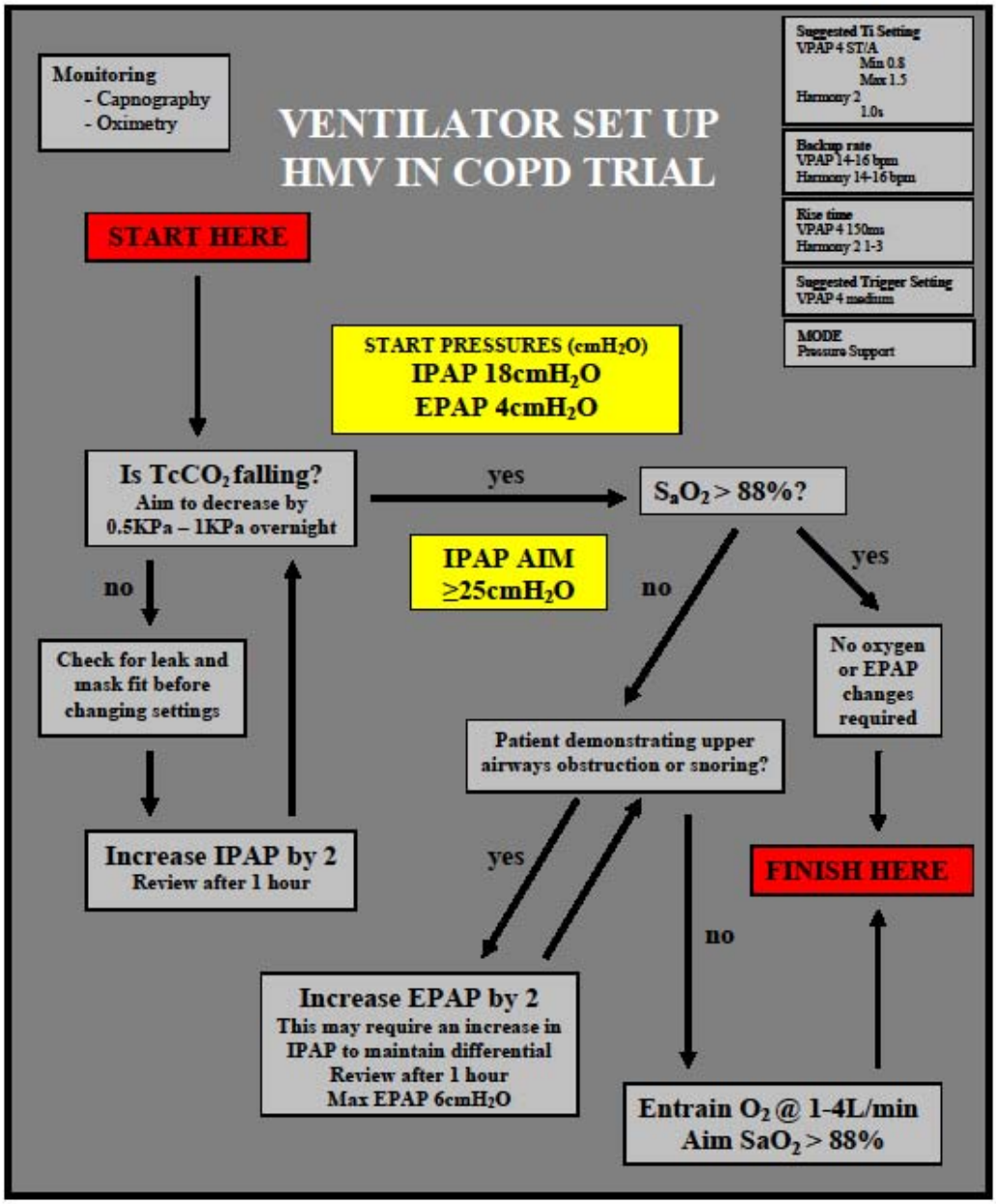
eReferences

1. Trappenburg JC, van Deventer AC, Troosters T, et al. The impact of using different symptom-based exacerbation algorithms in patients with COPD. *Eur Respir J.* Dec 22 2010.

2. Craig SE, Kohler M, Nicoll D, et al. Continuous positive airway pressure improves sleepiness but not calculated vascular risk in patients with minimally symptomatic obstructive sleep apnoea: the MOSAIC randomised controlled trial. *Thorax.* Dec 2012;67(12):1090-1096.

3. Bratton DJ, Stradling JR, Barbe F, Kohler M. Effect of CPAP on blood pressure in patients with minimally symptomatic obstructive sleep apnoea: a meta-analysis using individual patient data from four randomised controlled trials. *Thorax.* Dec 2014;69(12):1128-1135.

eAppendix 1. Trial ventilator setup protocol



eAppendix 2. Instructions for filling in the diary card

EVERY DAY…

1. Estimate the number of hours you used your oxygen therapy in the previous 24 hours.
2. Please record any **WORSENING** of symptoms from your usual daily level. The symptoms we are interested in are listed below, just put the appropriate letter in the box on the sheet. Continue recording until the symptom has gone away or got back to the level you consider 'normal'.

Letter	Symptom
A	increased BREATHLESSNESS.
B1	increased SPUTUM COLOUR.
B2	increased SPUTUM AMOUNT.
C	a COLD (such as a runny or blocked nose).
D	increased WHEEZE or CHEST TIGHTNESS.
E1	SORE THROAT.
E2	increased COUGH.
F	FEVER.

→

IF MORE BREATHLESS
A1- Slightly more
A2- Moderately more
A3- Severely more
A4- very severely more

3. Please record any **CHANGE** to your usual treatment for as many days as it applies. Again, just put the appropriate letter in the box on the sheet.

Letter	Treatment
H	I am in Hospital.
I	I am taking more than usual INHALED STEROID (red / brown).
R	I needed to take extra RELIEVER (blue / green / grey / nebuliser). **HOW MANY PUFFS?** Write, eg 'R3' for 3 puffs, 'R2' for 2 etc
S	I am taking STEROID (Prednisolone) TABLETS. **HOW MANY TABLETS?** Write, eg 'S6' for 6 tablets, 'S5' for 5 etc
X	I am taking ANTIBIOTIC TABLETS. **PLEASE RECORD WHICH** (write the name on the diary card).

4. Finally, please estimate the time that you were out of your own home on the previous day.

UNSCHEDULED VISITS TO GP / HOSPITAL

DATE	**GP / HOSPITAL** **(DELETE AS APPROPRIATE)**	**REASON FOR VISIT**
	GP / Hospital	
	GP / Hospital	
	GP / Hospital	
	GP / Hospital	
	GP / Hospital	
	GP / Hospital	
	GP / Hospital	
	GP / Hospital	
	GP / Hospital	
	GP / Hospital	

NAME											
Study Number											

April 2012	NEXT APPOINTMENT / / .

DATE	1	2	3	4	5	6	7	8	9	10	11
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	12	13	14	15	16	17	18	19	20	21	22
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	23	24	25	26	27	28	29	30
Hours of use of Oxygen								
CHANGE in Symptoms								
CHANGE in Treatment								
Hours out of the home								

NAME			**May 2012**	NEXT APPOINTMENT / / .
Study Number				

DATE	1	2	3	4	5	6	7	8	9	10	11
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	12	13	14	15	16	17	18	19	20	21	22
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	23	24	25	26	27	28	29	30	31
Hours of use of Oxygen									
CHANGE in Symptoms									
CHANGE in Treatment									
Hours out of the home									

NAME											
Study Number											

June 2012	NEXT APPOINTMENT / / .

DATE	1	2	3	4	5	6	7	8	9	10	11
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	12	13	14	15	16	17	18	19	20	21	22
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	23	24	25	26	27	28	29	30
Hours of use of Oxygen								
CHANGE in Symptoms								
CHANGE in Treatment								
Hours out of the home								

NAME			**July 2012**	NEXT APPOINTMENT / / .
Study Number				

DATE	1	2	3	4	5	6	7	8	9	10	11
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	12	13	14	15	16	17	18	19	20	21	22
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	23	24	25	26	27	28	29	30	31
Hours of use of Oxygen									
CHANGE in Symptoms									
CHANGE in Treatment									
Hours out of the home									

NAME											
Study Number											

August 2012	NEXT APPOINTMENT / / .

DATE	1	2	3	4	5	6	7	8	9	10	11
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	12	13	14	15	16	17	18	19	20	21	22
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	23	24	25	26	27	28	29	30	31
Hours of use of Oxygen									
CHANGE in Symptoms									
CHANGE in Treatment									
Hours out of the home									

NAME											
Study Number											

September 2012	NEXT APPOINTMENT / / .

DATE	1	2	3	4	5	6	7	8	9	10	11
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	12	13	14	15	16	17	18	19	20	21	22
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	23	24	25	26	27	28	29	30
Hours of use of Oxygen								
CHANGE in Symptoms								
CHANGE in Treatment								
Hours out of the home								

NAME							**October 2012**			NEXT APPOINTMENT / / .	
Study Number											

DATE	1	2	3	4	5	6	7	8	9	10	11
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	12	13	14	15	16	17	18	19	20	21	22
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	23	24	25	26	27	28	29	30	31
Hours of use of Oxygen									
CHANGE in Symptoms									
CHANGE in Treatment									
Hours out of the home									

NAME							**November 2012**			NEXT APPOINTMENT / / .	
Study Number											

DATE	1	2	3	4	5	6	7	8	9	10	11
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	12	13	14	15	16	17	18	19	20	21	22
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	23	24	25	26	27	28	29	30
Hours of use of Oxygen								
CHANGE in Symptoms								
CHANGE in Treatment								
Hours out of the home								

NAME							**December 2011**			NEXT APPOINTMENT / / .	
Study Number											

DATE	1	2	3	4	5	6	7	8	9	10	11
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	12	13	14	15	16	17	18	19	20	21	22
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	23	24	25	26	27	28	29	30	31
Hours of use of Oxygen									
CHANGE in Symptoms									
CHANGE in Treatment									
Hours out of the home									

NAME							**January 2012**			NEXT APPOINTMENT / / .	
Study Number											

DATE	1	2	3	4	5	6	7	8	9	10	11
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	12	13	14	15	16	17	18	19	20	21	22
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	23	24	25	26	27	28	29	30	31
Hours of use of Oxygen									
CHANGE in Symptoms									
CHANGE in Treatment									
Hours out of the home									

NAME							**February 2012**			NEXT APPOINTMENT / / .	
Study Number											

DATE	1	2	3	4	5	6	7	8	9	10	11
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	12	13	14	15	16	17	18	19	20	21	22
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	23	24	25	26	27	28
Hours of use of Oxygen						
CHANGE in Symptoms						
CHANGE in Treatment						
Hours out of the home						

NAME							**March 2012**			NEXT APPOINTMENT / / .	
Study Number											

DATE	1	2	3	4	5	6	7	8	9	10	11
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	12	13	14	15	16	17	18	19	20	21	22
Hours of use of Oxygen											
CHANGE in Symptoms											
CHANGE in Treatment											
Hours out of the home											

DATE	23	24	25	26	27	28	29	30	31
Hours of use of Oxygen									
CHANGE in Symptoms									
CHANGE in Treatment									
Hours out of the home									

eAppendix 3. Instructions for scoring diary card

SYMPTOMS

Major	Dyspnoea	A1-4
	Change in sputum colour or volume	B1-2
Minor	Cold	C
	Wheeze	D
	Sore throat	E1
	Cough	E2
	Fever	F

EXACERBATION DEFINITION

The onset of 2 or more new or worsening symptoms on ≥2 consecutive days, with at least one major symptom.

Exacerbations are defined as:

- Untreated
  - If exacerbation criteria are met but no treatment started prior to recovery
  - Date of onset is day exacerbation definition is reached.
- Self-treated
  - If treatment initiated in the community by the patient without review from health care professional
  - Date of onset is first day of treatment initiation
- Physician treated exacerbation
  - If patient is reviewed by a health care professional and additional course of steroids and or antibiotics (Anthonsien definition)
  - Date of onset is first day of treatment initiation

The exacerbation criteria are hierarchical, if the symptom score does not reach recovery prior to escalation the event is defined by the highest level reached. Therefore each event is only recorded once even if the exacerbation is initially self-treated in the community and then there is a subsequent hospital admission prior to recovery the event is defined by the hospital admission.

TOTAL SYMPTOM SCORE

Every symptom is scored in a binary fashion (1=symptom scored & 0=symptom absent) with the daily score being produced by totalling the score.

RECOVERY

Number of days from start of an exacerbation to the return of the total symptom score (3 day moving average) to return to baseline (average value for score on days 8-14 preceding the exacerbation)

eTable 1. Baseline comparison of patients undergoing sleep-disordered breathing assessed by either respiratory polygraphy or oximetry-capnometry

Baseline characteristics	**Respiratory polygraphy (N=44)**	**Oximetry-capnography only (N=72)**	**p-value**
*Age (years)[a]	65 ± 9	68 ± 10	0.21
*Median BMI (kg/m^2) (25th to 75th percentile)[b]	21 (17 to 26)	22 (18 to 26)	0.97
*Prior use of LTOT (n (%))[c]	29 (66%)	51 (71%)	0.58
*≥3 COPD related admissions in last year[c]	23 (52%)	38 (53%)	0.96
Gender (female) (n (%))[c]	23 (53%)	38 (53%)	0.96
Median smoking pack year history (25th to 75th percentile)[b]	44 (33 to 60)	44 (30 to 55)	0.51
Median neck circumference (cm) (25th to 75th percentile)[b]	36 (34 to 40)	38 (35 to 41)	0.26
Median waist circumference (cm) (25th to 75th percentile)[b]	87 (75 to 99)	88 (80 to 102)	0.40
FEV_1[a]	0.567 ± 0.228	0.568 ± 0.220	0.98
FEV_1 (%)[a]	23 ± 7	24 ± 9	0.46
FVC[a]	1.76 ± 0.66	1.58 ± 0.71	0.19
FVC (%)[a]	56 ± 14	51 ± 23	0.23
FEV_1/FVC[a]	0.34 ± 0.09	0.38 ± 0.11	0.02
PaO_2 on room air[a] (mmHg)	49 ± 8	47 ± 9	0.42
$PaCO_2$ on room air[a] (mmHg)	60 ± 7	58 ± 6	0.33
pH on room air	7.39 ± 0.04	7.40 ± 0.04	0.23
[d]Median SGRQ summary (25th to 75th percentile)[b]	71 (62 to 80)	74 (64 to 81)	0.58
[e]SRI summary[a]	45 ± 17	47 ± 14	0.45
[f]Median MRC dyspnea score (25th to 75th percentile)[b]	5 (4 to 5)	5 (4 to 5)	0.88

Data summarized as mean ± SD, median (IQR) or N (%) as appropriate.
*Minimization factors: selected variables used during randomization process to enhance chance of balanced groups.
Abbreviations: BMI=body mass index; *FEV_1=forced expiratory volume in 1 second; FEV_1 %=percentage predicted forced expiratory volume in 1 second; FVC=forced vital capacity; FVC %=percent predicted forced vital capacity;* LTOT=long term oxygen therapy; $PaCO_2$=Partial pressure of carbon dioxide in arterial blood; PaO_2=Partial pressure of oxygen in arterial blood; SGRQ=St George's Respiratory Questionnaire; SRI=Severe Respiratory Insufficiency Questionnaire.
[a] T-test for difference in means
[b] Mann-Whitney U test
[c] Chi^2 test
[d] SGRQ on a 0 to 100 scale where 0 is the best quality of life and 100 is the worst.
[e] SRI on a 0 to 100 scale where 100 is the best quality of life score and 0 is the worst.

[f] MRC Dyspnea score on a 1 to 5 categorical scale with higher scores indicating more limitation on daily activities due to breathlessness.

eTable 2. Follow up retention by visit

Treatment	Visit	Number of patients expected	Number of patients attended (%)	Number withdrawn	Number died
Home NIV and home oxygen therapy (N=57)	6 weeks	54	45 (83%)	1	2
	3 months	49	40 (82%)	3	5
	6 months	45	40 (89%)	4	8
	12 months	36	36 (100%)	5	16
Home oxygen therapy (N=59)	6 weeks	50	37 (74%)	5	4
	3 months	43	36 (84%)	9	7
	6 months	33	27 (82%)	11[a]	15
	12 months	28	28 (100%)	13	18

Abbreviations: NIV = non-invasive ventilation.
[a]One patient died after withdrawal, this patient is not included in deaths

eTable 3. Ventilator adherence over trial follow up in home NIV with home oxygen therapy arm

Visit	Number of patients attended	Number of patients with adherence data	Median usage[a] (25^{th} to 75^{th} percentile) hours/night
6 weeks	45	38	4.73 (2.50 to 5.6)
3 months	40	34	6.02 (4.0 to 7.4)
6 months	40	30	5.37 (3.48 to 7.1)
12 months	36	26	7.61 (3.55 to 8.37)

Abbreviations: NIV = non-invasive ventilation.

[a]Mean daily use (hours/night) from individual patient ventilator card for each period is presented as group medians.

eTable 4. Control of nocturnal transcutaneous carbon dioxide at baseline and following initiation of treatment, at 6 months and 12 months

Visit	Number of patients included in analyses		Mean (95% CI)		Treatment effect within each group (mean difference from baseline (95%CI))		Treatment effect (Mean between group difference from baseline (95% CI))	P-value	Treatment effect (Mean between group difference from baseline (95% CI))	P-value
	Home Oxygen Therapy and Home NIV	Home Oxygen therapy	Home NIV & home oxygen therapy (mmHg)	Home oxygen therapy (mmHg)	Home NIV & home oxygen therapy (mmHg)	Home oxygen therapy (mmHg)	Adjusted for baseline effect[a] (95% CI)		Adjusted effect[b] (95% CI)	
Mean $tcCO_2$										
Baseline[c] (pre-treatment)	57	59	65 (62 to 67)	65 (63 to 67)						
Day 1 (on treatment)	45	46	56 (53 to 59)	65 (62 to 67)	-8.9 (-11.7 to -6.2)	0.8 (-0.5 to 0.7)	-8.9 (-11.4 to -6.5)	<.001	-9.1 (-11.6 to -6.6)	<.001
6 months	24	16	53 (48 to 58)	56 (50 to 62)	-14.3 (-19.7 to -8.9)	-8.6 (-15.2 to -1.9)	-2.0 (-8.8 to 4.7)	.56	-4.7 (-11.6 to 2.3)	.18
12 months	24	19	50 (44 to 55)	61 (56 to 66)	-16.6 (-21.5 to -11.6)	-4.4 (-10.1 to 1.4)	-10.8 (-16.8 to -4.9)	<.001	-10.7 (-16.4 to -5.1)	<.001

Visit	Number of patients included in analyses		Mean (95% CI)		Treatment effect within each group (mean difference from baseline (95%CI))		Treatment effect (Mean between group difference from baseline (95% CI))	P-value	Treatment effect (Mean between group difference from baseline (95% CI))	P-value
	Home Oxygen Therapy and Home NIV	Home Oxygen therapy	Home NIV & home oxygen therapy (mmHg)	Home oxygen therapy (mmHg)	Home NIV & home oxygen therapy (mmHg)	Home oxygen therapy (mmHg)	Adjusted for baseline effect[a] (95% CI)		Adjusted effect[b] (95% CI)	
Max $tcCO_2$										
Baseline[c] (pre-treatment)	57	59	76 (73 to 79)	76 (74 to 79)						
Day 1	45	46	67 (48 to 71)	75 (72 to 78)	-9.2 (-13.0 to -5.3)	0.1 (-0.7 to 0.8)	-8.9 (-12.2 to -5.5)	<.001	-9.2 (-12.5 to -5.6)	<.001
6 months	24	16	8.1 (7.3 to 8.8)	65 (58 to 73)	-17.5 (-23.0 to -11.9)	-7.3 (-15.0 to 0.5)	-5.8 (-13.3 to 1.8)	.14	-8.2 (-16.1 to -0.3)	.04
12 months	23	18	7.7 (6.9 to 8.4)	74 (67 to 80)	-21.1 (-27.8 to -14.3)	-2.3 (-10.4 to 5.9)	-16.8 (-24.7 to -8.8)	<.001	-16.2 (-24.0 to -8.5)	<.001

Abbreviations: NIV = non-invasive ventilation; $tcCO_2$ = transcutaneous carbon dioxide.

[a]Adjusted for baseline values only.

[b]Adjusted for number of COPD admissions in previous year, prior use of long term oxygen therapy (LTOT), age and BMI

[c]Missing baseline (pre-treatment) results were replaced with mean imputation

[*]Repeated measures ANOVA p-value <0.001 between group difference.

eTable 5. Sensitivity analyses: time to hospital admission or death, up to 12 months

	Home NIV and home oxygen therapy (N=57)	**Home oxygen therapy (N=59)**
Worst case scenario[a]		
Median months to event (IQR)	2.04 (1.02 to 5.75)	0.85 (0.39 to 2.33)
Adjusted HR (95% CI)[b]	0.45 (0.29 to 0.69); P<0.001	
Unadjusted HR (95% CI)	0.48 (0.32 to 0.74); P=0.001	
Centre as a random effect (95% CI)	0.41 (0.26 to 0.64); P<0.001	
Best case scenario[a]		
Median months to event (IQR)	2.27 (1.18 to 9.43)	1.08 (0.46 to 3.32)
Adjusted HR (95% CI)[b]	0.60 (0.38 to 0.95); P=0.03	
Unadjusted HR (95% CI)	0.66 (0.42 to 1.04); P=0.07	
Centre as a random effect (95% CI)	0.62 (0.39 to 0.97); P=0.04	

[a] Worst case scenario where patients lost to follow-up prior to meeting the endpoint were classed as meeting the endpoint and time was taken from randomization up to the point of withdrawal.
Best case scenario where patients lost to follow-up prior to meeting the endpoint were classed as not meeting the endpoint (i.e. success) and time was taken from randomization up to 12 months.
[b]Adjusted for number of COPD admissions in previous year, prior use of long term oxygen therapy (LTOT), age and BMI.

eTable 6. Cause of death during 12 month trial period

Cause of death		**Number**		
		Home NIV & home oxygen therapy	**Home oxygen therapy**	**Total**
Respiratory	COPD	8	13	21
	Pneumonia	4	2	6
	Respiratory failure	2	2	4
	Lung cancer	1	1	2
	Cor Pulmonale		1	1
Non-respiratory	Congestive cardiac failure	1		1
Total		16	19	35

Abbreviations: COPD = chronic obstructive pulmonary disease; NIV = non-invasive ventilation.

eTable 7. Annual exacerbation frequency per treatment allocation

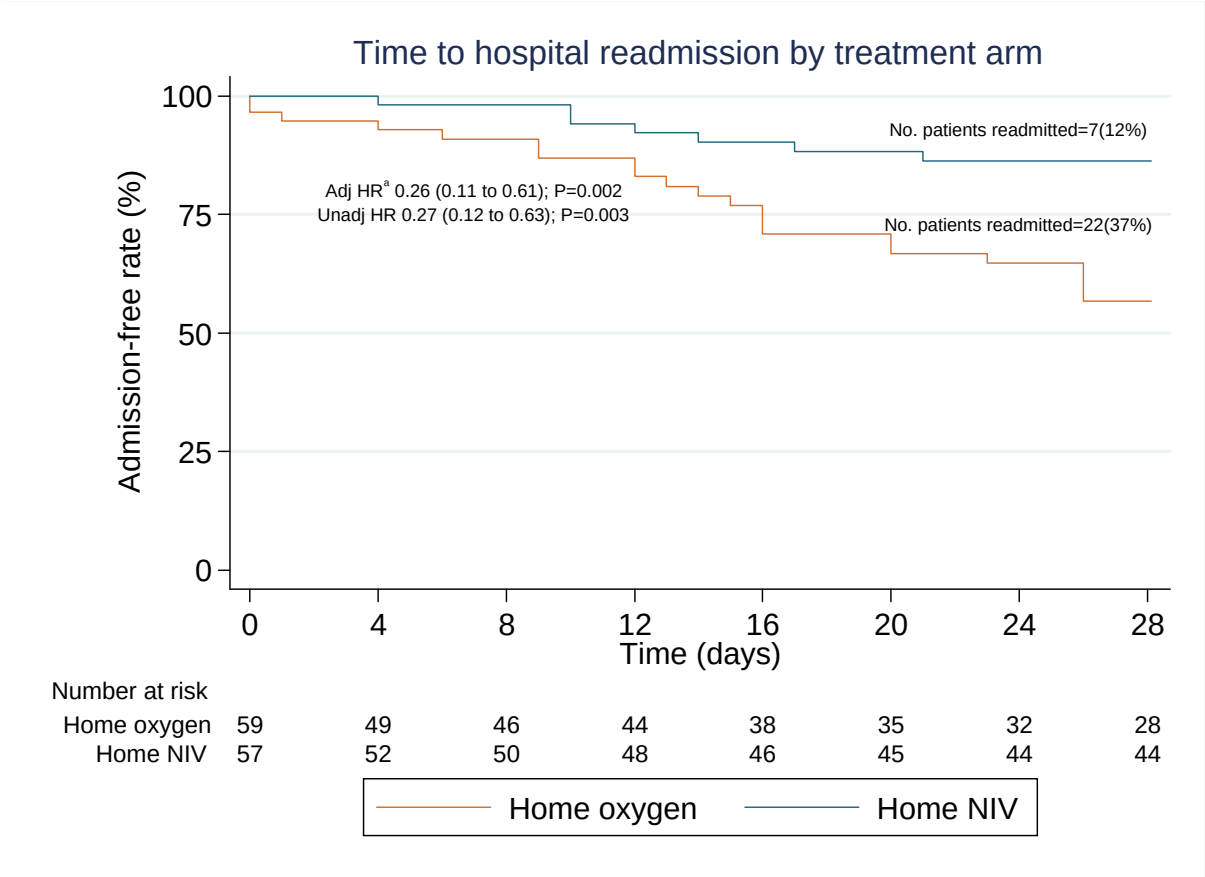
	Home NIV and home oxygen therapy (N=57)	**Home oxygen therapy (N=59)**
Median exacerbation[b] rate per year (25th to 75th percentile)	3.84 (1.68 to 6.02)	5.06 (0.99 to 9.19)
Adjusted rate ratio[a] (95% CI)	0.66 (0.46 to 0.95); p=0.03	
Unadjusted rate ratio (95% CI)	0.64 (0.44 to 0.94); p=0.02	

Abbreviations: NIV = non-invasive ventilation.

[a]Adjusted for number of COPD admissions in previous year, prior use of long term oxygen therapy (LTOT), age and BMI

[b]Exacerbation definition is provided in full the eMethods but in brief represented periods of deteriorating patient reported symptoms and treatment escalation initiated during hospital admission, community physician review or self-directed by patient.

eFigure. Time to readmission or death within 1st 28 days post randomization



Kaplan-Meier plot illustrating time (days) to hospital readmission or death within 28 days of randomization by treatment arm (NIV = non-invasive ventilation)

[a]Adjusted for number of COPD admissions in previous year, prior use of long term oxygen therapy (LTOT), age and BMI