Neuromuscular electrical stimulation to improve exercise capacity in patients with severe COPD: a randomised double-blind, placebo-controlled trial

Matthew Maddocks, Claire M Nolan, William D-C Man, Michael I Polkey, Nicholas Hart, Wei Gao, Gerrard F Rafferty, John Moxham, Irene J Higginson

Summary

Background Skeletal muscle dysfunction and exercise intolerance are common in severe chronic obstructive pulmonary disease (COPD). We assessed the effectiveness of neuromuscular electrical stimulation (NMES) as a home-based exercise therapy.

Methods In this double-blind, placebo-controlled trial, undertaken across three UK National Health Service sites, we randomly assigned (1:1) adults with COPD, a forced expiratory volume in 1 s (FEV_1) less than 50% predicted, and incapacitating breathlessness (Medical Research Council dyspnoea scale ≥4) to receive active or placebo NMES, daily over a 6-week period. Randomisation was by an independent system using minimisation to balance age, GOLD stage, and quadriceps strength. Participants and outcome assessors were masked to group allocation. The primary endpoint was change in 6-min walk test (6MWT) distance at 6 weeks. Analysis was by intention to treat. The trial was registered as ISRCTN15985261 and is now closed.

Findings Between June 29, 2012, and July 4, 2014, we enrolled 73 participants, of whom 52 participants were randomly assigned; 25 to receive active NMES and 27 to placebo NMES. Change in 6MWT distance was greater in the active NMES group (mean 29·9 [95% CI 8·9 to 51·0]) compared with in the placebo group (–5·7 [–19·9 to 8·4]; mean difference at 6 weeks 35·7 m [95% CI 10·5 to 60·9]; p=0·005). Sensitivity analyses for complete-cases and adjustment for baseline values showed similar results. 6 weeks after stopping the intervention the effect waned (7·3 m [95% CI –32·5 to 47·0]; p=0·50). The proportion of participants who had adverse events was similar between groups (five [20%] in the active NMES group and nine [33%] in the placebo group). Two participants, one from each group, reported persistent erythema, which was considered to be possibly related to NMES and the use of adhesive electrodes.

Interpretation NMES improves functional exercise capacity in patients with severe COPD by enhancing quadriceps muscle mass and function. These data support the use of NMES in the management of patients unable to engage with conventional pulmonary rehabilitation. More work is needed to study how to maintain the effect.

Funding National Institute for Health Research.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major contributor to global morbidity and mortality; it affects an estimated 210 million people worldwide,[1] places financial burden on health-care systems,[2] and is projected to be the third most frequent cause of death by 2020.[3] COPD has systemic impact and skeletal muscle dysfunction is a well recognised extrapulmonary manifestation, with preferential weakness and atrophy noted in the lower limbs—mainly as a consequence of physical inactivity.[4] Quadriceps dysfunction and the subsequent exercise intolerance are associated with increased service use and poor prognosis, independent of lung function.[5–7] These and other COPD-related symptoms, such as breathlessness, can be effectively managed with exercise training as part of pulmonary rehabilitation,[8] which is internationally accepted as a first-line disease management strategy.[9] Nonetheless, issues with service provision, uptake, and adherence—eg, lack of transport, restricting symptoms, or social isolation—restrict its reach for patient benefit, particularly for those most impaired by their disease.[10,11]

A proposed alternative treatment is neuromuscular electrical stimulation (NMES). This uses a portable stimulator and skin electrodes to produce a controlled contraction of the muscle.[12] NMES can be self-administered at home, unsupervised, and carries a low metabolic load, providing an acceptable therapy for patients living with a high-symptom burden who find travel to clinics and classes difficult.[13] The strengthening effect of NMES is well established among patients with severe disease compared with no exercise [12] and with lower limb resistance training.[14] The effect of NMES on functional exercise performance is not yet clear but is important to understand because this is a key determinant of health status, and relates to overall survival in this group.[6,12] Moreover, data to help to embed

Research in context

Evidence before this study
Pulmonary rehabilitation has known effectiveness on physical function and health status in chronic obstructive pulmonary disease (COPD), but uptake and adherence are restricted when patients have more severe disease. As a result, alternative, more accessible exercise therapies are sought. Home-based neuromuscular electrical stimulation (NMES) is one such approach, which is gaining interest. We extended our previous Cochrane systematic review by searching MEDLINE, Embase, and CINAHL databases with the terms "exp Electric Stimulation Therapy", "muscle* or muscular or neuromuscular or neuro-muscular and electric* and stimulant*" and "NMES", without language restrictions for randomised trials published up to Nov 1, 2015. We identified 15 trials across patients with COPD, chronic heart failure, and cancer, randomising a total of 445 patients to NMES offered alone or as an adjunct to another exercise programme. Common weaknesses with the methods included limited placebo models and no outcome assessor masking. A pooled estimate of effect indicated that NMES improved quadriceps strength by a standardised mean difference of 0·9 (95% CI 0·33–1·46). There was inconclusive evidence regarding an effect on functional exercise capacity, and no data for the duration of any effect following withdrawal of NMES, which is important to understand before uptake into clinical practice.

Added value of this study
This trial provides high-quality evidence supporting the use of NMES to manage exercise intolerance among patients with severe COPD experiencing disability due to breathlessness. To our knowledge, our study is the first powered with exercise capacity as a primary endpoint, and to include follow-up data. NMES led to a clinically meaningful improvement in 6-min walk test distance at 6 weeks in this patient group compared with the placebo group. During interviews, participants also reported greater ease in undertaking activities of daily living following NMES. However, the effect waned after withdrawal of NMES (a further 6 weeks). This short duration of effect underscores the need to carefully time use within clinical practice, and to explore longer programmes, which are supported by the low risk profile observed here.

Implications of all the available evidence
Current evidence supports the use of NMES in the management of patients who are unable to engage with pulmonary rehabilitation programmes. Staff within these services could offer NMES as an extension of their current scope of practice. Future research should consider trialling longer or more comprehensive NMES based programmes, which include education and behaviour change components.

NMES within routine clinical practice are lacking—for example, it is unclear if training effects can be maintained and how they translate into everyday benefit to patients.

Therefore, this trial aimed to determine the effectiveness of NMES on functional exercise capacity in breathless patients with severe COPD. Our null hypothesis was that patients receiving NMES to both quadriceps over 6 weeks would have no difference in change in exercise performance, compared with patients receiving a placebo intervention.

Methods

Study design and participants
In this parallel, two-group, double-blind, placebo-controlled trial with nested qualitative interviews, which was conducted and reported according to CONSORT guidelines, recruitment took place across three National Health Service trusts in London, UK. Patients were screened at multidisciplinary respiratory and palliative care meetings and across pulmonary rehabilitation services. Patients were eligible if they were aged 18 years or older, with a spirometrically defined diagnosis of COPD consistent with GOLD criteria (forced expiratory volume in 1 s:forced vital capacity [FEV$_1$:FVC] <70%), severe respiratory impairment (FEV$_1$ % predicted ≤50), and incapacitating breathlessness (Medical Research Council dyspnoea scale 4 or 5).[15] Patients were excluded if they had an implanted cardiac pacemaker, a coexisting neurological condition, had changed their medication, or

had experienced an acute exacerbation requiring a hospital admission or systemic corticosteroids in the preceding 4 weeks. This time period was chosen to allow patients to regain a degree of function that would allow engagement with the treatment programme, and so not to impede efforts to implement policy for patients to commence pulmonary rehabilitation within 4 weeks of hospital discharge.[9] We also excluded current regular exercisers, defined as those enrolled in pulmonary rehabilitation or undertaking structured exercise training (≥3 times per week) within the past month. All participants gave written informed consent before trial entry in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The trial protocol was pre-registered with ISRCTN (Ref 15985261) and approved by the London Camberwell St Giles Research Ethics Committee (Ref 12/LO/0263).

Randomisation and masking
After baseline assessment, participants were randomly assigned (1:1) at the individual level, using an independent web-based randomisation system within the independent UK Clinical Research Collaboration-registered King's Clinical Trials Unit (London, UK). Using a hybrid minimisation method, 20% of participants were entered using simple randomisation and 80% entered using computer-generated probabilistic minimisation to balance three potential confounders; age (<65 years or ≥65 years), GOLD stage (III or IV), and quadriceps strength (<20 kg

or ≥20 kg). Following randomisation to active or placebo NMES, the Clinical Trials Unit informed trial staff via secure email. The trial coordinator, who arranged subsequent masked assessment visits, was informed of trial entry but not group allocation. Participants were not informed of group allocation. Trial physiotherapists and nurses were informed of group allocation and selected an active or placebo NMES device accordingly. Two linked Good Clinical Practice compliant online data entry systems (InferMed, London, UK; MACRO version 4) were created to maintain blinding; the first was used by physiotherapists and nurses for data regarding compliance and safety, and the second was used by trial assessors for outcome data. The statistician undertaking the primary analysis (WG) was masked to group allocation.

Procedures

Treating clinicians identified potentially eligible patients and offered them a written information sheet. Interested patients attended a face-to-face appointment to confirm their eligibility, provide consent, and complete baseline assessments.

The therapy was a self-administered, 6-week programme consisting of 30 min of daily bilateral NMES to the quadriceps. NMES uses a battery powered unit to produce a controlled muscular contraction, via self-adhesive electrodes, equivalent to 15–25% of a maximum voluntary contraction (MVC). NMES was delivered with a two-channel MicroStim Exercise Stimulator MS2v2 (Odstock Medical Ltd, Wiltshire, UK) and self-adhesive PALS platinum electrodes (10 cm×13 cm) placed over the distal and proximal body of each quadriceps. Devices delivered current fixed at 50 Hz frequency in 350 µs pulses over an on:off duty cycle, which increased on a weekly basis from 2:15 s to 5:20 s to 10:15 s, remaining constant thereafter. These parameters were selected to minimise skin irritation and muscular fatigue.

Active devices had an amplitude range of 0–120 mA, whereas placebo devices had a range of 0–20 mA (both over 1 KΩ). The placebo amplitude range was selected following piloting of four different maximum outputs (12–30 mA) to provide a sensory stimulus that was detectable by the participant, but insufficient to elicit a tetanic muscular contraction. Devices were outwardly identical apart from a concealed "A" or "B" label, and were controlled by a physiotherapist or nurse who was aware of the participant's group allocation. The same physiotherapist or nurse instructed every participant on how to use the device during a standardised 30 min face-to-face training protocol, which included supervising the first self-administered set-up in hospital or home depending on participant preference. Participants were asked to increase the amplitude until the stimulation intensity was comfortable and not painful. To maximise compliance to the intervention, training was supplemented by standardised written instructions and a self-report diary, weekly telephone calls to troubleshoot
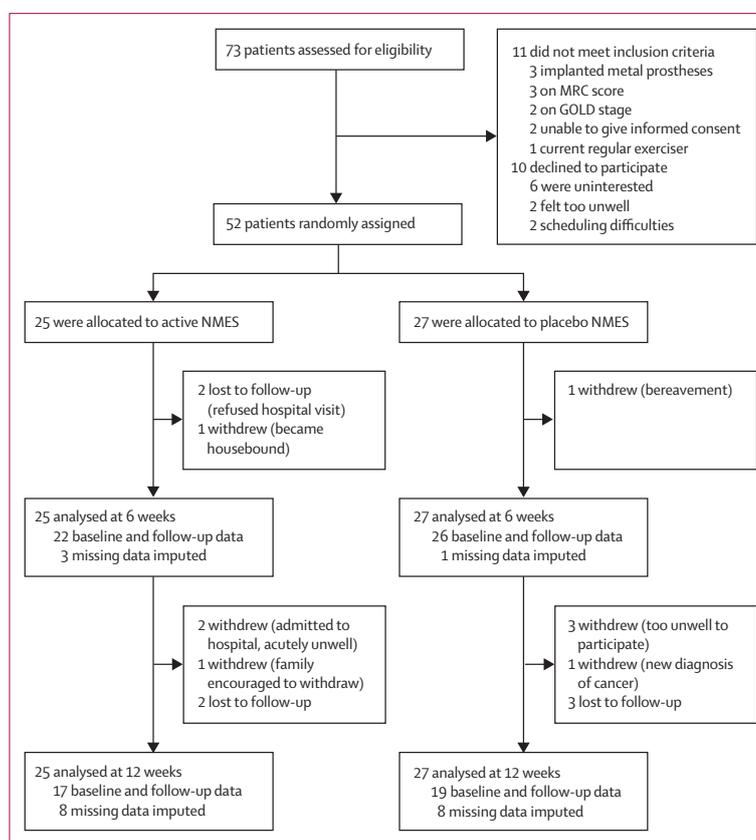

Figure 1: Trial profile
NMES=neuromuscular electrical stimulation. MRC=Medical Research Council.

any practical problems and to prompt participants to increase the stimulation amplitude as tolerated, and home visits to reinstruct patients as required. All were completed by the physiotherapist or nurse, and communication was standardised to maintain participant masking. Both active and control groups used their devices for 6 weeks, after which they were collected by the physiotherapist or nurse.

Follow-up assessments were completed 6 weeks and 12 weeks after randomisation by face-to-face visits. The trial coordinator (masked to group allocation) undertook physical assessments; questionnaires were self-completed independently by participants. Treatment compliance was assessed with a concealed in-built logger, which recorded the number of times the NMES device had been switched on and total duration of use. All other indicated rehabilitation treatments were permitted during the trial.

Outcomes

The primary outcome was change in distance covered in the 6-min walk test (6MWT) from baseline to 6 weeks. The 6MWT is a self-paced test of functional exercise

	Neuromuscular electrical stimulation (n=25)	Placebo (n=27)
Sex		
Men	11 (44%)	10 (37%)
Women	14 (56%)	17 (63%)
Age (years)	70 (11)	69 (9)
Weight (kg)	74·1 (20·1)	75·7 (20·1)
BMI (kg/m²)	25·7 (5·9)	27·8 (8·2)
Smoking status		
Current	5 (20%)	3 (11%)
Previous	19 (76%)	23 (85%)
Never	1 (4%)	1 (4%)
Pack-year history	49 (18)	49 (20)
Spirometry		
FEV₁ (L)	0·82 (0·29)	0·80 (0·49)
FEV₁ % predicted	30·8 (11·1)	30·7 (12·7)
FVC (L)	2·31 (0·79)	2·02 (0·90)
FVC % predicted	70·0 (19·0)	58·3 (21·0)
GOLD stage		
III	12 (48%)	11 (41%)
IV	13 (52%)	16 (59%)
SpO₂ on air	93 (3)	92 (8)
MRC score		
4	18 (72%)	16 (59%)
5	7 (28%)	11 (41%)
Charlson comorbidity index	1 (1–3)	1 (1–2)
Current medication		
Longacting bronchodilators	25 (100%)	27 (100%)
Shortacting bronchodilators	20 (80%)	25 (93%)
Inhaled corticosteroids	21 (84%)	22 (83%)
Oral steroids (maintenance)	7 (28%)	1 (4%)
Oxygen	8 (32%)	6 (22%)
Non-invasive ventilation	0	1 (4%)
Exacerbations previous year	4 (3–8)	3 (2–5)
Time since last exacerbation (weeks)	10 (4–21)	12 (10–32)
Total informal care (h per week)	17·4 (22·5)	13·8 (18·4)
Fat-free mass (kg)	49·5 (12·8)	46·9 (11·6)
Fat-free mass index (kg/m²)	17·1 (3·5)	16·7 (3·7)
6MWT		
Distance (m)	209·2 (98·6)	221·5 (100·8)
Heart rate pre (beats per min)	86·3 (13·8)	85·36 (14·6)
Heart rate post (beats per min)	103·7 (17·7)	104·8 (16·7)
SpO₂ pre	92·6 (2·7%)	93·0 (4·7%)
SpO₂ post	88·0 (4·6%)	88·5 (6·7%)
End SOB Borg rating	4 (4–5)	5 (4–6)
End leg fatigue Borg rating	3 (1–4)	3 (2–5)
Primary limiting symptom		
SOB	17 (68%)	15 (56%)
Leg fatigue	4 (16%)	2 (7%)
Both equally	4 (16%)	10 (37%)
Quadriceps MVC (kg)	24·5 (9·2)	23·1 (9·0)
Quadriceps MVC (% predicted)	58·9 (17·0)	57·3 (18·0)
(Table 1 continues in next column)		

	Neuromuscular electrical stimulation (n=25)	Placebo (n=27)
(Continued from previous column)		
Quadriceps twitch (kg)	6·68 (2·97)	7·07 (2·88)
RFcsa (mm²)	372·6 (147·2)	456·9 (172·5)
4 m gait speed (m/s)	0·79 (0·19)	0·83 (0·21)
Mean daily physical activity		
Step count	2057 (1591)	1900 (1564)
Up-down transitions	40 (16)	33 (20)
Time spent upright (h)	3·31 (1·59)	3·09 (2·20)
CRQ*		
Dyspnoea	2·29 (0·61)	2·58 (1·08)
Fatigue	3·23 (1·02)	3·12 (1·38)
Emotional	4·12 (1·28)	4·79 (1·14)
Mastery	4·84 (1·48)	4·78 (1·73)
SGRQ†		
Symptoms	63·1 (22·0)	69·5 (17·1)
Activity	88·1 (9·8)	83·9 (20·4)
Effect	53·2 (14·7)	49·9 (21·6)
EQ-5D index*	0·57 (0·20)	0·58 (0·28)
EQ-5D HRQL VAS*	58·1 (19·9)	55·0 (3·1)

Data are mean (SD), median (IQR), or n (%), unless otherwise stated. BMI=body-mass index. FEV₁=forced expiratory volume in 1 s. FVC=forced vital capacity. SpO₂=fingertip capillary oxygen saturation. MRC=Medical Reserch Council. SOB=shortness of breath. MVC=maximum voluntary contraction. RFcsa=rectus femoris cross-sectional area. CRQ=Chronic Respiratory Questionnaire. SGRQ=St George's Respiratory Questionnaire. 6MWT=6-min walk test. EQ-5D=EuroQol 5-dimension. EQ-5D HRQL VAS=EuroQol 5-dimension health-related quality of life visual analogue scale. *Scale interpretation: higher score better. †Scale interpretation: lower score better.

Table 1: Baseline characteristics of trial participants

capacity in which patients are asked to walk as far as possible in 6 min along a flat corridor.[16] Tests were conducted according to European Respiratory Society/American Thoracic Society Technical Standard.[17]

Secondary outcomes related to skeletal muscle were quadriceps twitch tension (TwQ) elicited in an unpotentiated state by supramaximal femoral nerve stimulation,[18] isometric quadriceps maximum voluntary contraction (QMVC) assessed using a chair-mounted strain gauge,[19] with percent predicted QMVC calculated using a disease-specific and sex-specific regression equation,[20] rectus femoris cross-sectional area (RF_{CSA}) assessed by ultrasonography,[21] and whole-body fat-free mass assessed by bioelectrical impedance analysis and disease-specific regression equations.[22] Physical activity level was assessed as mean daily step count, time spent upright, and number of sit-to-stand transitions using a multiaxial accelerometer (activPAL; PAL Technologies, Glasgow, UK) worn for 21 h or more per day over 6 days.[23]

We assessed health-related quality of life using the EuroQol 5-dimension (EQ-5D; visual analogue scale 0–100; lower score indicates poorer quality of life),[24] and health status using the St George's Respiratory Questionnaire (SGRQ; total scale 0–100; lower score

indicates better health status),[25] and Chronic Respiratory Questionnaire (CRQ; total scale 0–28; higher score indicates better health status). Formal and informal care was assessed with the Client Service Receipt Inventory, in which participants reported health, voluntary, and social care services and carer support received over the 12-week trial period.[26]

Participants allocated to receive active NMES were, following the 6-week assessment, routinely invited to complete semistructured interviews to explore their experiences and views about the intervention, and any perceived effect on their daily lives. Questions were open-ended and covered the areas of concern without being leading. Interviews were tape-recorded and transcribed verbatim.

Trial nurses and physiotherapists recorded adverse events during assessment visits and weekly telephone calls. These were classified without unmasking of group allocation by the trial lead (MM) as related, unrelated, or possibly related to treatment, using as much information as available to help to determine the potential attribution of the event.

Statistical analysis

Our sample size for the primary outcome, change in 6MWT distance, was based on a COPD specific clinically meaningful difference of 54 m[27] and an effect estimate from a pilot trial of NMES in a comparable population.[28] To detect this difference between groups using a two sample t test with 90% power at the 0·05 significance level (two-sided), assuming unequal variances, 25 participants per group were required. Allowing for a low (<5%) attrition rate based on pooled data from trials of similar duration,[12] we planned to recruit 52 participants overall.

The prespecified primary analysis was by intention to treat. Missing data were explored and reported according to cause.[29] Missing data were handled by a multiple imputation approach (20 datasets), using a Monte Carlo Markov chain method and assuming a multivariate normal distribution.[30] Missing outcome imputation was based on sex, baseline MRC dyspnoea scale, and baseline QMVC as moderators of 6MWT performance. The multiple imputation was implemented with SAS Proc MI and the results of mean change comparison were combined with SAS Proc MIanalyse.

Continuous data were expressed as mean (SD or 95% CI) and compared between groups with the Student's t test. Non-normally distributed data were expressed as median (IQR). Categorical data were presented as percentages, and compared between groups with the Pearson χ^2 test. Outcomes were summarised as change from baseline. We used independent samples Student's t test (two-sided) to compare change in 6MWT (primary outcome) and secondary outcomes at 6 weeks and 12 weeks, by trial group. Sensitivity analyses first used analysis of covariance to account for differences in baseline values and then considered complete-cases only—ie, with paired observations—to account for possible effect of data imputation. $p < 0·05$ indicated statistical significance. Graphical presentations were produced with Prism 5 (GraphPad Software, San Diego, CA, USA).

Qualitative interview data were handled with NVivo version 7 (QSR International Pty Ltd, Melbourne, Austr) and content analysis was used to explore participants' experience of the intervention and its effect. We identified categories inductively from the interview data, with attention to terms and content, and used simple counting to discover consistency of views.

	Neuromuscular electrical stimulation (n=25)	Placebo (n=27)	Treatment difference	p value (two-sided t test)
Primary outcome: 6MWT distance (m)	29·9 (8·9 to 51·0)	–5·7 (–19·9 to 8·4)	35·7 (10·5 to 60·9)	0·005
Secondary outcomes: quadriceps MVC (kg)	3·43 (1·3 to 5·6)	0·34 (–1·5 to 2·0)	3·09 (0·30 to 5·90)	0·028
Quadriceps twitch (kg)	0·99 (0·2 to 1·8)	0·30 (–0·4 to 1·0)	0·70 (–0·4 to 1·80)	0·17
RF$_{CSA}$ (mm^2)	73·3 (42·6 to 104·1)	3·7 (–32·1 to 39·4)	70·0 (23·5 to 115·9)	0·003
Fat-free mass (kg)	–1·49 (–4·3 to 1·3)	–0·02 (–2·0 to 1·9)	–1·46 (–4·8 to 1·9)	0·37
4MGS (m/s)	0·07 (0·0 to 0·1)	0·02 (0·0 to 0·1)	0·05 (0·0 to 0·1)	0·16
Daily step count	–53 (–369 to 264)	–89 (–485 to 307)	37 (–473 to 546)	0·65
Daily up-down transitions	–1·5 (–7·8 to 4·7)	3·1 (–1·8 to 8·0)	–4·6 (–12·5 to 3·2)	0·31
Daily time spent upright	0·08 (–0·5 to 0·7)	–0·37 (–1·1 to 0·4)	0·45 (–0·5 to 1·4)	0·21
CRQ total score*	0·26 (–1·4 to 1·9)	0·43 (–0·5 to 1·4)	–0·17 (–2·0 to 1·6)	0·77
SGRQ total score†	0·22 (–3·8 to 3·4)	0·07 (–3·1 to 3·2)	–0·30 (–5·0 to 4·4)	0·78
EQ-5D index*	–0·01 (–1·1 to 0·1)	–0·01 (–0·1 to 0·1)	–0·01 (–0·1 to 0·1)	0·78
EQ-5D HRQL VAS*	3·63 (–4·1 to 11·4)	–2·39 (–8·6 to 3·8)	7·3 (–3·7 to 15·7)	0·20

Data are mean (95% CI). Missing data were imputed using a Monte Carlo Markov chain method with 20 datasets and assuming a multivariate normal distribution. 6MWT=6-min walk test. MVC=maximum voluntary contraction. 4MGS=4 m gait speed. RF$_{CSA}$=rectus femoris cross-sectional area. CRQ=Chronic Respiratory Questionnaire. SGRQ=St George's Respiratory Questionnaire. EQ-5D=EuroQol 5-dimension. EQ-5D HRQL VAS=EuroQol 5-dimension health-related quality of life visual analogue scale. *Scale interpretation: higher score better. †Scale interpretation: lower score better.

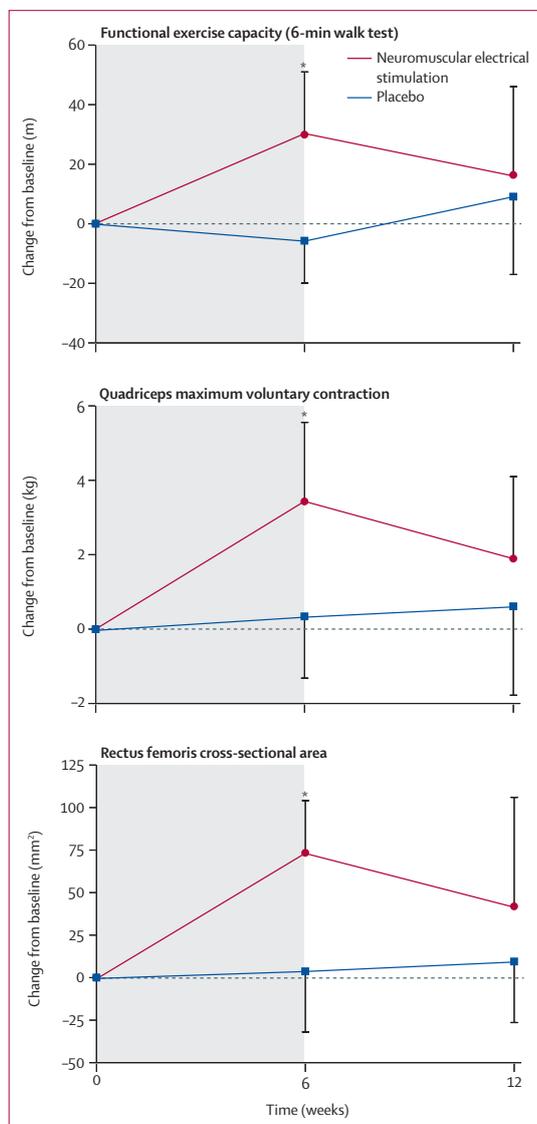*Table 2:* **Estimates of effect in primary and secondary outcome measures at 6 weeks**

Figure 2: Functional exercise capacity (primary outcome), quadriceps muscle strength, and mass outcomes (secondary outcomes) by treatment group
Data are mean (95% CI) change. Shaded area represents treatment period. Asterisks denote a significant between group difference of p<0·05.

Data were exported from the independent King's Clinical Trials Unit system and analysis was completed by the trial statistician (WG) with SAS version 9.4 (SAS Institute, Cary, NC, USA).

The trial was registered as ISRCTN15985261.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had the final

responsibility for the decision to submit the report for publication.

Results

Between June 29, 2012, and July 4, 2014, we screened 73 patients; 62 met eligibility criteria, of whom 52 were randomly assigned; 25 were allocated to active NMES and 27 to placebo NMES (figure 1). Most participants (56 [81%]) were recruited from outpatient clinics or pulmonary rehabilitation services if a referred patient declined to take up a programme. Trial participants had a mean age of 70 years (SD 10) and severe disease by spirometry criteria (mean FEV_1 31% predicted [SD 12]) with a median of four (IQR 2–5) exacerbations in the previous year (table 1). 22 participants (42%) had at least one comorbidity. Functional exercise capacity and physical activity were markedly low (mean 6MWT distance 216 m [SD 99] and daily step count 1980 [SD 1563]; table 1). Participants required on average 15·6 h (SD 20·3) of informal care each week (appendix p 1).

The prescribed programme consisted of 42 sessions lasting 1260 min in total. The mean number of recorded sessions was 34 (SD 14) in the active NMES group versus 33 (18) in the placebo NMES group (p=0·84). The total duration of use was also similar (923 min [SD 546] *vs* 938 min [588]; p=0·93). Initial to final NMES amplitudes were 49·3 mA (SD 9·8) to 72·6 mA (11·0) in the active group and 11·2 mA (SD 2·7) to 15·5 mA (2·8) in the placebo group. One participant from each group commenced pulmonary rehabilitation classes during the follow-up period, with three cumulative attendances between the 6-week and 12-week assessments in the active group and two in the placebo group.

Outcomes were obtained for 48 (92%) and 36 (69%) participants at 6 weeks and 12 weeks, respectively, with similar attrition rates across groups (figure 1). Missing data and dropouts were not associated with baseline FEV_1 % predicted, exacerbation frequency, exercise capacity or health status, or trial group and were considered missing at random (data not shown). Consequently, analyses involved all randomly assigned participants.

We noted a significantly greater improvement in the primary endpoint, 6MWT distance, in the active NMES group compared with the placebo group (mean between-group difference 35·7 m (95% CI 10·5–60·9; effect size 0·41; table 2; figure 2). In the prespecified sensitivity analyses, adjustment for baseline 6MWT changed the p value from 0·005 to 0·004, and when complete-cases only were considered the between-group difference for the primary outcome was increased by 1·0 m (appendix p 2).

This result was accompanied by positive changes in secondary outcomes related to muscle function: QMVC and RFcsa at 6 weeks (figure 2). The change in TwQ favoured NMES though the effect was only significant when adjusted for baseline (p=0·045). We observed no

significant between group differences for gait speed, physical activity level, health status, or health-related quality of life outcomes at 6 weeks (table 2). Absolute changes for gait speed, step count, and time upright and EQ-5D visual analogue scale favoured active NMES. No consistent differences in health status by SGRQ or CRQ were noted (table 2).

The treatment effects waned after withdrawing NMES, such that at 12 weeks, no between-group differences were noted (figure 2; appendix p 3). The between group-difference in 6MWT distance was 7·3 m (95% CI −32·5 to 47·0; p=0·50).

12 participants allocated to active NMES completed qualitative interviews. Perceived benefits of NMES treatment were: greater ease in undertaking basic (eg, stair climbing) and extended (eg, shopping) activities of daily living, and an ability to complete physical activities for longer periods (panel). No participants reported negative experiences or views of the therapy.

The proportion of participants who had adverse events was similar between groups; 5 (20%) in the active NMES group and nine (33%) in the placebo group. 11 (21%) acute exacerbations requiring antibiotics were reported during the study period; four (16%) in the active NMES group and seven (26%) in the placebo NMES group (p=0·25). Nine (17%) of these exacerbations led to hospital admission, resulting in a short course of oral corticosteroids; three (12%) in the active NMES group and six (22%) in the placebo group (p=0·22). One participant (4%) received a diagnosis of laryngeal cancer. Two participants, one from each group, reported persistent erythema, which was considered to be possibly related to NMES and the use of adhesive electrodes.

Discussion

Our study shows that 6 weeks of NMES to the quadriceps improved functional exercise capacity in patients with severe COPD and incapacitating levels of breathlessness. The degree of change was lower than that reported in earlier unblinded studies and the level used to inform our sample size calculation, but exceeded the recent estimate for the minimally important difference for 6MWT distance which, based on all available evidence, lies between 25 m and 33 m.[31] This effect on functional exercise capacity was achieved by treating lower limb muscle dysfunction, with changes in quadriceps strength and mass evident in the active group, but not in the placebo group.

NMES programmes have previously been shown to be acceptable to people with severe COPD across community,[32] inpatient rehabilitation,[14] and intensive care settings.[33] A strengthening effect is expected with a pooled mean difference in QMVC equivalent to about 2·5 kg,[12] consistent with the 3·1 kg difference we noted. The risk profile for NMES is low and adverse events tend to reflect the populations being trialled, as was the case here. Localised muscle discomfort can be reported in the

Panel: Illustrative quotes from qualitative interviews about perceived effect of neuromuscular electrical stimulation on daily life

"I think…I tend to walk better now…you see before me legs were a bit numbish, but once you had the machine…you tend to want to walk (yes) and then your legs feel a bit stronger… My legs used to ache a lot you see but they haven't ached since I've had that on…I used to ache I mean a lot, I was always worrying about my legs…I tend to walk a bit further now than what I did. I mean I've still got the breathing problem but my legs were still going. I could walk a lot further than what I did before…" (Man, 60 years)

"…I was able to get around quicker um in a shorter time…I felt that it speeded up the process of strengthening my muscles so I can get up and walk as much as my body allows if you like…I found that I was able to, um, increase the length of time I was actually walking…I felt I could move around easier and wasn't having to work so hard to do it" (Woman, 62 years)

"…Well, I don't think I can walk any faster…before I couldn't go for a walk up the road. I couldn't get no further than the corner, and I had to turn round and come back. But now I can get up as far as the paper shop, on a good day…I have my good days and my bad days, but I can get as far as the paper shop…go for a little walk round the shops…" (Man, 64 years)

"…improvement in the muscles you're looking at… enable me to get out of the chair easier, um, and with not too many details obviously get off the toilet easier and so forth…I struggle with steps and it made it a little bit easier…" (Man, 65 years

initial few days of use, but other side-effects, including skin abrasion, bruising, or both are rare.[12] NMES is a practical home-based therapy well suited to populations who have high levels of disability or symptom burden.[12] Although supervised pulmonary rehabilitation programmes offer much to address common symptoms of COPD, they are not suitable for the most severely affected often house-bound patients, or at all times—eg, during an exacerbation of disease.[10] These data support a role for NMES in the management of those unable or unwilling to engage with such programmes.

We purposefully selected patients with a high level of impairment as our systematic review suggested this group might respond favourably[12] and this population can have difficulty accessing pulmonary rehabilitation. Many participants had declined or dropped out of a pulmonary rehabilitation programme suggesting that we reached the intended population. Sillen and colleagues[14] previously compared resistance training to high (75 Hz) and low (15 Hz) frequency NMES in patients with COPD and breathlessness and lower limb weakness, as part of an 8-week inpatient rehabilitation programme. Functional exercise performance, breathlessness, mood, and overall health status improved with both stimulation

frequencies. They could not distinguish between the effect of exercise and non-exercise programme components, although no significant differences in muscle function outcomes were noted between high-frequency NMES and resistance training groups. When drawing any comparison between NMES and pulmonary rehabilitation, it is important to note the lack of observable effect on physical activity level, health status, or quality of life following our programme. Although our trial was not powered to detect small changes in these secondary outcomes, pulmonary rehabilitation would typically lead to changes in these outcomes.[8] The short NMES programme duration and absence of concurrent education and behavioural strategies might explain this limited response. Thus, based on current available data, NMES should not be regarded as a replacement for pulmonary rehabilitation. Instead, it might provide adjunct training,[34] or be an alternative means to improve aspects of physical function in those unable to access pulmonary rehabilitation.

The link between peripheral muscle function and whole-body exercise performance is well described in COPD.[35] The strength of association depends on the type of exercise test[36] and the extent of ventilatory versus muscular impairment, which dictate the limiting factors to exercise performance.[37] Vivodtzev and colleagues[32] highlighted this using NMES training. In their study, the level of improvement in exercise performance was related to stimulation intensity, and subsequent gains in quadriceps strength and reduced ventilatory demand during walking.[32] In this trial, 6MWT distance improved in all but two participants at 6 weeks, although treatment response was heterogeneous. In a post-hoc analysis, we explored baseline FEV_1, QMVC and NMES amplitude, and treatment compliance as possible mediators of treatment effect, but none explained the variation in response. Vivodtzev and colleagues[32] also showed gains in muscle mass following NMES, although we used ultrasonography and detected muscle hypertrophy without time-consuming or costly CT techniques. Because NMES was applied via skin electrodes, our imaging of rectus femoris as the most superficial of the quadriceps component muscles might have exaggerated the hypertrophic effect of NMES. However, our findings are in keeping with changes noted after 8 weeks of lower limb resistance training.[38] This measure of muscle mass has recently been shown as an independent risk factor of admission to hospital and survival[39] and modification of risk via exercise intervention is an attractive prospect.

Participants perceived and reported specific functional benefits during daily life, which were not captured by standard questionnaires—eg, finding toileting or stair climbing easier, or having improved outdoor mobility. The activities participants cited in the qualitative interviews generally depended on lower limb function, suggesting a link to the NMES therapy. The loss of ability to independently complete activities of daily living is pertinent to the trial population, who had substantial impairment at baseline and relied heavily on informal care. Indeed, 22 (42%) patients were enrolled with quadriceps strength below a functionally relevant cutoff point that precludes the ability to sit-to-stand unaided.[40] The discrete changes in function following NMES might be early signs that the so-called deconditioning spiral is starting to be addressed, and with additional time and support, patients might translate gains in physical capacity into changes in their independence.

To our knowledge, our trial is the first to follow patients after NMES is withdrawn. Disappointingly, improvements in exercise capacity and muscle function waned such that at 12 weeks between-group differences were no longer significant. This finding supports a causal effect of NMES. The transient gain in muscle function points towards neural changes supplementing muscle anabolism, with increased sensitivity of neural synapses and better synchronisation of motor units during contractions.[41] It also underscores the need to carefully time use within clinical practice as a standalone intervention. Potential roles might include preparing patients for supervised rehabilitation or enhancing functional recovery following acute illness. The latter indication has been questioned by the data of Greening and colleagues[42] in which NMES was a key component of an early rehabilitation approach following admission to hospital for an acute exacerbation of chronic respiratory disease. However, in that trial, only modest doses of exercise training could be offered during the short hospital stays, and compliance to the home-based intervention was poor. Importantly, uptake of formal outpatient pulmonary rehabilitation, offered to both groups after 3 months, was lower in the intervention group than in the usual care control group. This health behaviour suggests that patients receiving the early intervention might have considered their rehabilitation needs to have already been met.[43] Therefore, when treatments like NMES are introduced into clinical practice, clear communication about their role and what they cannot replace is paramount.

Strengths of this trial include the successful masking of participants and outcome assessors, a feature not identified in other NMES trials.[12] Participant masking is difficult for any physical intervention, but the use of an outwardly identical placebo device with a limited output and with careful randomisation conduct and communication ensured this was possible. A breadth of validated outcome measures, offering volitional and non-volitional assessments of muscle mass and function, provided strong mechanistic data to understand the mechanisms behind our primary finding. Our follow-up and qualitative data proved to better understand the clinical role of NMES compared with existing treatments. Finally, the high uptake of participants across multiple sites, low attrition rate, along with the pragmatic delivery of treatment that involved different staff and light supervision, enhances the

external validity of our findings. We perceive the delivery of NMES in this trial is closer to how it would be offered in clinical practice than in previous reports.

There are limitations to consider. We were not able to mask the nurses and physiotherapists who were involved in recording of adverse event data, although events were classified without unmasking of group allocation. We perceive our placebo model to have been successful, but we cannot entirely rule out an anabolic effect, and incidental features of NMES such as dedicated time for self-management might have affected participant behaviour. Our sample size was informed by effect estimate data from a pilot study and an established minimally important difference for COPD, and the expected difference of 54 m was not reached. Nonetheless, our homogeneous sample and well standardised assessments contributed to between-group differences that were significant and exceeded updated minimally important differences for our primary endpoint.[31] We were not powered to detect small changes in health status that might be expected following this modest intensity training. We noted a small number of hospital admissions during the short trial period. Although the number of exacerbations, hospital admissions, and courses of oral corticosteroids was higher in the placebo group than in the active group, this was unlikely to account for the differences in functional exercise capacity, which remained stable, and was enhanced following active NMES. Based on this research, future work should consider trialling longer programmes of NMES, potentially those that use improvements in function to dovetail into pulmonary rehabilitation, or add behaviour change and education components to NMES to enhance health status and quality of life. Once optimised, the effect of an NMES-based approach on outcomes pertaining to patient independence and health service use could be evaluated.

In conclusion, a 6-week programme of NMES improved functional exercise capacity in patients with severe COPD by enhancing quadriceps muscle mass and function. These data support a role for NMES in the management of those unable or unwilling to engage with current pulmonary rehabilitation programmes. The short duration of effect and little effect on health status suggest a need to explore longer programmes, or adding education and behaviour change interventions as part of a broader rehabilitation package.

Contributors
MM is the overall guarantor of this report and takes responsibility for the content, including the data and analysis. MM, WD-CM, MIP, NH, GFR, JM, and IJH contributed to the study concept and design. MM and CMN contributed to data acquisition. WG and IJH developed the statistical analysis plan. MM produced a first draft of the report. All authors critically revised the report and approved the submitted version.

Declaration of interests
MIP reports receiving personal or institutional payment for consultancy or for research from GlaxoSmithKline, Novartis, Lilly, Pfizer, AstraZeneca,

References
1   Murray CJ, Atkinson C, Bhalla K, et al. The state of US health, 1990–2010: burden of diseases, injuries, and risk factors. *JAMA* 2013; **310**: 591–608.
2   Perera PN, Armstrong EP, Sherrill DL, Skrepnek GH. Acute exacerbations of COPD in the United States: inpatient burden and predictors of costs and mortality. *COPD* 2012; **9**: 131–41.
3   Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2095–128.
4   Shrikrishna D, Patel M, Tanner RJ, et al. Quadriceps wasting and physical inactivity in patients with COPD. *Eur Respir J* 2012; **40**: 1115–22.
5   Swallow EB, Reyes D, Hopkinson NS, et al. Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. *Thorax* 2007; **62**: 115–20.
6   Polkey MI, Spruit MA, Edwards LD, et al. Six-minute-walk test in chronic obstructive pulmonary disease: minimal clinically important difference for death or hospitalization. *Am J Respir Crit Care Med* 2013; **187**: 382–86.
7   Decramer M, Gosselink R, Troosters T, Verschueren M, Evers G. Muscle weakness is related to utilization of health care resources in COPD patients. *Eur Respir J* 1997; **10**: 417–23.
8   McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2015; **2**: Cd003793.
9   Spruit MA, Singh SJ, Garvey C, et al. An Official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013; **188**: e13–64.
10 Jones SE, Green SA, Clark AL, et al. Pulmonary rehabilitation following hospitalisation for acute exacerbation of COPD: referrals, uptake and adherence. *Thorax* 2014; **69**: 181–82.
11 Hogg L, Garrod R, Thornton H, McDonnell L, Bellas H, White P. Effectiveness, attendance, and completion of an integrated, system-wide pulmonary rehabilitation service for COPD: prospective observational study. *COPD* 2012; **9**: 546–54.
12 Maddocks M, Gao W, Higginson IJ, Wilcock A. Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease. *Cochrane Database Syst Rev* 2013; **1**: Cd009419.

13 Sillen MJ, Franssen FM, Vaes AW, Delbressine JM, Wouters EF, Spruit MA. Metabolic load during strength training or NMES in individuals with COPD: results from the DICES trial. *BMC Pulm Med* 2014; **14:** 146.

14 Sillen MJH, Franssen FME, Delbressine JML, Vaes AW, Wouters EFM, Spruit MA. Efficacy of lower-limb muscle training modalities in severely dyspnoeic individuals with COPD and quadriceps muscle weakness: results from the DICES trial. *Thorax* 2014; **69:** 525–31.

15 Fletcher CM, Elmes PC, Fairbairn AS, Wood CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *BMJ* 1959; **2:** 257–66.

16 ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; **166:** 111–17.

17 Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J* 2014; **44:** 1428–46.

18 Polkey MI, Kyroussis D, Hamnegard CH, Mills GH, Green M, Moxham J. Quadriceps strength and fatigue assessed by magnetic stimulation of the femoral nerve in man. *Muscle Nerve* 1996; **19:** 549–55.

19 Man WD, Hopkinson NS, Harraf F, Nikoletou D, Polkey MI, Moxham J. Abdominal muscle and quadriceps strength in chronic obstructive pulmonary disease. *Thorax* 2005; **60:** 718–22.

20 Seymour J, Spruit M, Hopkinson N, et al. The prevalence of quadriceps weakness in COPD and the relationship with disease severity. *Eur Respir J* 2010; **36:** 81–88.

21 Seymour JM, Ward K, Sidhu PS, et al. Ultrasound measurement of rectus femoris cross-sectional area and the relationship with quadriceps strength in COPD. *Thorax* 2009; **64:** 418–23.

22 Steiner MC, Barton RL, Singh SJ, Morgan MD. Bedside methods versus dual energy X-ray absorptiometry for body composition measurement in COPD. *Eur Respir J* 2002; **19:** 626–31.

23 Maddocks M, Petrou A, Skipper L, Wilcock A. Validity of three accelerometers during treadmill walking and motor vehicle travel. *Br J Sports Med* 2010; **44:** 606–08.

24 Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Mede* 2001; **33:** 337–43.

25 Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. *Respir Med* 1991; **85B:** 25–31.

26 Higginson IJ, Bausewein C, Reilly CC, et al. An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. *Lancet Respir Med* 2014; **2:** 979–87.

27 Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the Six Minute Walk test in chronic lung disease patients. *Am J Respir Crit Care Med* 1997; **155:** 1278–82.

28 Bourjeily-Habr G, Rochester CL, Palermo F, Snyder P, Mohsenin V. Randomised controlled trial of transcutaneous electrical muscle stimulation of the lower extremities in patients with chronic obstructive pulmonary disease. *Thorax* 2002; **57:** 1045–49.

29 Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. *N Engl J Med* 2012; **367:** 1355–60.

30 Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009; **338:** b2393.

31 Singh SJ, Puhan MA, Andrianopoulos V, et al. An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. *Eur Respir J* 2014; **44:** 1447–78.

32 Vivodtzev I, Debigare R, Gagnon P, et al. Functional and muscular effects of neuromuscular electrical stimulation in patients with severe COPD: a randomized clinical trial. *Chest* 2012; **141:** 716–25.

33 Zanotti E, Felicetti G, Maini M, Fracchia C. Peripheral muscle strength training in bed-bound patients with COPD receiving mechanical ventilation: effect of electrical stimulation. *Chest* 2003; **124:** 292–96.

34 Tasdemir F, Inal-Ince D, Ergun P, et al. Neuromuscular electrical stimulation as an adjunct to endurance and resistance training during pulmonary rehabilitation in stable chronic obstructive pulmonary disease. *Expert Rev Respir Med* 2015; **9:** 493–502.

35 Steiner MC, Singh SJ, Morgan MD. The contribution of peripheral muscle function to shuttle walking performance in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 2005; **25:** 43–49.

36 Man WD, Soliman MG, Gearing J, et al. Symptoms and quadriceps fatigability after walking and cycling in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003; **168:** 562–67.

37 Jones NL, Killian KJ. Exercise limitation in health and disease. *N Engl J Med* 2000; **343:** 632–41.

38 Menon MK, Houchen L, Harrison S, Singh SJ, Morgan MD, Steiner MC. Ultrasound assessment of lower limb muscle mass in response to resistance training in COPD. *Respir Res* 2012; **13:** 119.

39 Greening NJ, Harvey-Dunstan TC, Chaplin EJ, et al. Bedside assessment of quadriceps muscle using ultrasound following admission for acute exacerbations of chronic respiratory disease. *Am J Respir Crit Care Med* 2015; **192:** 810–16.

40 Canavan JL, Maddocks M, Nolan CM, et al. Functionally relevant cut point for isometric quadriceps muscle strength in chronic respiratory disease. *Am J Respir Crit Care Med* 2015; **192:** 395–97.

41 Banerjee P, Caulfield B, Crowe L, Clark A. Prolonged electrical muscle stimulation exercise improves strength and aerobic capacity in healthy sedentary adults. *J Appl Physiol* 2005; **99:** 2307–11.

42 Greening NJ, Williams JEA, Hussain SF, et al. An early rehabilitation intervention to enhance recovery during hospital admission for an exacerbation of chronic respiratory disease: randomised controlled trial. *BMJ* 2014; **349:** g4315.

43 Maddocks M, Kon SS, Singh SJ, Man WD. Rehabilitation following hospitalization in patients with COPD: can it reduce readmissions? *Respirology* 2015; **20:** 395–404.