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Complete List of Authors:

Nolan, Claire; Royal Brompton and Harefield NHS Foundation Trust, Harefield Respiratory Research Group; Imperial College London, National Heart and Lung Institute
Patel, Suhani; Royal Brompton and Harefield NHS Foundation Trust, Harefield Respiratory Research Group; Imperial College London, National Heart and Lung Institute
Barker, Ruth; Royal Brompton and Harefield NHS Foundation Trust, Harefield Respiratory Research Group; Imperial College London, National Heart and Lung Institute
Walsh, Jessica; Royal Brompton and Harefield NHS Foundation Trust, Harefield Respiratory Research Group
Polgar, Oliver; Royal Brompton and Harefield NHS Foundation Trust, Harefield Respiratory Research Group
Maddocks, Matthew; King's College London, Cicely Saunders Institute of Palliative Care, Policy & Rehabilitation
George , Peter M ; Royal Brompton and Harefield NHS Foundation Trust, Interstitial Lung Disease Unit; Imperial College London, National Heart and Lung Institute
Renzoni, Elisabetta A.; Royal Brompton and Harefield NHS Foundation Trust, Interstitial Lung Disease Unit; Imperial College London, National Heart and Lung Institute
Wells, Athol ; Royal Brompton and Harefield NHS Foundation Trust, Interstitial Lung Disease Unit; Imperial College London, National Heart and Lung Institute
Molyneaux, Philip ; Royal Brompton and Harefield NHS Foundation Trust, Interstitial Lung Disease Unit; Imperial College London, National Heart and Lung Institute
Kouranos, Vasilis; Royal Brompton and Harefield NHS Foundation Trust, Interstitial Lung Disease Unit; Imperial College London, National Heart and Lung Institute
Chua, Felix; Royal Brompton and Harefield NHS Foundation Trust, Interstitial Lung Disease Unit; Imperial College London, National Heart and Lung Institute
Maher, Toby; Imperial College London, National Heart and Lung Institute; University of Southern California, Keck Medicine
Man, William; Royal Brompton and Harefield NHS Foundation Trust, Harefield Respiratory Research Group; Imperial College London, National Heart and Lung Institute

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Muscle stimulation in advanced idiopathic pulmonary fibrosis: a randomised placebo-controlled feasibility study

Dr Claire M. Nolan PhD [1,2]	c.nolan@rbht.nhs.uk
Ms. Suhani Patel MSc [1,2]	s.patel1@rbht.nhs.uk
Ms Ruth E. Barker MSc [1,2]	r.barker2@rbht.nhs.uk
Ms Jessica Walsh [1]	j.walsh@rbht.nhs.uk
Mr Oliver Polgar MSc[1]	o.polgar@rbht.nhs.uk
Dr Matthew Maddocks PhD [3]	matthew.maddocks@kcl.ac.uk
Dr Peter M George PhD [2,4]	p.george@rbht.nhs.uk
Dr Elisabetta A Renzoni [2,4]	e.renzoni@rbht.nhs.uk
Prof Athol U Wells [2,4]	a.wells@rbht.nhs.uk
Dr Philip L Molyneux PhD [2,4]	p.molyneux@rbht.nhs.uk
Dr Vasilis Kouranos PhD [2,4]	v.kouranos@rbht.nhs.uk
Dr Felix Chua PhD [2,4]	f.chua@rbht.nhs.uk
Professor Toby M Maher [2,4,5]	toby.maher@usc.edu
Dr William D-C. Man PhD [1,2,6]	w.man@rbht.nhs.uk

Affiliations:

1. Harefield Respiratory Research Group, Royal Brompton and Harefield NHS Foundation Trust, UK
2. National Heart and Lung Institute, Imperial College London, UK
3. King's College London, Cicely Saunders Institute of Palliative Care, Policy & Rehabilitation, UK
4. Interstitial Lung Disease Unit, Royal Brompton and Harefield NHS Foundation Trust, UK
5. Keck Medicine, University of Southern California, USA
6. Harefield PR Unit, Royal Brompton and Harefield NHS Foundation Trust, UK

Corresponding author: Dr Claire Nolan, Senior Research Physiotherapist, Royal Brompton and Harefield NHS Foundation Trust, Harefield Hospital, Middlesex, UB9 6JH, United Kingdom, Tel: +44 (0)1895 828851, Email: c.nolan@rbht.nhs.uk

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ABSTRACT

Objectives: To assess the acceptability of neuromuscular electrical stimulation (NMES) of the quadriceps muscles in people with idiopathic pulmonary fibrosis (IPF) and to identify whether a future definitive trial is feasible.

Design: A randomised, parallel, two-group, participant- and assessor-blinded, placebo-controlled feasibility trial with embedded qualitative interviews.

Setting: Outpatient department, Royal Brompton and Harefield NHS Foundation Trust.

Participants: Twenty-two people with IPF: median (25^{th}, 75^{th} centile) age 76 (74, 82) years, forced vital capacity 62 (50, 75) %predicted, six minute walk test distance 289 (149, 360) metres.

Interventions: Usual care (home-based exercise, weekly telephone support, breathlessness management leaflet) with either placebo or active NMES for six weeks, with follow up at six- and 12-weeks.

Primary outcome measures: Feasibility of recruitment and retention, treatment uptake and adherence, outcome assessments, participant and outcome assessor blinding and adverse events related to interventions.

Secondary outcome measures: Outcome measures with potential to be primary or secondary outcomes in a definitive clinical trial. In addition, purposively sampled participants were interviewed to capture their experiences and acceptability of the trial.

Results: Out of 364 people screened, 23 were recruited: 11 were allocated to each group and one was withdrawn prior to randomisation. Compared to the control group, a greater proportion of the intervention group completed the intervention, remained in the trial blinded to group allocation and experienced intervention-related adverse events. Assessor-blinding was maintained. The secondary outcome measures were feasible with most missing data associated with the accelerometer. Small participant numbers precluded identification of an outcome measure suitable for a definitive trial.

Qualitative findings demonstrated that trial process and active NMES were acceptable but there were concerns about the credibility of placebo NMES.

Conclusions: A definitive trial using the current protocol to evaluate NMES in people with IPF is not feasible.

Trial registration: clinicaltrials.gov NCT03499275

Article Summary

1. This is the first study to examine the feasibility of neuromuscular electrical stimulation in people with idiopathic pulmonary fibrosis.
2. The intervention was developed using a combination of patient and public involvement feedback and previously published studies.
3. We blinded the outcome assessor to group allocation and used an existing placebo neuromuscular electrical stimulator device to blind participants in the control group.
4. We conducted qualitative interviews to capture participant experiences.
5. The study took place at a single site may have been a limiting factor for participant recruitment.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is characterised by progressive dyspnoea, reduction in functional capacity and subsequent loss of independence.[1 2] Several factors contribute to this, including declining lung function and peripheral muscle weakness.[3] There is growing interest in the latter, as it is known that people with IPF have smaller rectus femoris cross-sectional area[4] as well as reduced quadriceps strength[3-5] and endurance[5] compared to matched healthy controls.

The National Institute for Health and Care Excellence (NICE) recommends regular assessment for and offering pulmonary rehabilitation (PR) to people with IPF.[6] However, people with advanced disease and severe breathlessness may have difficulties undertaking PR as ventilatory limitation may preclude effective whole body training.[7] Centre-based PR or exercise programme completion rates range from 43%[8] to 94%.[9] People with more severe disease and those unwilling to participate in group programmes are less likely to complete these programmes.[10] Accordingly, home-based ways of conferring the benefits of exercise are required.

Guidance from NICE states that in people not suitable for, or unable to participate in, existing rehabilitation programmes, neuromuscular electrical stimulation (NMES) of the quadriceps offers an alternative means of enhancing muscle strength.[11] NMES uses a small battery-operated stimulator which, via surface electrodes placed on the anterior thigh, produces a controlled contraction and relaxation of the underlying muscles. It is safe, relatively inexpensive and is performed seated at home. In people with advanced chronic disease including COPD, heart failure, and cancer, a meta-analysis demonstrated that compared to placebo, NMES led to a significant improvement in quadriceps strength, muscle mass and exercise capacity.[12] Therefore, NMES may be a potential treatment for muscle weakness in advanced progressive disease and could be considered a suitable home intervention for people with muscle weakness who have difficulty engaging with existing PR services.[11 12] To date there are no studies exploring the role or effects of

NMES in IPF. Therefore, we aimed to determine the acceptability of NMES of the quadriceps in people with IPF and to identify whether a future definitive trial is feasible.

MATERIALS AND METHODS

Study design and subjects

We conducted a randomised, parallel, two-group, participant- and assessor-blinded, placebo-controlled feasibility trial with embedded qualitative interviews. The trial was conducted and reported according to the CONSORT 2010 statement: extension to randomised pilot and feasibility trials.[13] Participants were recruited from outpatient clinics at the Royal Brompton and Harefield NHS Foundation Trust, UK between November 2018 and February 2020. The inclusion criteria were 1) diagnosis of IPF according to international guidelines,[14] 2) Medical Research Council (MRC) dyspnoea score ≥3, 3) quadriceps maximum voluntary contraction (QMVC) <80% predicted, 4) declined or failed to complete supervised centre-based PR and 5) ability to provide informed consent. People were excluded for the following reasons 1) cardiac pacemaker, 2) co-existing neurological condition e.g. lower limb paralysis, 3) completion of PR within the previous six months, 4) change in medication and/or exacerbation requiring hospitalisation within the previous four weeks or 5) current regular exerciser (structured exercise ≥3/week in the previous month). All participants provided written informed consent. The trial was pre-registered on clinicaltrials.gov (NCT03499275) and the study was approved by London-Harrow Research Ethics Committee and Health Research Authority (18/LO/0209).

Randomisation and blinding

Following baseline assessment, participants were randomly allocated 1:1 at the individual level to receive active or placebo NMES. Minimization was used to balance groups for age (<65 years vs. ≥65 years), sex (male vs. female) and quadriceps strength (<20kg vs. ≥20kg). The allocation sequence was generated using an independent web-based randomisation system within the UK Clinical Research Collaboration-registered

King's Clinical Trials Unit. Following randomisation, the Clinical Trials Unit informed trial staff by secure email. An unblinded researcher selected an active or placebo device accordingly. Blinded researchers were informed of trial entry but not group allocation. The participant was not informed of group allocation. Subsequent assessment visits were completed immediately after the six-week intervention period and at 12 weeks by a researcher blinded to group allocation. Qualitative in-depth, topic-guided interviews were completed in a sub-group of participants who were selected purposively to include both intervention and control groups, sexes, and a range of baseline MRC scores so that different perspectives could be explored.

Interventions

The treating healthcare professionals provided potential participants with the study information leaflet who were then screened by the research team via telephone. Those interested in participating in the study attended an assessment to confirm eligibility.

The interventions were based on a combination of patient and public involvement feedback and published studies.[15] The NMES programme was a self-administered, home-based protocol involving 30 minutes stimulation of bilateral quadricep muscles for six weeks. The active device was KneeHab®XP (Neurotech, USA) and the placebo device, MicroStim Exercise Stimulator MS2v2 (Odstock Medical Ltd, UK). Although different machines were used for the active and placebo devices, they were outwardly identical as both were covered in the same garment (online supplement). The parameters of both devices were the same (frequency 50Hz, pulse width 400µs, duty cycle 18–33% which increased weekly for the first three weeks) except for the amplitude range (active: 0-120mA; placebo: 0-20mA). Consequently, participants in the control group received sensory feedback during stimulation but the device did not elicit a tetanic muscle contraction.

Participants in both groups also received a leaflet on how to manage breathlessness and an individualised home exercise programme supplemented with a manual which they were instructed to perform at least three times per week (online supplement).

The unblinded researcher delivered a standardised 40-minute training session to participants in both groups to demonstrate and supervise NMES application and the home exercise programme. Participants were provided with a diary to record NMES and exercise performance. During the six-week intervention period, the unblinded researcher telephoned participants weekly to review and progress NMES use and home exercise performance. To progress NMES, participants were asked to increase the amplitude of the electrical current, within the limits of the device.

Outcome measures

Primary outcome measures

The primary outcomes were related to feasibility: participant recruitment and retention, treatment uptake and adherence, feasibility of outcome assessments, feasibility of participant and assessor blinding and adverse events related to the interventions. To assess recruitment- and retention-related feasibility outcomes, the numbers of potential eligible participants as well as recruitment and retention rates at the six- and 12-week assessments were recorded. To assess treatment uptake and adherence, the following were recorded; feasibility, outcomes, rates of uptake of and adherence to the allocated intervention and frequency and time spent using the NMES device and performing the home exercise programme. Feasibility of outcome assessment was measured by recording the amount of missing data for each outcome measure at each assessment. Participant and assessor blinding were assessed by the unblinded researcher at the six-week assessment, and six- and 12-week assessment respectively. Research staff recorded adverse events during assessment visits and weekly telephone calls. These were classified as related or unrelated to the allocated intervention, using as much information as available to determine the potential attribution of the event.

Secondary outcome measures

The secondary outcome measures were those that had the potential to be primary or secondary outcomes in a definitive clinical trial. These were: exercise capacity (six-minute walk test-6MWT),[16] functional

performance (Short Physical Performance Battery-SPPB),[17] four metre gait speed (4MGS),[18] rectus femoris size (ultrasound of rectus femoris cross-sectional area (Mindray DP-50, Caiyside Imaging Ltd., Scotland), quadriceps strength (isometric QMVC),[19] health-related quality of life (King's Brief Interstitial Lung Disease questionnaire-KBILD),[20] activities of daily living (London Chest Activities of Daily Living-LCADL),[21] and physical activity parameters (daily step count, time spent in sedentary, light and moderate intensity activity (SenseWear, Bodymedia, USA)).[22]

Following the 12-week assessment, purposively sampled participants were invited to take part in semi-structured, topic-guided, telephone-based interviews. The audio-recorded interviews explored experiences of the intervention, how it impacted perceptions of outcome, acceptability of outcome measures and trial conduct in order to inform the rationale for and conduct of a definitive trial. The topic guides were updated inductively to reflect experiences and perceptions raised during previous interviews.

Sample size

Sample size estimation was performed to achieve the primary feasibility outcomes, and not to detect differences in the secondary outcome measures. Based on guidance in the literature, we estimated that a sample size of 60 (30 per group) would be sufficient to adequately evaluate the feasibility of undertaking a definitive trial. A sample size of ten was chosen for the qualitative interviews as it was based on the predicted minimum number of interviews required to achieve data saturation and is based on the concept of Information Power.[23]

Statistical analysis

The feasibility outcomes and baseline demographics were described and summarised overall and by trial group using proportions (percentage) or median (25^{th}, 75^{th} centile). The baseline data and change at six and 12 weeks was reported as median (25^{th}, 75^{th} centile) or median (25^{th}, 75^{th} centile) change for each trial group.

Anonymised interview transcripts were transcribed verbatim and imported into NVIVo (QSR International, Australia) to facilitate analysis using the Framework Method.[24] The coding frame was pre-defined and included experiences of the interventions, impact of intervention on perceived outcome, acceptability and experiences of trial conduct and acceptability of the outcome measures. During indexing, secondary codes were inductively applied. A mixed-method matrix[25] of qualitative and key quantitative data was used to illuminate barriers and facilitators for intervention completion by participants to inform protocol adaptation and/or optimisation.

Patient and public involvement (PPI)

This research has included PPI throughout each stage. Two PPI representatives were involved in the design of the study and intervention, and met the project manager at regular intervals throughout the study. The PPI representatives also provided input into written material for participants and topic guides for qualitative interviews. Going forward, they will have a role in in dissemination of research findings to lay audiences.

RESULTS

Primary outcome

Feasibility of recruitment and retention

We screened 364 people, of whom 153 were assessed for eligibility and 23 consented to participate in the study: 11 were allocated to both the intervention and control groups and one was withdrawn prior to randomisation for safety reasons (figure 1). By far the most common reason for failing the telephone-based screening assessment was the distance participants were required to travel to the research centre (n=153). MRC<3 (n=55) or PR completion within six months (n=24) were the most common reasons for failing the eligibility assessment. At the six-week assessment, two participants in both groups were lost to

follow-up (intervention: n=2 missed visit, control: n=2 withdrew from the study). At the 12-week assessment, all participants in the intervention group were assessed whereas three participants in the control group were lost to follow-up (withdrew from the study).

Feasibility of treatment uptake and adherence

All participants started their allocated intervention. Both groups received the same median number of weekly telephone calls but there was a trend for higher frequency and duration of use of the NMES device and home exercise programme in the intervention compared to the control group (table 1). All participants in the intervention group completed the allocated intervention. In contrast, four participants in the control group discontinued the intervention: n=2: did not tolerate placebo NMES, n=1 unwell, n=1: felt NMES was ineffective.

Table 1. Intervention uptake, adherence and completion

Variable	**Intervention**	**Control**
Number of weekly telephone calls	6 (5, 6)	6 (4, 6)
Number of times device* used between V1 and V2	31 (22, 44)	24 (4, 40)
Total minutes device* used between V1 and V2	930 (660, 1110)	570 (120, 1230)
Number of times HEP performed between V1 and V2	20 (17, 32)	14 (4, 26)
Total minutes HEP performed between V1 and V2	906 (600, 1527)	648 (110, 1399)

Data reported number or median (25^{th}, 75^{th}) centile.

**Device: Intervention group: Active stimulator; Control group: Placebo stimulator.*

Abbreviations: HEP: Home Exercise Programme; NC: Not Computed; V: Visit.

Feasibility of outcome assessment

Missing data for each clinical outcome according to assessment timepoint are described in the online supplement. There were no missing data at the baseline assessment. Missing data at the six- and 12-week assessments mostly related to participants that were lost to follow up. The outcome measures with the most missing data were the physical activity parameters (intervention, control: baseline: n=4, n=4; six and 12 weeks: n=5, n=6). Reasons for missingness included participants declining to wear the device and insufficient data to analyse.

Feasibility of participant and outcome assessor blinding

Participant blinding was maintained in the intervention group but three participants in the control group were unblinded as they did not believe the placebo NMES was credible. The outcome assessor remained blinded to intervention allocation of all participants.

Adverse and serious adverse events

There was one serious adverse event in the intervention group and four in the control group. None of these events were unexpected or related to the allocated intervention or assessments. One participant experienced two adverse events prior to randomisation. A total of 10 and five adverse events in the intervention and control groups were experienced by eight and four participants respectively. None of the events prior to randomisation or in the control group were unexpected or related to the study. Three adverse events in the intervention group were expected and related to the study. These included redness on anterior thigh and itchiness on anterior thigh following NMES use as well as “burning sensation” on anterior thigh during NMES use. The remaining seven adverse events were expected and unrelated to the intervention.

Secondary outcomes

The groups were balanced in terms of age, gender, disease severity, body mass index and quadriceps strength (table 2). However, compared to the intervention group, the control group had a greater proportion of participants diagnosed with pulmonary hypertension, prescribed supplementary oxygen and former smokers as well as worse exercise capacity, activities of daily life performance, walking speed and physical activity levels. Due to the small number of participants in each group, it was not possible to test for between-group differences.

Table 2. Baseline characteristics

	Whole group (n=22)	**Intervention (n=11)**	**Control (n=11)**
Gender: male (%)	16 (73)	7 (64)	8 (73)
Age (years)	76 (74, 82)	77 (73, 81)	76 (74, 84)
MRC Dyspnoea score	4 (4, 4)	4 (4, 4)	4 (4, 4)
BMI (kg/m^2)	24.4 (22.4, 29.1)	24.2 (22.0, 26.5)	25.2 (22.6, 29.2)
FEV_1/FVC	0.84 (0.78, 0,86)	0.80 (0.77, 0,85)	0.84 (0.78, 0,87)
FVC (L)	1.83 (1.39, 2.44)	1.83 (1.44, 2.45)	1.82 (1.22, 2.44)
FVC (% predicted)	61.8 (49.8, 75.0)	63.0 (49.0, 78.2)	60.5 (50.0, 68.0)
Smoking status: never/former/current: (%)	13 (59) / 9 (41) / 0 (0)	7 (64)/ 4 (36) / 0 (0)	6 (55) / 5 (45) / 0 (0)
Smoking pack year history	0 (0, 8)	0 (0, 5)	0 (0, 13)
Age-adjusted Charlson Co-morbidity Index	2 (0, 5)	4 (0, 5)	0 (0, 6)
COPD: n (%)	3 (14)	1 (10)	2 (18)
Pulmonary hypertension: n (%)	2 (9)	0 (0)	2 (18)
Ischaemic heart disease: n (%)	8 (36)	5 (46)	3 (27)
Obstructive sleep apnoea: n (%)	0 (0)	0 (0)	0 (0)
Self-reported hospitalisations in previous year: n (%)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Self-reported chest infections in previous year: n (%)	1 (1, 2)	1 (1, 2)	1 (1, 1)
Oxygen: n (%)			
Long-term	4 (18)	1 (10)	3 (27)
Ambulatory	9 (41)	4 (36)	5 (46)

Walking aid: n (%)	5 (23)	2 (18)	3 (27)
Prescribed pirfenidone: n (%)	6 (27)	4 (36)	2 (18)
Prescribed nintedanib: n (%)	7 (32)	4 (36)	3 (27)
6MWT (m)	289 (149, 360)	326 (150, 361)	240 (130, 325)
SPPB score	9 (6, 11)	10 (6, 11)	7 (4, 11)
Four metre gait speed (m/s)	0.71 (0.50, 0.94)	0.82 (0.38, 0.97)	0.66 (0.51, 0.84)
QMVC (kg)	22.4 (15.6, 28.7)	22.5 (15.1, 28.3)	22.4 (15.7, 31.3)
Rectus femoris cross-sectional area (mm^2)	459 (371, 534)	451 (321, 579)	479 (375, 581)
KBILD - Psychological	54.4 (53.2, 69.1)	58.8 (41.2, 71.6)	53.5 (43.8, 65.5)
KBILD – Breathlessness and activities	35.6 (21.6, 45.9)	37.8 (27.0, 50.2)	35.6 (17.7, 41.9)
KBILD – Chest symptoms	68.6 (44.0, 85.2)	63.7 (44.0, 85.2)	73.4 (54.3, 85.2)
KBILD – Total score	53.5 (46.4, 59.4)	56.1 (43.9, 66.4)	53.5 (47.2, 56.1)
LCADL – Self-care	6.0 (4.0, 8.0)	7.0 (4.0, 8.0)	6.0 (4.0, 7.0)
LCADL – Domestic	10.5 (4.8, 18.5)	5.0 (1.0, 17.0)	14.0 (10.0, 22.0)
LCADL – Physical	4.0 (3.0, 6.0)	4.0 (3.0, 5.0)	4.0 (3.0, 6.0)
LCADL – Leisure	4.0 (3.0, 6.0)	4.0 (3.0, 6.0)	5.0 (4.0, 6.0)
LCADL – Total score	26.0 (17.5, 37.3)	20.0 (14.0, 28.0)	33.0 (22.0, 29.0)
Daily step count	1511 (776, 3456)	1820 (1148, 3232)	988 (657, 4115)
Daily mins spent in moderate intensity PA	34 (20, 84)	47 (25, 100)	22 (5, 74)
Daily mins spent in light intensity PA	194 (147, 221)	217 (126, 248)	187 (153, 199)
Daily mins spent sedentary	1144 (1098, 1206)	1123 (1095, 1151)	1194 (1137, 1237)

Data reported as number (percentage) or median (25^{th} centile, 75^{th} centile).

Abbreviations: 6MWT: Six Minute Walk Test; CI: Confidence Interval; EQ5D5L: EQ5D 5-Levels; KBILD: King's Brief Interstitial Lung Disease questionnaire; LCADL: London Chest Activities of Daily Living questionnaire; P: p-value; PA: Physical Activity; QMVC: Quadriceps Maximum Voluntary Contraction; SPPB: Short Physical Performance Battery.

KBILD domains and total score: Range 0-100; higher scores indicate better health-related quality of life.

LCADL range: Self-care: 0-20; Domestic: 0-30; Physical: 0-10; Leisure: 0-15; Total: 0-75; higher scores indicate greater impact on ADL performance.

The response to the intervention between baseline and six-week assessment, and baseline and 12-week assessment are shown in tables 3 and 4 respectively. Again, owing to the small numbers of participants, it

is not possible to draw firm conclusions from these data. However, between the baseline and six-week assessment, there was trend for a greater reduction in sedentary time in the intervention group, compared to an increase in sedentary time in the control group (table 3). Similarly, between the baseline and 12-week assessment, there was a trend for a greater increase in rectus femoris cross-sectional area, self-care related to activities of daily living performance and time spent in light intensity physical activity in the intervention compared to the control group (table 4).

Table 3. Draft table for the within and between group response of the secondary outcome measures to the intervention from Visit 1 to Visit 2.

Outcome	Intervention		Control	
	n	Within group difference	n	Within group difference
Δ 6MWT (m)	9	6 (-16, 45)	8	-17 (-74, 4)
Δ SPPB	9	0 (-1, 1)	8	0 (0, 0)
Δ Four metre gait speed (m/s)	9	0.03 (0.01, 0.06)	8	-0.04 (-0.09, 0.03)
Δ QMVC (kg)	9	-0.1 (-1.9, 2.5)	8	-0.2 (-1.7, 2.0)
Δ Rectus femoris cross-sectional area (mm^2)	9	18.0 (-32.6, 48.3)	8	16.0 (-50.6, 33.0)
Δ KBILD - Psychological	9	5.9 (-3.4, 12.8)	9	0 (-7.2, 9.6)
Δ KBILD - Breathlessness and activities	9	9.3 (-7.8, 13.8)	9	0 (-8.4, 13.5)
Δ KBILD – Chest symptoms	9	9.7 (-5.9, 16.7)	9	9.7 (-5.9, 22.9)
Δ KBILD – Total score	9	2.7 (-0.2, 7.4)	9	0.1 (-2.2, 3.9)
Δ LCADL – Self-care	9	-1.0 (-2.0, 0.0)	9	1.0 (-0.5, 1.5)
Δ LCADL - Domestic	9	1.0 (-3.0, 4.5)	9	-1.0 (-3.0, -5.0)
Δ LCADL – Physical	9	0.0 (-0.5, 0.5)	9	0.0 (-1.0, 1.5)
Δ LCADL – Leisure	9	0.0 (-1.0, 1.0)	9	0.0 (-1.0, 1.5)
Δ LCADL – Total score	9	0.0 (-5.0, 2.0)	9	4.0 (-3.0, 10.0)
Δ Daily step count	5	-270 (-504, 877)	5	-740 (-2026, -230)
Δ Daily mins spent in moderate intensity PA	5	-3 (-20, 4)	5	-19 (-51, -5)
Δ Daily mins spent in light intensity PA	5	24 (5, 71)	5	-39 (-65, 15)

Δ Daily mins spent sedentary	5	-40 (-58, -21)	5	54 (22, 86)

Data reported as median (25th centile, 75th centile) difference.

Abbreviations: 6MWT: Six Minute Walk Test; CI: Confidence Interval; EQ5D5L: EQ5D 5-Levels; KBILD: King's Brief Interstitial Lung Disease questionnaire; LCADL: London Chest Activities of Daily Living questionnaire; P: p-value; QMVC: Quadriceps Maximum Voluntary Contraction; SPPB: Short Physical Performance Battery.

KBILD domains and total score: Range 0-100; higher scores indicate better health-related quality of life.

LCADL range: Self-care: 0-20; Domestic: 0-30; Physical: 0-10; Leisure: 0-15; Total: 0-75; higher scores indicate greater impact on ADL performance.

Table 4. Draft table for the within and between group response of the secondary outcome measures to the intervention from Visit 1 to Visit 3.

Outcome	Intervention		Control	
	n	Within group difference	n	Within group difference
Δ 6MWT (m)	10	-13 (-73, -15)	6	-23 (-100, 18)
Δ SPPB	10	0 (-1, 0)	7	0 (-1, 1)
Δ Four metre gait speed (m/s)	10	-0.03 (-0.14, 0.08)	7	0.01 (-0.12, 0.09)
Δ QMVC	11	1.0 (-0.9, 4.3)	7	-1.7 (-3.4, 3.7)
Δ Rectus femoris cross-sectional area (mm^2)	11	32.6 (2.5, 54.4)	7	-48.6 (-87.8, 10.0)
Δ KBILD - Psychological	11	7.8 (4.6, 19.1)	8	4.2 (-4.1, 8.7)
Δ KBILD - Breathlessness and activities	11	9.3 (-7.5, 13.6)	8	0 (-10.0, 5.9)
Δ KBILD – Chest symptoms	11	10.3 (0, 19.7)	8	10.8 (0, 24.9)
Δ KBILD – Total score	11	5.4 (1.1, 8.8)	8	2.6 (-4.1, 4.3)
Δ LCADL – Self-care	11	-1.0 (-2.0, 0.0)	8	1.0 (0.3, 2.5)
Δ LCADL - Domestic	11	1.0 (-1.0, 3.0)	8	4.0 (-2.5, 9.5)
Δ LCADL – Physical	11	0.0 (-1.0, 0.0)	8	0.0 (-1.0, 1.8)
Δ LCADL – Leisure	11	0.0 (0.0, 1.0)	8	0.5 (-0.8, 2.8)
Δ LCADL – Total score	11	1.0 (-2.0, 5.0)	8	4.5 (0.8, 15.3)
Δ Daily step count	5	-215 (-966, 176)	5	-334 (-2712, 7)
Δ Daily mins spent in moderate intensity PA	5	2 (-29, 22)	5	2 (-31, -11)
Δ Daily mins spent in light intensity PA	5	37 (-46, 54)	5	-3 (-61, 35)

Δ Daily mins spent sedentary	5	8 (-29, 87)	5	7 (-24, 50)

Data reported as median (25th centile, 75th centile) difference.

Abbreviations: 6MWT: Six Minute Walk Test; CI: Confidence Interval; EQ5D5L: EQ5D 5-Levels; KBILD: King's Brief Interstitial Lung Disease questionnaire; LCADL: London Chest Activities of Daily Living questionnaire; P: p-value; QMVC: Quadriceps Maximum Voluntary Contraction; SPPB: Short Physical Performance Battery.

KBILD domains and total score: Range 0-100; higher scores indicate better health-related quality of life.

LCADL range: Self-care: 0-20; Domestic: 0-30; Physical: 0-10; Leisure: 0-15; Total: 0-75; higher scores indicate greater impact on ADL performance.

Six participants (four male, two female), aged between 54 and 84 years, participated in the qualitative interviews. The majority had been allocated to the intervention group, with only one participant from the control group. Despite interviewing almost one third of participants that were recruited to the trial, new data was being gained up to and including the last interview.

All participants found the research staff, trial processes and outcome measures acceptable:

> *"I was able to comply with what was required,…, other than the fact that the walking is limited, but at least I could rest."* [Male, 80's, intervention group]

Most participants stated that the NMES device was feasible and acceptable:

> *"The instructions were pretty straightforward, and once you have done it the first time,…, you just got it out of the bag and off you went."* [Male, 80's, intervention group]

However two participants reported negative NMES experiences:

> *"It was a damn nuisance, to be perfectly frank,…, no, it was a bit of a performance and a bit of a nuisance."* [Female, 70's, intervention group]

> *"It was as if it was a placebo in place of the real thing,…, yes, I would say that it was the placebo, it wasn't the real thing."* [Male, 70's, control group]

All participants reported that the exercise programme was feasible, acceptable and beneficial:

> *"I'm still doing them, actually. It's a good programme"* [Female, 70's, intervention group]

However, maintaining motivation to complete the programme was difficult with one participant stating that he did so because it was part of the study:

> *"I made sure I did the leg exercises [even when unwell] because that's what I promised I would do"* [Male, 60's, intervention group]

There was disparity in participants' experience of the weekly telephone support during the six-week intervention period. Some found it burdensome and suggested that digital monitoring would have been preferable:

"That [provision of electronic version of home exercise programme] would have better. Yes, that would have been brilliant, and to then send it [diary reporting compliance and progress] back that way too"

[Female, 70's, intervention group]

In contrast, other participants found it to be a positive experience and suggested more frequent monitoring would have been preferable:

"I think once a week, or maybe twice a week would be a secondary call, if you did it on a Monday and then on a Friday" [Male, 60's, intervention group]

In addition, some participants reported that diary completion was difficult which affected their compliance with this tool:

"I didn't fill in the form right. I didn't find the form very easy. I did it my own way" [Female, 70's, intervention group]

DISCUSSION

We aimed to determine the acceptability of NMES of the quadriceps muscles in people with IPF and identify whether a future definitive trial is feasible. The qualitative interviews suggest that participants found the trial process, active NMES device and home exercise programme acceptable, but there were concerns about the credibility of placebo NMES and divergent opinions regarding the telephone support and diary. The quantitative data demonstrates that a definitive trial using this protocol should not be undertaken because of challenges in participant recruitment as well as between-group differences in retention of, treatment adherence and blinding of participants in the control compared to the intervention

group. However, this feasibility study provided important additional information that could inform future rehabilitation-based interventions.

Primary feasibility outcomes

The principle reason this protocol in its current format should not be tested in a definitive trial is that an insufficient number of participants were recruited to satisfy the a priori sample size requirement. A total of 364 potential participants were screened with 211 excluded prior to the eligibility assessment. The main reason for exclusion was the distance between the person's home and assessment centre, despite the provision of transport. The Interstitial Lung Disease (ILD) Unit at our hospital provides specialist care to people that live in a large geographic area, which may explain the reluctance to participate in the study. Although we have not faced such recruitment issues in other studies, our experience with this protocol suggests future rehabilitation-based research should be multi-site and conducted alongside clinical appointments and/or located in centres accessible to participants and/or in participants' homes. Out of 153 participants that attended the eligibility assessment, 23 consented to participate in the study. The most common reason for failing this assessment was MRC<3 or PR completion within six months. These conditions formed part of the inclusion criteria to ensure that people with advanced disease and a sedentary lifestyle respectively were recruited to the study. Going forward, trial eligibility based on indication for NMES rather than PR completion status may be more appropriate.

There was a trend for a greater proportion of participants in the control group to withdraw from the study, discontinue and perform less of the intervention, and/or become unblinded to group allocation. These findings may be related to statistical chance because of the small sample size, differences in between-group baseline characteristics and/or poor placebo NMES device credibility. The between-group difference in baseline characteristics and concerns about placebo NMES credibility were unexpected findings, because the minimisation criteria used in the randomisation process and the placebo device were informed by previous studies.[15] Furthermore, although two different devices were used to deliver active and placebo

NMES, the outward appearance of both were identical and as such, should not have contributed to the differences in participant perception. However, qualitative findings demonstrated that a participant in the control group believed he used a placebo device as the sensation was insufficiently strong. Future research should consider reviewing the intensity and/or individualise the intensity of the placebo device.

In contrast to the control group, qualitative findings demonstrated that active NMES was acceptable to participants in the intervention group. In addition, the home exercise programme was also acceptable to both groups. However, there was a difference of opinion regarding the frequency of the telephone support and utility of the NMES and exercise diary. Exploration of these aspects of the intervention are important for future home-based rehabilitation studies in IPF.

Although blinding of some participants was not maintained, assessor blinding was successful. This was achieved by provision of an office isolated from the research laboratory that allowed the unblinded researcher inform participants of group allocation, deliver the training session and schedule telephone calls.

The majority of the outcome measures were acceptable to participants and feasible to perform. However, there were a significant volume of missing accelerometer data because participants declined to wear the device or there was insufficient data to analyse. Going forward, researchers may decide to make wearing the device a prerequisite to study entry, shorten the device-wearing time or consider an alternative device that is more acceptable to participants.

There was a difference in the amount of expected and related adverse events in the intervention compared to the control group. These events occurred during or following NMES use and did not result in discontinuation of the intervention. Although not categorised as serious, these findings reinforce the importance of explaining the risks associated with this type of intervention in the patient information sheet.

Secondary outcome measures

Although the intervention and control groups were balanced in terms of some outcome measures, there was imbalance in important variables that could influence exercise and physical activity capacity as a greater proportion of the control group were diagnosed with pulmonary hypertension and had a supplementary oxygen prescription as well as worse exercise capacity, activities of daily life performance, walking speed and physical activity levels. This may have arisen because of statistical chance given the small participant numbers, however, the minimisation variables used for randomisation may also have contributed to the problem. The minimisation variables: age, gender and quadriceps strength, were chosen as they were relevant to the population of interest and intervention, and were also informed by previous studies.[15] However, although there is a strong correlation between quadriceps strength and exercise capacity ($r=0.56$, $p<0.001$) in ILD,[26] accounting for exercise capacity itself, as well as co-morbidities and physical activity levels may be important in ensuring balance between trial groups in future research.

Owing to the small sample size, imbalance in between-group baseline characteristics and smaller number of control versus intervention group participants, it is challenging to identify an outcome measure that has the potential to be a primary or secondary outcome measure in a definitive trial. However, as there was a trend for greater reduction in sedentary time between baseline and six weeks as well as a greater increase in self-care ability and light intensity physical activity between baseline and 12 weeks that favoured the intervention group, these outcomes may be worth exploring. However, as previously discussed, there was a significant amount of missing accelerometer data.

Strengths and limitations

There are several strengths to this research. It was performed in line with the CONSORT 2010 statement.[13] One of the inclusion criteria was a measure of quadriceps strength, which ensured NMES was indicated in the trial population. The intervention was based on patient and public involvement feedback and informed by published trials.[15] We used an accepted placebo intervention to maintain participant blinding with

outcomes assessed by a blinded assessor. We tested numerous relevant outcome measures that could be used in a definitive trial and undertook qualitative interviews that complemented the quantitative findings. However, there were some limitations. The use of a single-centre in this trial likely contributed to under-recruitment of participants and consequently, we conclude that the current protocol should not be used in a definitive trial. This in turn led to insufficient recruitment of participants to the qualitative aspect of the study, and as such data saturation of experiences and perceptions was not achieved. Accordingly, the transferability of the qualitative findings may be limited.

Conclusion

We conclude that a definitive clinical trial to investigate the efficacy of NMES of the quadriceps muscles in advanced IPF using this protocol is not feasible. However, novel findings such as the frequency of telephone support, exercise and NMES diary format and choice of support and monitoring platform e.g. online versus telephone, could inform trials of future home rehabilitation interventions in this population.

Author contributions: Concept and Design of Study: CMN, MM, WM; Acquisition of Data: CMN, OP, SP, REB, JAW; Analysis of Data: CMN, REB, WM; Drafting of Manuscript: CMN, REB, WM; Revision of manuscript critically for important intellectual content: All authors; Approval of final manuscript: All authors

Competing interest statement:

- CMN reports receiving fees from Novartis, outside of this work
- SP, REB, JAW, OP, MM report no competing interests
- PMG reports fees, honoraria and grants from Roche Pharmaceuticals, Boehringer Ingelheim, Cippla and Brainomix.
- EAR reports lecture and/or advisory board fees and/or grants from Roche Pharmaceuticals and Boehringer Ingelheim.
- AUW reports speaking and consultancy fees from Roche and Boehringer Ingelheim.
- PLM reports receiving fees from AstraZeneca, Boehringer Ingelheim and Hoffman-La Roche, outside the submitted work.
- VK reports fees from Roche outside of the submitted work.
- FC reports fees from Boehringer-Ingelheim and Roche outside of the submitted work.
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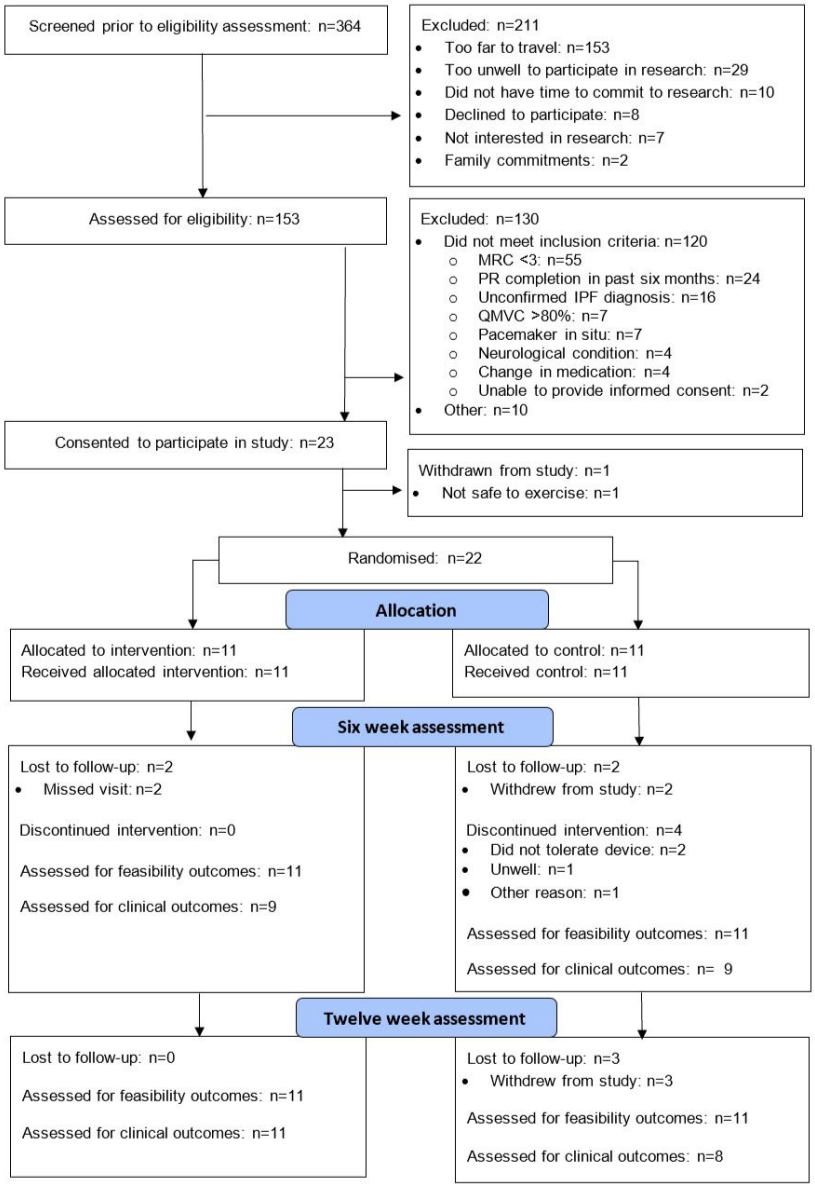

Figure 1. CONSORT diagram
Abbreviations: IPF: Idiopathic Pulmonary Fibrosis; MRC: Medical Research Council; PR: Pulmonary Rehabilitation; QMVC: Quadriceps Maximum Voluntary Contraction

116x170mm (192 x 192 DPI)

Muscle stimulation in advanced idiopathic pulmonary fibrosis: a randomised placebo-controlled feasibility study

Online supplement

MATERIALS AND METHODS

Interventions

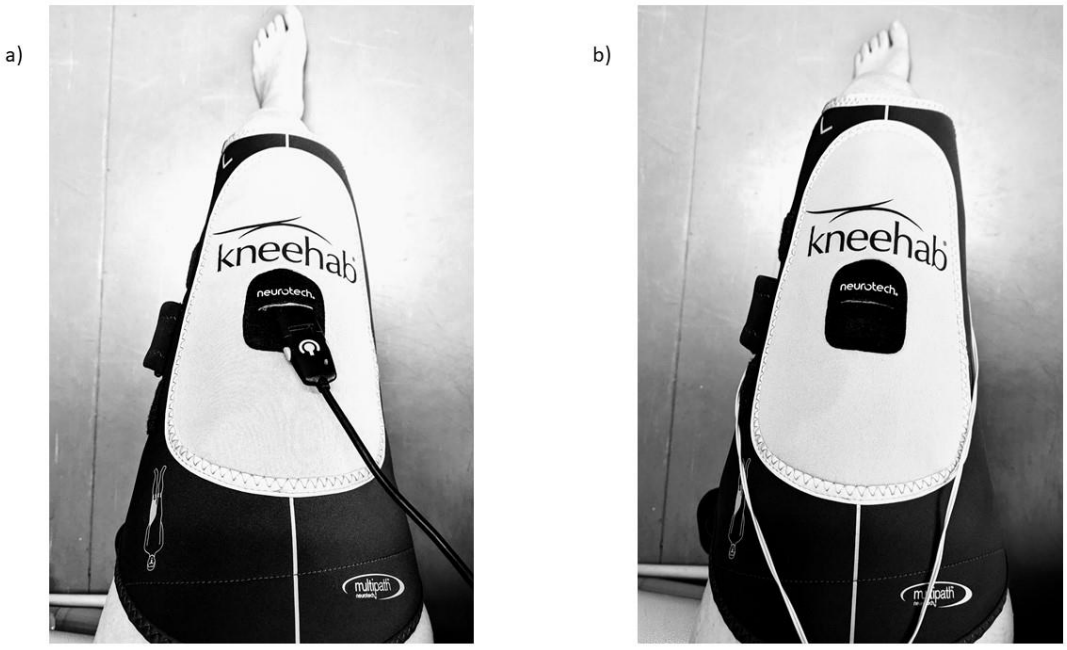

Figure 1: Image of the a) active and b) placebo NMES device

Abbreviations: NMES: Neuromuscular Electrical Stimulation

Home exercise programme:

Participants in both groups were provided with an individualised home exercise programme supplemented with a manual in which they were instructed to perform exercises at least three times per week. The programme included prescribed aerobic and resistance exercises specific to each participant. For aerobic exercise e.g. walking, participants were prescribed an exercise intensity of Borg CR10 Dyspnoea score 3 to 4[1] and distance was progressed to a maximum of 30 minutes. Upper and lower limb resistance exercise was prescribed and progressed in line with the American College of Sports Medicine guidelines.[2] Participants were provided with a simple diary to record home exercise performance. Over the six-week intervention period, the unblinded researcher telephoned participants weekly to review performance and progress home exercises. To progress the exercise programme, participants were asked to increase the intensity or duration of aerobic exercise or the intensity or volume of resistance training.

RESULTS

Table S1. Missing data in clinical outcomes

Outcome	All	Intervention group	Control group
6MWT baseline	0	0	0
6MWT 6 weeks	5	2	3
6MWT 12 weeks	6	1	5
SPPB baseline	0	0	0
SPPB 6 weeks	5	3	2
SPPB 12 weeks	5	1	4
Four metre gait speed baseline	0	0	0
Four metre gait speed 6 weeks	5	3	2
Four metre gait speed 12 weeks	5	1	4
QMVC baseline	0	0	0
QMVC 6 weeks	5	2	3
QMVC 12 weeks	4	0	4
Rectus femoris CSA baseline	0	0	0
Rectus femoris CSA 6 weeks	5	2	3
Rectus femoris CSA 12 weeks	4	0	4
KBILD (domains and total) baseline	0	0	0
KBILD (domains and total) 6 weeks	4	2	2
KBILD (domains and total) 12 weeks	3	0	3
EQ5D5L (domains) 12 weeks	3	0	3
LCADL (domains and total) baseline	0	0	0
LCADL (domains and total) 6 weeks	4	2	2
LCADL (domains and total) 12 weeks	3	0	3
Physical activity data baseline	8	4	4
Physical activity data 6 weeks	11	5	6
Physical activity data 12 weeks	11	5	6

Data presented as number.

Abbreviations: 6MWT: Six Minute Walk Test; CI: Confidence Interval; EQ5D5L: EQ5D 5-Levels; KBILD: King's Brief Interstitial Lung Disease questionnaire; LCADL: London Chest Activities of Daily Living questionnaire; QMVC: Quadriceps Maximum Voluntary Contraction; SPPB: Short Physical Performance Battery.

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CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	4, 5
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	6, 7
	2b	Specific objectives or research questions for pilot trial	7
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	7, 8
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	7
	4c	How participants were identified and consented	7, 8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8, 9
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	9, 10
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	NA
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	NA
Sample size	7a	Rationale for numbers in the pilot trial	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7, 8
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	7, 8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7, 8

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7, 8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	8, 9
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	10, 11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	11
	13b	For each group, losses and exclusions after randomisation, together with reasons	11, 12
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7
	14b	Why the pilot trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	14, 15
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	12, 14-19
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	12, 14-19
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	20, 21
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	13
	19a	If relevant, other important unintended consequences	NA
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	25
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	21-25
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	21-25
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	22-25
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	5, 7
Protocol	24	Where the pilot trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	2, 3
	26	Ethical approval or approval by research review committee, confirmed with reference number	7

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Muscle stimulation in advanced idiopathic pulmonary fibrosis: a randomised placebo-controlled feasibility study

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Primary Subject Heading:	Rehabilitation medicine

Secondary Subject Heading:	Rehabilitation medicine, Respiratory medicine, Qualitative research
Keywords:	Interstitial lung disease < THORACIC MEDICINE, REHABILITATION MEDICINE, RESPIRATORY MEDICINE (see Thoracic Medicine)

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Muscle stimulation in advanced idiopathic pulmonary fibrosis: a randomised placebo-controlled feasibility study

Dr Claire M. Nolan PhD [1,2] c.nolan@rbht.nhs.uk

Ms. Suhani Patel MSc [1,2] s.patel1@rbht.nhs.uk

Ms Ruth E. Barker MSc [1,2] r.barker2@rbht.nhs.uk

Ms Jessica Walsh [1] j.walsh@rbht.nhs.uk

Mr Oliver Polgar MSc[1] o.polgar@rbht.nhs.uk

Dr Matthew Maddocks PhD [3] matthew.maddocks@kcl.ac.uk

Dr Peter M George PhD [2,4] p.george@rbht.nhs.uk

Dr Elisabetta A Renzoni [2,4] e.renzoni@rbht.nhs.uk

Prof Athol U Wells [2,4] a.wells@rbht.nhs.uk

Dr Philip L Molyneaux PhD [2,4] p.molyneux@rbht.nhs.uk

Dr Vasilis Kouranos PhD [2,4] v.kouranos@rbht.nhs.uk

Dr Felix Chua PhD [2,4] f.chua@rbht.nhs.uk

Professor Toby M Maher [2,4,5] toby.maher@usc.edu

Dr William D-C. Man PhD [1,2,6] w.man@rbht.nhs.uk

Affiliations:

1. Harefield Respiratory Research Group, Royal Brompton and Harefield Clinical Group, Guy's and St Thomas' NHS Foundation Trust, UK
2. National Heart and Lung Institute, Imperial College London, UK
3. King's College London, Cicely Saunders Institute of Palliative Care, Policy & Rehabilitation, UK
4. Interstitial Lung Disease Unit, Royal Brompton and Harefield Clinical Group, Guy's and St Thomas' NHS Foundation Trust, UK
5. Keck Medicine, University of Southern California, USA

6. Harefield Pulmonary Rehabilitation Unit, Royal Brompton and Harefield Clinical Group, Guy's and St Thomas' NHS Foundation Trust, UK

Corresponding author: Dr Claire Nolan, Senior Research Physiotherapist, Royal Brompton and Harefield Clinical Group, Guy's and St Thomas' NHS Foundation Trust, Harefield Hospital, Middlesex, UB9 6JH, United Kingdom, Tel: +44 (0)1895 828851, Email: c.nolan@rbht.nhs.uk

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ABSTRACT

Objectives: To assess the acceptability of neuromuscular electrical stimulation (NMES) of the quadriceps muscles in people with idiopathic pulmonary fibrosis (IPF) and to identify whether a future definitive trial is feasible.

Design: A randomised, parallel, two-group, participant- and assessor-blinded, placebo-controlled feasibility trial with embedded qualitative interviews.

Setting: Outpatient department, Royal Brompton and Harefield Hospitals.

Participants: Twenty-two people with IPF: median (25^{th}, 75^{th} centile) age 76 (74, 82) years, forced vital capacity 62 (50, 75) %predicted, six-minute walk test distance 289 (149, 360) metres.

Interventions: Usual care (home-based exercise, weekly telephone support, breathlessness management leaflet) with either placebo or active NMES for six weeks, with follow up at six- and 12-weeks.

Primary outcome measures: Feasibility of recruitment and retention, treatment uptake and adherence, outcome assessments, participant and outcome assessor blinding and adverse events related to interventions.

Secondary outcome measures: Outcome measures with potential to be primary or secondary outcomes in a definitive clinical trial. In addition, purposively sampled participants were interviewed to capture their experiences and acceptability of the trial.

Results: Out of 364 people screened, 23 were recruited: 11 were allocated to each group and one was withdrawn prior to randomisation. Compared to the control group, a greater proportion of the intervention group completed the intervention, remained in the trial blinded to group allocation and experienced intervention-related adverse events. Assessor-blinding was maintained. The secondary outcome measures were feasible with most missing data associated with the accelerometer. Small participant numbers precluded identification of an outcome measure suitable for a definitive trial.

Qualitative findings demonstrated that trial process and active NMES were acceptable but there were concerns about the credibility of placebo NMES.

Conclusions: Primarily owing to recruitment difficulties, a definitive trial using the current protocol to evaluate NMES in people with IPF is not feasible.

Trial registration: clinicaltrials.gov NCT03499275

Article Summary

1. This is the first study to examine the feasibility of neuromuscular electrical stimulation in people with idiopathic pulmonary fibrosis.
2. The intervention was developed using a combination of patient and public involvement feedback and previously published studies.
3. We blinded the outcome assessor to group allocation and used an existing placebo neuromuscular electrical stimulator device to blind participants in the control group.
4. We conducted qualitative interviews to capture participant experiences.
5. The study took place at a single site may have been a limiting factor for participant recruitment.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is characterised by progressive dyspnoea, reduction in functional capacity and subsequent loss of independence.[1 2] Several factors contribute to this, including declining lung function and peripheral muscle weakness.[3] There is growing interest in the latter, as it is known that people with IPF have smaller rectus femoris cross-sectional area[4] as well as reduced quadriceps strength[3-5] and endurance[5] compared to matched healthy controls.

The National Institute for Health and Care Excellence (NICE) recommends regular assessment for and offering pulmonary rehabilitation (PR) to people with IPF.[6] However, people with advanced disease and severe breathlessness may have difficulties undertaking PR as ventilatory limitation may preclude effective whole body training.[7] Centre-based PR or exercise programme completion rates range from 43%[8] to 94%.[9] People with more severe disease and those unwilling to participate in group programmes are less likely to complete these programmes.[10] Accordingly, home-based ways of conferring the benefits of exercise are required.

Guidance from NICE states that in people not suitable for, or unable to participate in, existing rehabilitation programmes, neuromuscular electrical stimulation (NMES) of the quadriceps offers an alternative means of enhancing muscle strength.[11] NMES uses a small battery-operated stimulator which, via surface electrodes placed on the anterior thigh, produces a controlled contraction and relaxation of the underlying muscles. It is safe, relatively inexpensive and is performed seated at home. In people with advanced chronic disease including COPD, heart failure, and cancer, a meta-analysis demonstrated that compared to placebo, NMES led to a significant improvement in quadriceps strength, muscle mass and exercise capacity.[12] Therefore, NMES may be a potential treatment for muscle weakness in advanced progressive disease and could be considered a suitable home intervention for people with muscle weakness who have difficulty engaging with existing PR services.[11 12] To date there are no published studies exploring the role or effects of NMES in IPF, although there is one small randomised control trial (n=30) comparing active

NMES plus aerobic exercise to placebo NMES plus aerobic exercise that is currently recruiting people with IPF (NCT03890250).. Therefore, we aimed to determine the acceptability of NMES of the quadriceps in people with IPF and to identify whether a future definitive trial is feasible.

MATERIALS AND METHODS

Study design and participants

We conducted a randomised, parallel, two-group, participant- and assessor-blinded, placebo-controlled feasibility trial with embedded qualitative interviews. The trial was conducted and reported according to the CONSORT 2010 statement: extension to randomised pilot and feasibility trials.[13] Participants were recruited from outpatient clinics at the Royal Brompton and Harefield Hospitals, UK between November 2018 and February 2020. The inclusion criteria were 1) diagnosis of IPF according to international guidelines,[14] 2) Medical Research Council (MRC) dyspnoea score ≥3, 3) quadriceps maximum voluntary contraction (QMVC) <80% predicted,[15] 4) declined or failed to complete supervised centre-based PR and 5) ability to provide informed consent. People were excluded for the following reasons 1) cardiac pacemaker, 2) co-existing neurological condition e.g. lower limb paralysis, 3) completion of PR within the previous six months, 4) change in medication and/or exacerbation requiring hospitalisation within the previous four weeks or 5) current regular exerciser (structured exercise ≥3/week in the previous month). All participants provided written informed consent. The trial was pre-registered on clinicaltrials.gov (NCT03499275) and the study was approved by London-Harrow Research Ethics Committee and Health Research Authority (18/LO/0209).

Randomisation and blinding

Following baseline assessment, participants were randomly allocated 1:1 at the individual level to receive active or placebo NMES. Minimization was used to balance groups for age (<65 years vs. ≥65 years), sex (male vs. female) and quadriceps strength (<20kg vs. ≥20kg). The allocation sequence was generated using

an independent web-based randomisation system within the UK Clinical Research Collaboration-registered King's Clinical Trials Unit. Following randomisation, the Clinical Trials Unit informed trial staff by secure email. An unblinded researcher selected an active or placebo device accordingly. Blinded researchers were informed of trial entry but not group allocation. The participant was not informed of group allocation. Subsequent assessment visits were completed immediately after the six-week intervention period and at 12 weeks by a researcher blinded to group allocation. Qualitative in-depth, topic-guided interviews were completed in a sub-group of participants who were selected purposively to include both intervention and control groups, sexes, and a range of baseline MRC scores so that different perspectives could be explored.

Interventions

The treating healthcare professionals provided potential participants with the study information leaflet who were then screened by the research team via telephone. Those interested in participating in the study attended an assessment to confirm eligibility.

The interventions were based on a combination of patient and public involvement feedback and published studies.[16] The NMES programme was a self-administered, home-based protocol involving 30 minutes stimulation of bilateral quadricep muscles for six weeks. The active device was KneeHab®XP (Neurotech, USA) and the placebo device, MicroStim Exercise Stimulator MS2v2 (Odstock Medical Ltd, UK). Although different machines were used for the active and placebo devices, they were outwardly identical as both were covered in the same garment (online supplement). The parameters of both devices were the same (frequency 50Hz, pulse width 400µs, duty cycle 18–33% which increased weekly for the first three weeks) except for the amplitude range (active: 0-120mA; placebo: 0-20mA). Consequently, participants in the control group received sensory feedback during stimulation but the device did not elicit a tetanic muscle contraction.

Participants in both groups also received a leaflet on how to manage breathlessness and an individualised home exercise programme supplemented with a manual which they were instructed to perform at least three times per week (online supplement).

The unblinded researcher delivered a standardised 40-minute training session to participants in both groups to demonstrate and supervise NMES application and the home exercise programme. Participants were provided with a diary to record NMES and exercise performance. During the six-week intervention period, the unblinded researcher telephoned participants weekly to review and progress NMES use and home exercise performance. To progress NMES, participants were asked to increase the amplitude of the electrical current, within the limits of the device.

Outcome measures

Primary outcome measures

The primary outcomes were related to feasibility: participant recruitment and retention, treatment uptake and adherence, feasibility of outcome assessments, feasibility of participant and assessor blinding and adverse events related to the interventions. To assess recruitment- and retention-related feasibility outcomes, the numbers of potential eligible participants as well as recruitment and retention rates at the six- and 12-week assessments were recorded. To assess treatment uptake and adherence, the following were recorded; feasibility, outcomes, rates of uptake of and adherence to the allocated intervention and frequency and time spent using the NMES device and performing the home exercise programme. Feasibility of outcome assessment was measured by recording the amount of missing data for each outcome measure at each assessment. Participant and assessor blinding were assessed by the unblinded researcher at the six-week assessment, and six- and 12-week assessment respectively. Research staff recorded adverse events during assessment visits and weekly telephone calls. These were classified as related or unrelated to the allocated intervention, using as much information as available to determine the potential attribution of the event.

Secondary outcome measures

The secondary outcome measures were those that had the potential to be primary or secondary outcomes in a definitive clinical trial. These were: exercise capacity (six-minute walk test-6MWT),[17] functional performance (Short Physical Performance Battery-SPPB),[18] four metre gait speed (4MGS),[19] rectus femoris size (ultrasound of rectus femoris cross-sectional area (Mindray DP-50, Caiyside Imaging Ltd., Scotland), quadriceps strength (isometric QMVC),[20] health-related quality of life (King's Brief Interstitial Lung Disease questionnaire-KBILD),[21] activities of daily living (London Chest Activities of Daily Living-LCADL),[22] and physical activity parameters (daily step count, time spent in sedentary, light and moderate intensity activity (SenseWear, Bodymedia, USA)).[23]

Following the 12-week assessment, purposively sampled participants were invited to take part in semi-structured, topic-guided, telephone-based interviews. The audio-recorded interviews explored experiences of the intervention, how it impacted perceptions of outcome, acceptability of outcome measures and trial conduct in order to inform the rationale for and conduct of a definitive trial. The topic guides were updated inductively to reflect experiences and perceptions raised during previous interviews.

Sample size

Sample size estimation was performed to achieve the primary feasibility outcomes, and not to detect differences in the secondary outcome measures. Based on guidance in the literature, we estimated that a sample size of 60 (30 per group) would be sufficient to adequately evaluate the feasibility of undertaking a definitive trial. A sample size of ten was chosen for the qualitative interviews as it was based on the predicted minimum number of interviews required to achieve data saturation and is based on the concept of Information Power.[24]

Statistical analysis

The feasibility outcomes and baseline demographics were described and summarised overall and by trial group using proportions (percentage) or median (25^{th}, 75^{th} centile). The baseline data and change at six

and 12 weeks was reported as median (25th, 75th centile) or median (25th, 75th centile) change for each trial group.

Anonymised interview transcripts were transcribed verbatim and imported into NVIVo (QSR International, Australia) to facilitate analysis using the Framework Method.[25] The coding frame was pre-defined and included experiences of the interventions, impact of intervention on perceived outcome, acceptability and experiences of trial conduct and acceptability of the outcome measures. During indexing, secondary codes were inductively applied. A mixed-method matrix[26] of qualitative and key quantitative data was used to illuminate barriers and facilitators for intervention completion by participants to inform protocol adaptation and/or optimisation.

Patient and public involvement (PPI)

This research has included PPI throughout each stage. Two PPI representatives were involved in the design of the study and intervention and met the project manager at regular intervals throughout the study. The PPI representatives also provided input into written material for participants and topic guides for qualitative interviews. Going forward, they will have a role in in dissemination of research findings to lay audiences.

RESULTS

Primary outcome

Feasibility of recruitment and retention

We screened 364 people, of whom 153 were assessed for eligibility and 23 consented to participate in the study: 11 were allocated to both the intervention and control groups and one was withdrawn prior to randomisation for safety reasons (figure 1). By far the most common reason for failing the telephone-based screening assessment was the distance participants were required to travel to the research centre (n=153). MRC<3 (n=55) or PR completion within six months (n=24) were the most common reasons for

failing the eligibility assessment. At the six-week assessment, two participants in both groups were lost to follow-up (intervention: n=2 missed visit, control: n=2 withdrew from the study). At the 12-week assessment, all participants in the intervention group were assessed whereas three participants in the control group were lost to follow-up (withdrew from the study).

Feasibility of treatment uptake and adherence

All participants started their allocated intervention. Both groups received the same median number of weekly telephone calls but there was a trend for higher frequency and duration of use of the NMES device and home exercise programme in the intervention compared to the control group (table 1). All participants in the intervention group completed the allocated intervention. In contrast, four participants in the control group discontinued the intervention: n=2: did not tolerate placebo NMES, n=1 unwell, n=1: felt NMES was ineffective.

Table 1. Intervention uptake, adherence and completion

Variable	**Intervention**	**Control**
Number of weekly telephone calls	6 (5, 6)	6 (4, 6)
Number of times device* used between V1 and V2	31 (22, 44)	24 (4, 40)
Total minutes device* used between V1 and V2	930 (660, 1110)	570 (120, 1230)
Number of times HEP performed between V1 and V2	20 (17, 32)	14 (4, 26)
Total minutes HEP performed between V1 and V2	906 (600, 1527)	648 (110, 1399)

Data reported number or median (25^{th}, 75^{th}) centile.

**Device: Intervention group: Active stimulator; Control group: Placebo stimulator.*

Abbreviations: HEP: Home Exercise Programme; NC: Not Computed; V: Visit.

Feasibility of outcome assessment

Missing data for each clinical outcome according to assessment timepoint are described in the online supplement. There were no missing data at the baseline assessment. Missing data at the six- and 12-week assessments mostly related to participants that were lost to follow up. The outcome measures with the most missing data were the physical activity parameters (intervention, control: baseline: n=4, n=4; six and 12 weeks: n=5, n=6). Reasons for missingness included participants declining to wear the device and insufficient data to analyse.

Feasibility of participant and outcome assessor blinding

Participant blinding was maintained in the intervention group but three participants in the control group were unblinded as they did not believe the placebo NMES was credible. The outcome assessor remained blinded to intervention allocation of all participants.

Adverse and serious adverse events

There was one serious adverse event in the intervention group and four in the control group. None of these events were unexpected or related to the allocated intervention or assessments. One participant experienced two adverse events prior to randomisation. A total of 10 and five adverse events in the intervention and control groups were experienced by eight and four participants respectively. None of the events prior to randomisation or in the control group were unexpected or related to the study. Three adverse events in the intervention group were expected and related to the study. These included redness on anterior thigh and itchiness on anterior thigh following NMES use as well as “burning sensation” on anterior thigh during NMES use. The remaining seven adverse events were expected and unrelated to the intervention.

Secondary outcomes

The groups were balanced in terms of age, gender, absolute and relative forced vital capacity (FVC) values, body mass index and quadriceps strength (table 2). However, compared to the intervention group, the

control group had a greater proportion of participants diagnosed with pulmonary hypertension, prescribed supplementary oxygen and corticosteroid, former smokers and worse absolute and relative diffusing capacity of the lung for carbon monoxide (DLCO) values, exercise capacity, activities of daily life performance, walking speed and physical activity levels. Due to the small number of participants in each group, it was not possible to test for between-group differences.

Table 2. Baseline characteristics

	Whole group (n=22)	**Intervention (n=11)**	**Control (n=11)**
Gender: male (%)	16 (73)	7 (64)	8 (73)
Age (years)	76 (74, 82)	77 (73, 81)	76 (74, 84)
MRC Dyspnoea score	4 (4, 4)	4 (4, 4)	4 (4, 4)
BMI (kg/m^2)	24.4 (22.4, 29.1)	24.2 (22.0, 26.5)	25.2 (22.6, 29.2)
FEV_1/FVC	0.84 (0.78, 0,86)	0.80 (0.77, 0,85)	0.84 (0.78, 0,87)
FVC (L)	1.83 (1.39, 2.44)	1.83 (1.44, 2.45)	1.82 (1.22, 2.44)
FVC (% predicted)	61.8 (49.8, 75.0)	63.0 (49.0, 78.2)	60.5 (50.0, 68.0)
DLCO (ml/mi/mmHg)	2.16 (1.71, 2.77)	2.50 (1.92, 3.36)	1.88 (1.64, 2.20)
DLCO (% predicted)	26.0 (21.9, 36.7)	36.5 (22.3, 40.4)	25.0 (20.8, 29.8)
Smoking status: never/former/current: (%)	13 (59) / 9 (41) / 0 (0)	7 (64)/ 4 (36) / 0 (0)	6 (55) / 5 (45) / 0 (0)
Smoking pack year history	0 (0, 8)	0 (0, 5)	0 (0, 13)
Age-adjusted Charlson Co-morbidity Index	2 (0, 5)	4 (0, 5)	0 (0, 6)
COPD: n (%)	3 (14)	1 (10)	2 (18)
Pulmonary hypertension: n (%)	2 (9)	0 (0)	2 (18)
Ischaemic heart disease: n (%)	8 (36)	5 (46)	3 (27)
Obstructive sleep apnoea: n (%)	0 (0)	0 (0)	0 (0)
Self-reported hospitalisations in previous year: n (%)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Self-reported chest infections in previous year: n (%)	1 (1, 2)	1 (1, 2)	1 (1, 1)
Oxygen: n (%)			
Long-term	4 (18)	1 (10)	3 (27)
Ambulatory	9 (41)	4 (36)	5 (46)

Walking aid: n (%)	5 (23)	2 (18)	3 (27)
Prescribed pirfenidone: n (%)	6 (27)	4 (36)	2 (18)
Prescribed nintedanib: n (%)	7 (32)	4 (36)	3 (27)
Prescribed corticosteroid: n (%)	4 (18)	3 (27)	1 (9)
6MWT (m)	289 (149, 360)	326 (150, 361)	240 (130, 325)
SPPB score	9 (6, 11)	10 (6, 11)	7 (4, 11)
Four metre gait speed (m/s)	0.71 (0.50, 0.94)	0.82 (0.38, 0.97)	0.66 (0.51, 0.84)
QMVC (kg)	22.4 (15.6, 28.7)	22.5 (15.1, 28.3)	22.4 (15.7, 31.3)
QMVC (% predicted)	62.4 (52.0, 69.1)	64.3 (44.0, 68.1)	61.6 (52.8, 72.2)
Rectus femoris cross-sectional area (mm^2)	459 (371, 534)	451 (321, 579)	479 (375, 581)
KBILD - Psychological	54.4 (53.2, 69.1)	58.8 (41.2, 71.6)	53.5 (43.8, 65.5)
KBILD – Breathlessness and activities	35.6 (21.6, 45.9)	37.8 (27.0, 50.2)	35.6 (17.7, 41.9)
KBILD – Chest symptoms	68.6 (44.0, 85.2)	63.7 (44.0, 85.2)	73.4 (54.3, 85.2)
KBILD – Total score	53.5 (46.4, 59.4)	56.1 (43.9, 66.4)	53.5 (47.2, 56.1)
LCADL – Self-care	6.0 (4.0, 8.0)	7.0 (4.0, 8.0)	6.0 (4.0, 7.0)
LCADL – Domestic	10.5 (4.8, 18.5)	5.0 (1.0, 17.0)	14.0 (10.0, 22.0)
LCADL – Physical	4.0 (3.0, 6.0)	4.0 (3.0, 5.0)	4.0 (3.0, 6.0)
LCADL – Leisure	4.0 (3.0, 6.0)	4.0 (3.0, 6.0)	5.0 (4.0, 6.0)
LCADL – Total score	26.0 (17.5, 37.3)	20.0 (14.0, 28.0)	33.0 (22.0, 29.0)
Daily step count	1511 (776, 3456)	1820 (1148, 3232)	988 (657, 4115)
Daily mins spent in moderate intensity PA	34 (20, 84)	47 (25, 100)	22 (5, 74)
Daily mins spent in light intensity PA	194 (147, 221)	217 (126, 248)	187 (153, 199)
Daily mins spent sedentary	1144 (1098, 1206)	1123 (1095, 1151)	1194 (1137, 1237)

Data reported as number (percentage) or median (25^{th} centile, 75^{th} centile).

Abbreviations: 6MWT: Six Minute Walk Test; CI: Confidence Interval; DLCO: Diffusing Capacity of the Lung for Carbon Monoxide; EQ5D5L: EQ5D 5-Levels; KBILD: King's Brief Interstitial Lung Disease questionnaire; LCADL: London Chest Activities of Daily Living questionnaire; P: p-value; PA: Physical Activity; QMVC: Quadriceps Maximum Voluntary Contraction; SPPB: Short Physical Performance Battery.

KBILD domains and total score: Range 0-100; higher scores indicate better health-related quality of life.

LCADL range: Self-care: 0-20; Domestic: 0-30; Physical: 0-10; Leisure: 0-15; Total: 0-75; higher scores indicate greater impact on ADL performance.

The response to the intervention between baseline and six-week assessment, and baseline and 12-week assessment are shown in tables 3 and 4 respectively. Again, owing to the small numbers of participants, it is not possible to draw firm conclusions from these data. However, between the baseline and six-week assessment, there was trend for a greater reduction in sedentary time in the intervention group, compared to an increase in sedentary time in the control group (table 3). Similarly, between the baseline and 12-week assessment, there was a trend for a greater increase in rectus femoris cross-sectional area, self-care related to activities of daily living performance and time spent in light intensity physical activity in the intervention compared to the control group (table 4).

Table 3. Draft table for the within and between group response of the secondary outcome measures to the intervention from Visit 1 to Visit 2.

Outcome	Intervention		Control	
	n	Within group difference	n	Within group difference
Δ 6MWT (m)	9	6 (-16, 45)	8	-17 (-74, 4)
Δ SPPB	9	0 (-1, 1)	8	0 (0, 0)
Δ Four metre gait speed (m/s)	9	0.03 (0.01, 0.06)	8	-0.04 (-0.09, 0.03)
Δ QMVC (kg)	9	-0.1 (-1.9, 2.5)	8	-0.2 (-1.7, 2.0)
Δ Rectus femoris cross-sectional area (mm^2)	9	18.0 (-32.6, 48.3)	8	16.0 (-50.6, 33.0)
Δ KBILD - Psychological	9	5.9 (-3.4, 12.8)	9	0 (-7.2, 9.6)
Δ KBILD - Breathlessness and activities	9	9.3 (-7.8, 13.8)	9	0 (-8.4, 13.5)
Δ KBILD – Chest symptoms	9	9.7 (-5.9, 16.7)	9	9.7 (-5.9, 22.9)
Δ KBILD – Total score	9	2.7 (-0.2, 7.4)	9	0.1 (-2.2, 3.9)
Δ LCADL – Self-care	9	-1.0 (-2.0, 0.0)	9	1.0 (-0.5, 1.5)
Δ LCADL - Domestic	9	1.0 (-3.0, 4.5)	9	-1.0 (-3.0, -5.0)
Δ LCADL – Physical	9	0.0 (-0.5, 0.5)	9	0.0 (-1.0, 1.5)
Δ LCADL – Leisure	9	0.0 (-1.0, 1.0)	9	0.0 (-1.0, 1.5)
Δ LCADL – Total score	9	0.0 (-5.0, 2.0)	9	4.0 (-3.0, 10.0)
Δ Daily step count	5	-270 (-504, 877)	5	-740 (-2026, -230)
Δ Daily mins spent in moderate intensity PA	5	-3 (-20, 4)	5	-19 (-51, -5)
Δ Daily mins spent in light intensity PA	5	24 (5, 71)	5	-39 (-65, 15)

Δ Daily mins spent sedentary	5	-40 (-58, -21)	5	54 (22, 86)

Data reported as median (25th centile, 75th centile) difference.

Abbreviations: 6MWT: Six Minute Walk Test; CI: Confidence Interval; EQ5D5L: EQ5D 5-Levels; KBILD: King's Brief Interstitial Lung Disease questionnaire; LCADL: London Chest Activities of Daily Living questionnaire; P: p-value; QMVC: Quadriceps Maximum Voluntary Contraction; SPPB: Short Physical Performance Battery.

KBILD domains and total score: Range 0-100; higher scores indicate better health-related quality of life.

LCADL range: Self-care: 0-20; Domestic: 0-30; Physical: 0-10; Leisure: 0-15; Total: 0-75; higher scores indicate greater impact on ADL performance.

Table 4. Draft table for the within and between group response of the secondary outcome measures to the intervention from Visit 1 to Visit 3.

Outcome	Intervention		Control	
	n	Within group difference	n	Within group difference
Δ 6MWT (m)	10	-13 (-73, -15)	6	-23 (-100, 18)
Δ SPPB	10	0 (-1, 0)	7	0 (-1, 1)
Δ Four metre gait speed (m/s)	10	-0.03 (-0.14, 0.08)	7	0.01 (-0.12, 0.09)
Δ QMVC	11	1.0 (-0.9, 4.3)	7	-1.7 (-3.4, 3.7)
Δ Rectus femoris cross-sectional area (mm^2)	11	32.6 (2.5, 54.4)	7	-48.6 (-87.8, 10.0)
Δ KBILD - Psychological	11	7.8 (4.6, 19.1)	8	4.2 (-4.1, 8.7)
Δ KBILD - Breathlessness and activities	11	9.3 (-7.5, 13.6)	8	0 (-10.0, 5.9)
Δ KBILD – Chest symptoms	11	10.3 (0, 19.7)	8	10.8 (0, 24.9)
Δ KBILD – Total score	11	5.4 (1.1, 8.8)	8	2.6 (-4.1, 4.3)
Δ LCADL – Self-care	11	-1.0 (-2.0, 0.0)	8	1.0 (0.3, 2.5)
Δ LCADL - Domestic	11	1.0 (-1.0, 3.0)	8	4.0 (-2.5, 9.5)
Δ LCADL – Physical	11	0.0 (-1.0, 0.0)	8	0.0 (-1.0, 1.8)
Δ LCADL – Leisure	11	0.0 (0.0, 1.0)	8	0.5 (-0.8, 2.8)
Δ LCADL – Total score	11	1.0 (-2.0, 5.0)	8	4.5 (0.8, 15.3)
Δ Daily step count	5	-215 (-966, 176)	5	-334 (-2712, 7)
Δ Daily mins spent in moderate intensity PA	5	2 (-29, 22)	5	2 (-31, -11)
Δ Daily mins spent in light intensity PA	5	37 (-46, 54)	5	-3 (-61, 35)

Δ Daily mins spent sedentary	5	8 (-29, 87)	5	7 (-24, 50)

Data reported as median (25th centile, 75th centile) difference.

Abbreviations: 6MWT: Six Minute Walk Test; CI: Confidence Interval; EQ5D5L: EQ5D 5-Levels; KBILD: King's Brief Interstitial Lung Disease questionnaire; LCADL: London Chest Activities of Daily Living questionnaire; P: p-value; QMVC: Quadriceps Maximum Voluntary Contraction; SPPB: Short Physical Performance Battery.

KBILD domains and total score: Range 0-100; higher scores indicate better health-related quality of life.

LCADL range: Self-care: 0-20; Domestic: 0-30; Physical: 0-10; Leisure: 0-15; Total: 0-75; higher scores indicate greater impact on ADL performance.

Six participants (four male, two female), aged between 54 and 84 years, participated in the qualitative interviews. The majority had been allocated to the intervention group, with only one participant from the control group. Other participants allocated to the control group who were approached to take part in the interviews declined or were unable to take part because of illness or death. Despite interviewing almost one third of participants that were recruited to the trial, new data was being gained up to and including the last interview.

All participants found the research staff, trial processes and outcome measures acceptable:

> *"I was able to comply with what was required,…, other than the fact that the walking is limited, but at least I could rest."* [Male, 80's, intervention group]

Most participants stated that the NMES device was feasible and acceptable:

> *"The instructions were pretty straightforward, and once you have done it the first time,…, you just got it out of the bag and off you went."* [Male, 80's, intervention group]

However two participants reported negative NMES experiences:

> *"It was a damn nuisance, to be perfectly frank,…, no, it was a bit of a performance and a bit of a nuisance."* [Female, 70's, intervention group]

> *"It was as if it was a placebo in place of the real thing,…, yes, I would say that it was the placebo, it wasn't the real thing."* [Male, 70's, control group]

All participants reported that the exercise programme was feasible, acceptable and beneficial:

> *"I'm still doing them, actually. It's a good programme"* [Female, 70's, intervention group]

However, maintaining motivation to complete the programme was difficult with one participant stating that he did so because it was part of the study:

"I made sure I did the leg exercises [even when unwell] because that's what I promised I would do" [Male, 60's, intervention group]

There was disparity in participants' experience of the weekly telephone support during the six-week intervention period. Some found it burdensome and suggested that digital monitoring would have been preferable:

"That [provision of electronic version of home exercise programme] would have better. Yes, that would have been brilliant, and to then send it [diary reporting compliance and progress] back that way too" [Female, 70's, intervention group]

In contrast, other participants found it to be a positive experience and suggested more frequent monitoring would have been preferable:

"I think once a week, or maybe twice a week would be a secondary call, if you did it on a Monday and then on a Friday" [Male, 60's, intervention group]

In addition, some participants reported that diary completion was difficult which affected their compliance with this tool:

"I didn't fill in the form right. I didn't find the form very easy. I did it my own way" [Female, 70's, intervention group]

DISCUSSION

We aimed to determine the acceptability of NMES of the quadriceps muscles in people with IPF and identify whether a future definitive trial is feasible. The qualitative interviews suggest that participants found the trial process, active NMES device and home exercise programme acceptable, but there were concerns about the credibility of placebo NMES and divergent opinions regarding the telephone support

and diary. The quantitative data demonstrate that a definitive trial using this protocol should not be undertaken because of challenges in participant recruitment as well as between-group differences in retention of, treatment adherence and blinding of participants in the control compared to the intervention group. However, this feasibility study provided important additional information that could inform future rehabilitation-based interventions.

Primary feasibility outcomes

The principle reason this protocol in its current format should not be tested in a definitive trial is that an insufficient number of participants were recruited to satisfy the a priori sample size requirement. A total of 364 potential participants were screened with 211 excluded prior to the eligibility assessment. The main reason for exclusion was the distance between the person's home and assessment centre, despite the provision of transport. The Interstitial Lung Disease (ILD) Unit at our hospital provides specialist care to people that live in a large geographic area, which may explain the reluctance to participate in the study. Although we have not faced such recruitment issues in other studies, our experience with this protocol suggests future rehabilitation-based research should be multi-site and conducted alongside clinical appointments and/or located in centres accessible to participants and/or in participants' homes. Out of 153 participants that attended the eligibility assessment, 23 consented to participate in the study. The most common reason for failing this assessment was MRC<3 or PR completion within six months. These conditions formed part of the inclusion criteria to ensure that people with advanced disease and a sedentary lifestyle respectively were recruited to the study. Going forward, trial eligibility based on indication for NMES rather than PR completion status may be more appropriate.

There was a trend for a greater proportion of participants in the control group to withdraw from the study, discontinue and perform less of the intervention, and/or become unblinded to group allocation. These findings may be related to statistical chance because of the small sample size, differences in between-group baseline characteristics and/or poor placebo NMES device credibility. The between-group difference

in baseline characteristics and concerns about placebo NMES credibility were unexpected findings, because the minimisation criteria used in the randomisation process and the placebo device were informed by previous studies.[16] Furthermore, although two different devices were used to deliver active and placebo NMES, the outward appearance of both were identical and as such, should not have contributed to the differences in participant perception. However, qualitative findings demonstrated that a participant in the control group believed he used a placebo device as the sensation was insufficiently strong. However as only one participant allocated to the control group agreed to participate in the qualitative interviews, it is unclear if this finding is generalisable. Future research should consider reviewing the intensity and/or individualise the intensity of the placebo device.

In contrast to the control group, qualitative findings demonstrated that active NMES was acceptable to participants in the intervention group. In addition, the home exercise programme was also acceptable to both groups. However, there was a difference of opinion regarding the frequency of the telephone support and utility of the NMES and exercise diary. Exploration of these aspects of the intervention are important for future home-based rehabilitation studies in IPF.

Although blinding of some participants was not maintained, assessor blinding was successful. This was achieved by provision of an office isolated from the research laboratory that allowed the unblinded researcher inform participants of group allocation, deliver the training session and schedule telephone calls.

The majority of the outcome measures were acceptable to participants and feasible to perform. However, there were a significant volume of missing accelerometer data because participants declined to wear the device or there was insufficient data to analyse. Going forward, researchers may decide to make wearing the device a prerequisite to study entry, shorten the device-wearing time or consider an alternative device that is more acceptable to participants.

There was a difference in the amount of expected and related adverse events in the intervention compared to the control group. These events occurred during or following NMES use and did not result in discontinuation of the intervention. Although not categorised as serious, these findings reinforce the importance of explaining the risks associated with this type of intervention in the patient information sheet.

Secondary outcome measures

Although the intervention and control groups were balanced in terms of the minimisation variables, there was imbalance in important variables that might influence exercise and physical activity capacity as a greater proportion of the control group were diagnosed with pulmonary hypertension and had a supplementary oxygen prescription associated with worse absolute and relative DLCO values, exercise capacity, activities of daily life performance, walking speed and physical activity levels. This may have arisen because of statistical chance given the small participant numbers, however, the minimisation variables used for randomisation may also have contributed to the problem. The minimisation variables: age, gender and quadriceps strength, were chosen as they were relevant to the population of interest and intervention, and were also informed by previous studies.[16] However, although there is a strong correlation between quadriceps strength and exercise capacity ($r=0.56$, $p<0.001$) in ILD,[27] accounting for exercise capacity itself, as well as co-morbidities and physical activity levels may be important in ensuring balance between trial groups in future research.

Owing to the small sample size, imbalance in between-group baseline characteristics and smaller number of control versus intervention group participants, it is challenging to identify an outcome measure that has the potential to be a primary or secondary outcome measure in a definitive trial. However, as there was a trend for greater reduction in sedentary time between baseline and six weeks as well as a greater increase in self-care ability and light intensity physical activity between baseline and 12 weeks that favoured the

intervention group, these outcomes may be worth exploring. However, as previously discussed, there was a significant amount of missing accelerometer data.

Strengths and limitations

There are several strengths to this research. It was performed in line with the CONSORT 2010 statement.[13] One of the inclusion criteria was a measure of quadriceps strength, which ensured NMES was indicated in the trial population. The intervention was based on patient and public involvement feedback and informed by published trials.[16] We used an accepted placebo intervention to maintain participant blinding with outcomes assessed by a blinded assessor. We tested numerous relevant outcome measures that could be used in a definitive trial and undertook qualitative interviews that complemented the quantitative findings. However, there were some limitations. The use of a single-centre in this trial likely contributed to under-recruitment of participants and consequently, we conclude that the current protocol should not be used in a definitive trial. This in turn led to insufficient recruitment of participants to the qualitative aspect, specifically to the control group which is in part a limitation, but also provides initial data on feasibility. Consequently, data saturation of experiences and perceptions was not achieved. Accordingly, the transferability of the qualitative findings may be limited.

Conclusion

We conclude that a definitive clinical trial to investigate the efficacy of NMES of the quadriceps muscles in advanced IPF using this protocol is not feasible. However, novel findings such as the frequency of telephone support, exercise and NMES diary format and choice of support and monitoring platform e.g. online versus telephone, could inform trials of future home rehabilitation interventions in this population.

Figure legend

Figure 1. CONSORT diagram

Author contributions: Concept and Design of Study: CMN, MM, WM; Acquisition of Data: CMN, OP, SP, REB, JAW; Analysis of Data: CMN, REB, WM; Drafting of Manuscript: CMN, REB, WM; Revision of manuscript critically for important intellectual content: CMN, MM, WM, OP, SP, REB, JAW, PMG, EAR, AUW, PLM, VK, FC, TMM; Approval of final manuscript: CMN, MM, WM, OP, SP, REB, JAW, PMG, EAR, AUW, PLM, VK, FC, TMM authors.

Competing interest statement:

- CMN reports receiving fees from Novartis, outside of this work
- SP, REB, JAW, OP, MM report no competing interests
- PMG reports fees, honoraria and grants from Roche Pharmaceuticals, Boehringer Ingelheim, Cippla and Brainomix.
- EAR reports lecture and/or advisory board fees and/or grants from Roche Pharmaceuticals and Boehringer Ingelheim.
- AUW reports speaking and consultancy fees from Roche and Boehringer Ingelheim.
- PLM reports receiving fees from AstraZeneca, Boehringer Ingelheim and Hoffman-La Roche, outside the submitted work.
- VK reports fees from Roche outside of the submitted work.
- FC reports fees from Boehringer-Ingelheim and Roche outside of the submitted work.
- TMM has, via his institution, received industry-academic funding from Astra Zeneca and GlaxoSmithKline R&D and has received consultancy or speakers fees from Astra Zeneca, Bayer, Blade Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Galapagos, Galecto, GlaxoSmithKline R&D, Indalo, IQVIA, Pliant, Respivant, Roche and Theravance.
- WDCM reports personal fees from Jazz Pharmaceuticals, personal fees from Mundipharma, personal fees from Novartis, grants from Pfizer, non-financial support from GSK, grants from

National Institute for Health Research, grants from British Lung Foundation, outside the submitted work.

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Data sharing statement: We did not obtain participant consent to share data.

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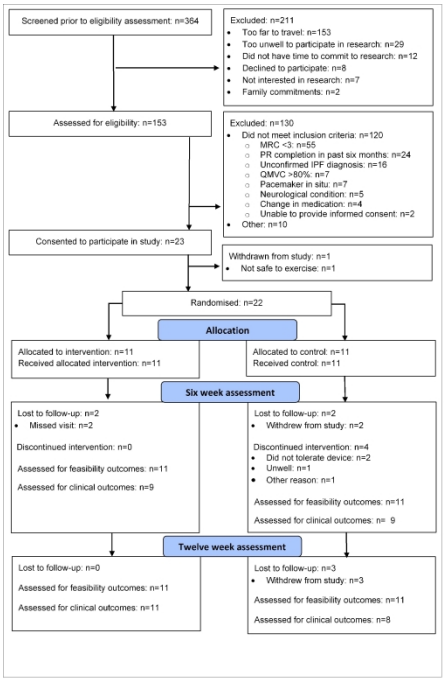

Figure 1. CONSORT diagram

458x314mm (240 x 240 DPI)

Muscle stimulation in advanced idiopathic pulmonary fibrosis: a randomised placebo-controlled feasibility study

Online supplement

MATERIALS AND METHODS

Interventions

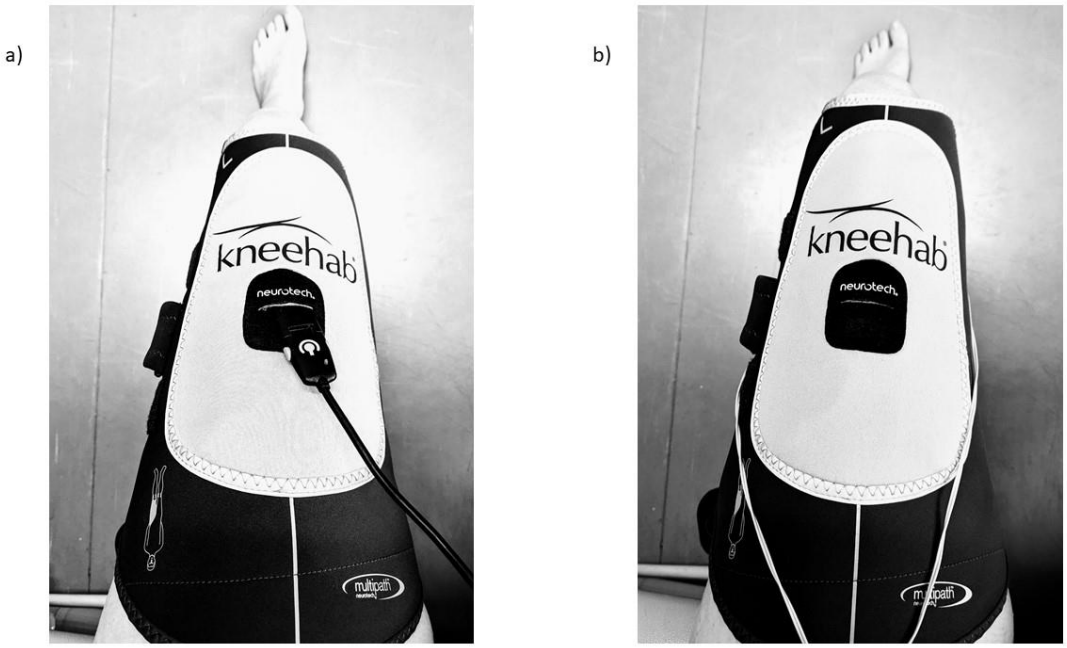

Figure 1: Image of the a) active and b) placebo NMES device

Abbreviations: NMES: Neuromuscular Electrical Stimulation

Note: The person depicted is not patient and these images were taken with the participant's knowledge.

Home exercise programme:

Participants in both groups were provided with an individualised home exercise programme supplemented with a manual in which they were instructed to perform exercises at least three times per week. The programme included prescribed aerobic and resistance exercises specific to each participant. For aerobic exercise e.g. walking, participants were prescribed an exercise intensity of Borg CR10 Dyspnoea score 3 to 4[1] and distance was progressed to a maximum of 30 minutes. Upper and lower limb resistance exercise was prescribed and progressed in line with the American College of Sports Medicine guidelines.[2] Participants were provided with a simple diary to record home exercise performance. Over the six-week intervention period, the unblinded researcher telephoned participants weekly to review performance and progress home exercises. To progress the exercise programme, participants were asked to increase the intensity or duration of aerobic exercise or the intensity or volume of resistance training. The home exercise manual can be provided on application to the authors.

RESULTS

Table S1. Missing data in clinical outcomes

Outcome	All	Intervention group	Control group
6MWT baseline	0	0	0
6MWT 6 weeks	5	2	3
6MWT 12 weeks	6	1	5
SPPB baseline	0	0	0
SPPB 6 weeks	5	3	2
SPPB 12 weeks	5	1	4
Four metre gait speed baseline	0	0	0
Four metre gait speed 6 weeks	5	3	2
Four metre gait speed 12 weeks	5	1	4
QMVC baseline	0	0	0
QMVC 6 weeks	5	2	3
QMVC 12 weeks	4	0	4
Rectus femoris CSA baseline	0	0	0
Rectus femoris CSA 6 weeks	5	2	3
Rectus femoris CSA 12 weeks	4	0	4
KBILD (domains and total) baseline	0	0	0
KBILD (domains and total) 6 weeks	4	2	2
KBILD (domains and total) 12 weeks	3	0	3
EQ5D5L (domains) 12 weeks	3	0	3
LCADL (domains and total) baseline	0	0	0
LCADL (domains and total) 6 weeks	4	2	2
LCADL (domains and total) 12 weeks	3	0	3
Physical activity data baseline	8	4	4
Physical activity data 6 weeks	11	5	6
Physical activity data 12 weeks	11	5	6

Data presented as number.

Abbreviations: 6MWT: Six Minute Walk Test; CI: Confidence Interval; EQ5D5L: EQ5D 5-Levels; KBILD: King's Brief Interstitial Lung Disease questionnaire; LCADL: London Chest Activities of Daily Living questionnaire; QMVC: Quadriceps Maximum Voluntary Contraction; SPPB: Short Physical Performance Battery.

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CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	4, 5
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	6, 7
	2b	Specific objectives or research questions for pilot trial	7
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	7, 8
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	7
	4c	How participants were identified and consented	7, 8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8, 9
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	9, 10
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	NA
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	NA
Sample size	7a	Rationale for numbers in the pilot trial	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7, 8
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	7, 8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7, 8

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7, 8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	8, 9
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	10, 11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	11
	13b	For each group, losses and exclusions after randomisation, together with reasons	11, 12
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7
	14b	Why the pilot trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	14, 15
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	12, 14-19
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	12, 14-19
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	20, 21
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	13
	19a	If relevant, other important unintended consequences	NA
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	25
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	21-25
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	21-25
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	22-25
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	5, 7
Protocol	24	Where the pilot trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	2, 3
	26	Ethical approval or approval by research review committee, confirmed with reference number	7

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.