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ORIGINAL RESEARCH

Supervised pulmonary tele-rehabilitation versus pulmonary rehabilitation in severe COPD: a randomised multicentre trial

Henrik Hansen,[1] Theresa Bieler,[2] Nina Beyer,[3] Thomas Kallemose,[4] Jon Torgny Wilcke,[5] Lisbeth Marie Østergaard,[6] Helle Frost Andeassen,[6] Gerd Martinez,[7] Marie Lavesen,[8] Anne Frølich,[9] Nina Skavlan Godtfredsen[3,7]

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For numbered affiliations see end of article.

Correspondence to
Dr Henrik Hansen, Respiratory Research Unit, Department of Respiratory Medicine, Hvidovre Hospital, Hvidovre, Denmark; henrik.hansen.09@regionh.dk

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ABSTRACT

Rationale Pulmonary rehabilitation (PR) is an effective, key standard treatment for people with COPD. Nevertheless, low participant uptake, insufficient attendance and high drop-out rates are reported. Investigation is warranted of the benefits achieved through alternative approaches, such as pulmonary tele-rehabilitation (PTR).

Objective To investigate whether PTR is superior to conventional PR on 6 min walk distance (6MWD) and secondarily on respiratory symptoms, quality of life, physical activity and lower limb muscle function in patients with COPD and FEV_1 <50% eligible for routine hospital-based, outpatient PR.

Methods In this single-blinded, multicentre, superiority randomised controlled trial, patients were assigned 1:1 to 10 weeks of groups-based PTR (60 min, three times weekly) or conventional PR (90 min, two times weekly). Assessments were performed by blinded assessors at baseline, end of intervention and at 22 weeks' follow-up from baseline. The primary analysis was based on the intention-to-treat principle.

Measurements and main results The primary outcome was change in 6MWD from baseline to 10 weeks; 134 participants (74 females, mean±SD age 68±9 years, FEV_1 33%±9% predicted, 6MWD 327±103 metres) were included and randomised. The analysis showed no between-group differences for changes in 6MWD after intervention (9.2 metres (95% CI: −6.6 to 24.9)) or at 22 weeks' follow-up (−5.3 metres (95% CI: −28.9 to 18.3)). More participants completed the PTR intervention (n=57) than conventional PR (n=43) (χ^2 test p<0.01).

Conclusion PTR was not superior to conventional PR on the 6MWD and we found no differences between groups. As more participants completed PTR, supervised PTR would be relevant to compare with conventional PR in a non-inferiority design.

Trialregistration number
ClinicalTrials.gov(NCT02667171), 28 January 2016.

Key messages

What is the key question?

► Can a supervised pulmonary tele-rehabilitation programme, including structured exercise and education, deliver higher programme-adherence and thereby superior benefits to a conventional hospital-based pulmonary rehabilitation (PR) programme for patients with severe COPD?

What is the bottom line?

► This pulmonary tele-rehabilitation model demonstrated short-term and medium-term improvements in functional capacity and disease-related symptoms that were not superior to conventional hospital-based PR for patients with severely progressed COPD.

Why read on?

► Despite the benefits, PR programmes are challenged by low participant uptake, insufficient attendance and high drop-out rates; supervised pulmonary tele-rehabilitation may be a useful second-line option to improve access for patients with severe COPD who cannot participate in or comply with a conventional hospital-based PR programme.

INTRODUCTION

Pulmonary rehabilitation (PR) is recognised as an important, standard treatment for people with chronic obstructive pulmonary disease (COPD). PR is well documented to reduce symptoms and increase walking capacity and quality of life (QoL), but its effect on physical activity level (PAL) is limited.[1–5] Despite the benefits, PR programmes are challenged by low participant uptake, insufficient attendance and high drop-out rates.[6–9] Barriers have previously been reported, including transportation issues, symptom severity, acute exacerbations, lack of energy and disruption of daily routines.[6 8 10 11] Recently, the American Thoracic Society (ATS)/European Respiratory Society (ERS) recommended investigating alternative approaches to PR, such as tele-rehabilitation, in an attempt to increase uptake and make PR available to more patients.[12] To date, two randomised controlled trials (RCTs) have explored the effect of unsupervised web-based or video-demonstrated individual exercise and education compared with conventional group-based PR in patients with stable moderate-to-severe COPD.[13 14] The studies did not find differences between interventions for outcomes of walking capacity and respiratory symptoms.[13 14]

One study including patients with COPD and comorbid heart failure (NYHA II-IV) compared home-monitored exercise and weekly individual telephone supervision with usual care (no intervention). The intervention provided clinically relevant differences in walking capacity, respiratory symptoms and QoL compared with usual care. Furthermore per-protocol analyses showed that the gains were maintained at the 2-month follow-up.[15] Lastly, in patients with moderate COPD, one small RCT study (n=37) compared usual care (no intervention) with a supervised pulmonary tele-rehabilitation (PTR) programme in groups of two to four patients.[16] This study showed significant and clinically relevant between-group difference on endurance shuttle walk, anxiety and depression symptoms and self-efficacy in favour of supervised PTR.[16] All four studies are limited in their conclusions as none declared a priori-design (superior, equivalence, non-inferior) in the trial registry protocol, and just two studies stated a hypothesis.[14 16] Although results from the recent PTR studies are promising, effects from supervised PTR in groups compared with conventional outpatient supervised PR in groups remain to be investigated. Consequently, evidence is needed to ascertain any possible effect of a fully supervised real-time PTR programme on relevant outcomes. To our knowledge, our study is the first RCT investigating the short-term and medium-term effect of a supervised PTR programme compared with a supervised conventional PR programme on walking capacity, symptoms, QoL and PAL in patients with COPD, FEV_1 <50% and a high symptom burden eligible for routine hospital-based outpatient PR. We hypothesised that the supervised PTR programme would be superior to a supervised conventional PR regarding change in 6 min walk distance (6MWD) because of an expected higher adherence rate, leading to a greater response.[17] This paper reports on the clinical outcomes. A full economic analysis will be published separately.

METHODS

Trial design and participants

We conducted a randomised clinical, assessor-blinded and statistician-blinded, superiority, multicentre trial with two parallel groups to investigate the effect of supervised PTR compared with conventional PR on walking capacity in patients eligible for outpatient hospital-based PR. Patients were recruited from the respiratory departments of eight different university hospitals in Greater Copenhagen during March 2016 to October 2017. Inclusion and exclusion criteria corresponded to the criteria for outpatient hospital-based routine PR in the Capital Region of Copenhagen, Denmark, and pertained to adults with a clinical diagnosis of COPD defined as FEV1/FVC <0.70, FEV1 <50%, Medical Research Council ≥2 and no participation in PR within 6 months of the start of intervention.[17 18] All patients provided written and verbal informed consent.

Randomisation and blinding

After baseline assessments, patients were randomly allocated 1:1 to receive PTR or conventional hospital-based PR. The allocation followed a computer-generated randomisation list made by a biostatistician for each recruiting hospital; treatment was denoted as A and B to ensure blinding of the biostatistician. A senior manager from an independent research department was responsible for the randomisation list and provided the draw to ensure concealment. All assessors were blinded to group allocation, hypotheses and intervention details. Patients were not possible to blind for allocation. In the case of failure to keep the assessor blinded, a second assessor was available to conduct the blinded assessment on another day. The biostatistician had the main responsibility for the data analyses.

Intervention

Pulmonary tele-rehabilitation

The details and appropriate dosage set-up from both intervention programs are available in the online supplementary material and in our previously published protocol article.[17] In brief, the PTR programme was designed by the study group and aligned with exercise intensities and education themes from conventional PR. It was a group-based, supervised and standardised programme performed by the patients in their homes three times weekly for 10 weeks via a videoconference software system installed on a single touch screen. The exercise sessions lasted 35 min (weekly exercise volume 105 min) with incorporated warm-up and high repetitive time-based muscle endurance training followed by 5 min' rest before beginning a patient education session of 20 min (weekly education volume 60 min).

Conventional pulmonary rehabilitation

The conventional outpatient hospital-based PR programme was group-based, supervised and standardised and was performed twice a week for 10 weeks (in one hospital, for 12 weeks). The programme followed the Danish Health Authority's National Clinical Guideline and the Regional Guidelines.[17 19 20] The exercise sessions lasted 60 min and incorporated warm-up, endurance and resistance training and a cool-down period (weekly exercise volume 120 min). The patient education sessions lasted 60 to 90 min and took place once a week after the exercise session (detailed online supplementary available).

Outcomes

Full details on outcome, assessment procedures and quality control are available in the online supplementary material. Briefly, the primary outcome was change in the 6MWD on completion of the programme. Secondary outcomes were COPD Assessment Test (CAT), Hospital Anxiety and Depression Scale (HADS), EuroQol 5-Dimension Questionnaire (EQ-5D), the 30 s sit-to-stand test (30sec-STS), Clinical COPD Questionnaire (CCQ) and Physical Activity Level (PAL). The PAL was measured with activePAL triaxial accelerometer (PAL Technologies Ltd, Glasgow, UK) worn 24 hours for 5 days. PAL was measured on 73 patients residing within a radius of 25 km of Bispebjerg University Hospital. All assessment procedures were performed at baseline, end of intervention and at 22 weeks' follow-up from baseline. The procedures were reproducible and have been published.[21] Descriptive variables included body mass index, smoking status, medication and Charlson Comorbidity Index, spirometry and anthropometric measures, which followed the standardised protocols from the Danish Society of Respiratory Medicine.[22] Adverse events, hospitalisations and deaths were recorded throughout the trial by the National Health Data Authorities.

Statistical analysis

For the 6MWD, a change of 26 m is considered a minimal clinically important difference (MCID) in patients with COPD and FEV1 <50%.[23–25] Based on a two-sample independent t-test with an MCID of 26 m, a SD of 44.6 m,[24] a power of 80%, a significance level of 0.05 and an anticipated drop-out rate of 30%, 134 patients were recruited. Using this sample size, expected SD and existing MCID, power estimations for the secondary outcomes revealed 80% power to detect MCID in all

secondary outcomes except CCQ and PAL.[17] Descriptive data for the PTR and conventional PR are presented as mean and SD for continuous variables and frequency for categorical variables. Differences between the intervention groups in change of primary and secondary outcomes (end of intervention - baseline and 22 weeks' follow-up - baseline) were analysed by mixed effect models. The models included adjustment for treatment group, age, sex, body mass index, FEV_1, Charlson Comorbidity Index, smoking status and a random effect for hospital allocation. To account for possible regression to the mean effect, the baseline measure for the outcome was also included as a fixed effect variable in the models. Normal distribution of the model residuals was evaluated by Q-Q plots. All data are considered missing at random, using this with the likelihood-estimation in the mixed effect model, the ignorability assumption for the likelihood estimator is used to account for missing data in the model estimates[26] (number of data sets is stated in tables 1 and 2 and online supplementary tables S2 and S3). Group differences on number of patients remaining in their programmes for the full intervention period, adherence, hospitalisation and death were analysed with χ^2 test. Adherence/attendance was defined as a patient participating in an entire scheduled exercise and education session. Analysis of age and sex differences between patients with and without outcome measures was done by χ^2 and Wilcoxon rank-sum test. Per-protocol analysis included patients attending ≥70% of the planned sessions. Statistical analyses were carried out using R 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). P values of less than 0.05 were considered statistically significant.

RESULTS

Recruitment

Of the patients suitable for hospital-based PR, 1099 met the inclusion criteria and were considered; 714 patients refused PR and were thus deemed ineligible. Of 385 eligible patients, the majority (n=251) wished to undertake conventional PR and declined participation in the study. One hundred and thirty-four patients provided informed consent and were randomised (n=67 in each group) (figure 1). Baseline characteristics are shown in table 1.

Primary outcome

Tables 2 and 3 show the differences between and the changes within the groups at the end of PR/PTR and at the 22 weeks' follow-up from baseline. We found no statistically significant between-group difference for change in the 6MWD after intervention (table 2). Both groups demonstrated statistically significant improvements in the 6MWD after intervention, but the gain was sustained and significant only in the PTR group at 22 weeks' follow-up from baseline (table 3). None of the group improvements exceeded the MCID at any measurement time point.

Secondary outcomes

The between-group difference for changes in respiratory symptoms (CAT) was statistically different at the end of intervention with a greater symptom reduction difference of −1.6 points (p=0.04) in the PTR group that did not exceed the MCID (table 2). There was no between-group difference at the 22 weeks' follow-up from baseline. The groups did not exceed the MCID in respiratory symptom reduction at any measurement time point (table 3). The PTR group had a statistically significant reduction in anxiety and depression scores (HADS-A and HADS-D) compared with the conventional PR group after intervention,

Table 1 Baseline characteristics

Variables	All (n=134)	PTR (n=67)	PR (n=67)
Female sex, n (%)	74 (55)	35 (52)	39 (58)
Age, year	68.3 (9.0)	68.4 (8.7)	68.2 (9.4)
Body mass index, kg/m^2	25.7 (5.8)	25.5 (5.0)	25.9 (6.4)
FEV1, % predicted	33.1 (9.4)	32.6 (10.3)	33.7 (8.4)
FEV1/FVC, %	43.3 (11.2)	43.9 (11.3)	42.7 (11.1)
GOLD I/II/III/IV, %	0/0/61/39	0/0/55/45	0/0/67/33
A/B/C/D, %	2/34/4/60	5/34/3/58	0/33/4/63
LTOT, n (%)	20 (15)	11 (16)	9 (13)
SpO2 at rest, %	94.6 (2.8)	94.6 (2.4)	94.8 (3.1)
MRC 1/2/3/4/5, n	0/2/65/50/17	0/2/30/27/8	0/0/35/23/9
Smoking status, n (%)			
Never	3 (2)	2 (3)	1 (1)
Former	99 (75)	51 (79)	48 (72)
Current	30 (23)	12 (18)	18 (27)
Pack-year history, mean (SD)	43.5 (20.2)	42.4 (23.1)	44.5 (17.3)
BODE index points, median (IQR)	5.0 (4–6)	5.0 (4–7)	5.0 (4–6)
Charlson Comorbidity Index 1/2/≥3, (%)	40/37/23	45/40/15	34/33/33
Exacerbations, previous 12 month, (median, IQR)	2 (0–3)	2 (0–4)	2 (1–3)
Current medication, n (%)			
SABA	112 (84)	56 (84)	56 (84)
SABA + SAMA	11 (8)	6 (9)	5 (7)
LABA	2 (1)	1 (1)	1 (1)
LAMA	3 (2)	2 (3)	1 (1)
LABA + LAMA	24 (18)	12 (18)	12 (18)
LABA + ICS	8 (6)	5 (7)	3 (5)
LABA + LAMA + ICS	93 (69)	45 (67)	48 (71)
Oral steroids	2 (1)	2 (3)	0 (0)
Walking aid, walker/other, n (%)	27/18 (34)	14/9 (34)	13/9 (33)
Highest 6MWD, metre	327.3 (102.8)	322.3 (108.3)	332.3 (97.5)
Highest 30sec-STS, repetitions	9.8 (4.3)	9.9 (4.7)	9.6 (3.8)
Physical activity level*			
Daily step count, steps	3091 (2161)	2779 (1966)	3422 (2335)
Time sedentary, min	1205 (133)	1244 (121)	1164 (134)
Time active, min	235 (133)	196 (121)	276 (134)
CAT, score	20.1 (7.0)	19.8 (7.3)	20.4 (6.6)
HADS, score			
HADS-anxiety	6.3 (3.5)	6.8 (3.8)	5.9 (3.1)
HADS-depression	4.3 (3.0)	4.5 (2.)	4.1 (3.1)
EQ-5D, VAS score	52.7 (19.2)	51.5 (19.4)	53.9 (19.1)
EQ-5D, index score	0.68 (0.16)	0.66 (0.20)	0.70 (0.12)
CCQ, score			
Symptoms	2.9 (1.2)	2.8 (1.2)	3.0 (1.2)
Functional	2.9 (1.2)	2.8 (1.1)	3.0 (1.3)
Mental	2.8 (1.4)	2.8 (1.5)	2.9 (1.4)
Total	2.8 (0.9)	2.7 (0.9)	2.9 (1.0)

Data are presented as mean (SD) except where otherwise indicated.
*ActivePAL triaxial accelerometer worn by in total 73 patients (PTR/PR: 37/36). Any statistically significant difference between PTR and PR denoted *p<0.05.
A/B/C/D, risk stratification, airflow obstruction, dyspnea and exercise capacity; BODE index, body mass index; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; EQ-5D, Euro-Qol 5-dimension; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; GOLD, Global initiative for Chronic Obstructive Lung Disease; HADS, Hospital Anxiety and Depression Score; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; LTOT, long-term oxygen therapy; MRC, Medical Research Council; 6MWD, 6 min walk distance; PR, pulmonary rehabilitation; PTR, pulmonary tele-rehabilitation; SABA, short-action β2-agonist; SAMA, short-acting muscarinic antagonist; 30-sec STS, 30 s sit-to-stand test; SpO2, arterial oxygen saturation as measured by pulse oximetry; VAS, Visual Analogue Scale.

Table 2 Between-group differences in primary and secondary outcomes in PTR and PR groups. Intention-to-treat principle

	Between-group differences from baseline (95% CI)			
	PR-PTR (unadjusted)		PR-PTR (adjusted)	
	End rehabilitation†	22 weeks from baseline‡	End rehabilitation†	22 weeks from baseline‡
Primary outcome				
6MWD, min	6.3 (–9.8 to 22.5)	–11.0 (–34.4 to 12.4)	8.3 (–7.7 to 24.3)	–3.9 (–27.9 to 19.9)
Secondary outcomes				
30sec-STS, reps	0.5 (–0.6 to 1.5)	0.4 (–0.7 to 1.4)	0.5 (–0.6 to 1.5)	0.5 (–0.6 to 1.6)
CAT, points	1.4 (–0.1 to 3.0)	–0.5 (–2.6 to 1.5)	1.6 (0.1 to 3.3)*	–0.2 (–2.1 to 1.8)
HADS				
Anxiety, points	1.1 (0.1 to 2.1)*	0.2 (–0.9 to 1.4)	1.2 (0.2 to 2.3)*	0.4 (–0.8 to 1.6)
Depression, points	0.7 (–0.1 to 1.5)	–0.2 (–1.3 to 1.0)	0.9 (0.1 to 1.7)*	–0.2 (–1.3 to 1.0)
EQ-5D-VAS, points	–0.2 (–6.4 to 5.9)	0.8 (–5.8 to 7.5)	–0.2 (–6.2 to 5.9)	1.6 (–5.1 to 8.3)
CCQ				
Function, points	0.1 (–0.2 to 0.5)	0.1 (–0.2 to 0.5)	0.1 (–0.2 to 0.5)	0.2 (–0.2 to 0.5)
Mental, points	0.1 (–0.3 to 0.6)	–0.1 (–0.4 to 0.3)	0.3 (–0.2 to 0.7)	0.1 (–0.3 to 0.5)
Symptoms, points	0.2 (–0.1 to 0.5)	0.1 (–0.3 to 0.5)	0.2 (–0.1 to 0.5)	0.1 (–0.2 to 0.5)
Total, points	0.2 (–0.1 to 0.4)	0.1 (–0.2 to 0.3)	0.2 (–0.1 to 0.5)	0.1 (–0.1 to 0.4)
PAL				
Steps per day	–283 (–845 to 278)	–302 (–1035 to 419)	–436 (–1010 to 138)	–103 (–886 to 597)
Sedentary, min	9.4 (–35.2 to 51.3)	8.6 (–53.8 to 36.6)	7.7 (–49.0 to 52.2)	14.6 (–32.5 to 58.5)
Active, min	–9.4 (–51.3 to 35.4)	–8.6 (–36.6 to 53.8)	–7.7 (–52.2 to 49.0)	–14.6 (–58.5 to 32.5)

Data are mean difference (95% CI).
*P value for group mean change differences <0.05.
†Complete observations (n) used for the likelihood estimate from end of rehabilitation to baseline (total): 6MWD: (115); 30sec-STS: (115); CAT: (119); HADS: (110); EQ-5d-VAS: (119); CCQ: (119); PAL: (59).
‡Complete observations (n) used for the likelihood estimate from 22 weeks' follow-up from baseline to baseline (total): 6MWD: (95); 30sec-STS: (95); CAT: (106); HADS: (100); EQ-5d-VAS: (104); CCQ: (106); PAL: (55).
CAT, COPD Assessment Test; CCQ, COPD Clinical Questionnaire; EQ-5D, EuroQol 5-Dimension Questionnaire; HADS, Hospital Anxiety and Depression Scale; 6MWD, 6 min walk distance; PAL, physical activity level; PR, pulmonary rehabilitation; PTR, pulmonary tele-rehabilitation; 30sec-STS, 30 s sit-to-stand test; VAS, Visual Analogue Scale.

but it did not exceed the MCID. There were no between-group differences at the 22-week follow-up (table 2). The within group improvements on the anxiety domain were significant for the PTR group after intervention but did not exceed the MCID and the improvement was not sustained at the 22-week follow-up. No group exceeded the MCID for QoL (EQ-5D-VAS) and lower limb muscle function (30sec-STS) (table 3). We registered a statistically significant decrease in number of daily steps per day in the PR group from baseline to end of intervention and to the 22-week follow-up, whereas daily steps per day remained unchanged in the PTR group (table 3). There was no difference between groups in the per-protocol analyses in any outcome at any measurement time point (see online supplementary tables S2 and S3).

The attendance rate was a median of 25 session (IQR: 20 to 28) in the PTR group and 16 session (IQR: 8 to 19) in the PR group and thus the exercise volume was a median of 750 min (IQR: 600 to 840) in the PTR group and 960 min (IQR: 480 to 1140) in the PR group. A significantly higher number of patients remained in the PTR programme for the full intervention period compared with the PR programme (PTR: 57/67 vs PR: 43/67; OR: 3.18 (95% CI: 1.37 to 7.35), p<0.01). However, there was no difference between groups for those who attended ≥70% of the programs' total sessions, (PTR: 49/67 vs PR: 42/67; OR: 1.68 (95% CI: 0.78 to 3.37), p<0.27). The mean adherence rate among drop-outs who attended at least one session was 50% of all sessions (IQR%: 42 to 64) in the PTR programme versus 33% of all sessions (IQR%: 18 to 49) in the PR programme. Two drop-outs, both in the PR group, were potentially related to adverse effects of the PR programme. Both events were related to overload with subsequent pain in the knee and groin, respectively, and did not require medical treatment. In total, 41 hospital admissions related to COPD exacerbations were recorded (PTR: n=21; PR: n=20; p=0.77) during the rehabilitation period, and 74 hospitalisations related to COPD exacerbations (PTR: n=38; PR: n=36; p=0.97) were recorded at the 22-week follow-up (see the online supplementary S for diagnostic codes used in the registry from the National Health Data Authorities and online supplementary S5 for hospital days and outpatient visits). There was no significant difference between groups for all cause hospitalisations during rehabilitation. Three deaths (PTR: n=1; PR: n=2) occurred during the rehabilitation period, and another three had died at the 22-week follow-up (p=1.0).

No difference could be shown between patients with and without missing outcome measurement on sex, all p values >0.07. By contrast, the median age was significantly higher among patients with missing values for 6MWD, 30sec-STS, repetitions and CCQ mental score.

Registered problems with the technical solution

Major technical issues leading to cancellation and rescheduling of group sessions affected 2 of 360 group sessions. Minor temporary technical issues (ie, sound artefacts, screen freezes) not leading to cancellation or delay were present in 14% of the total

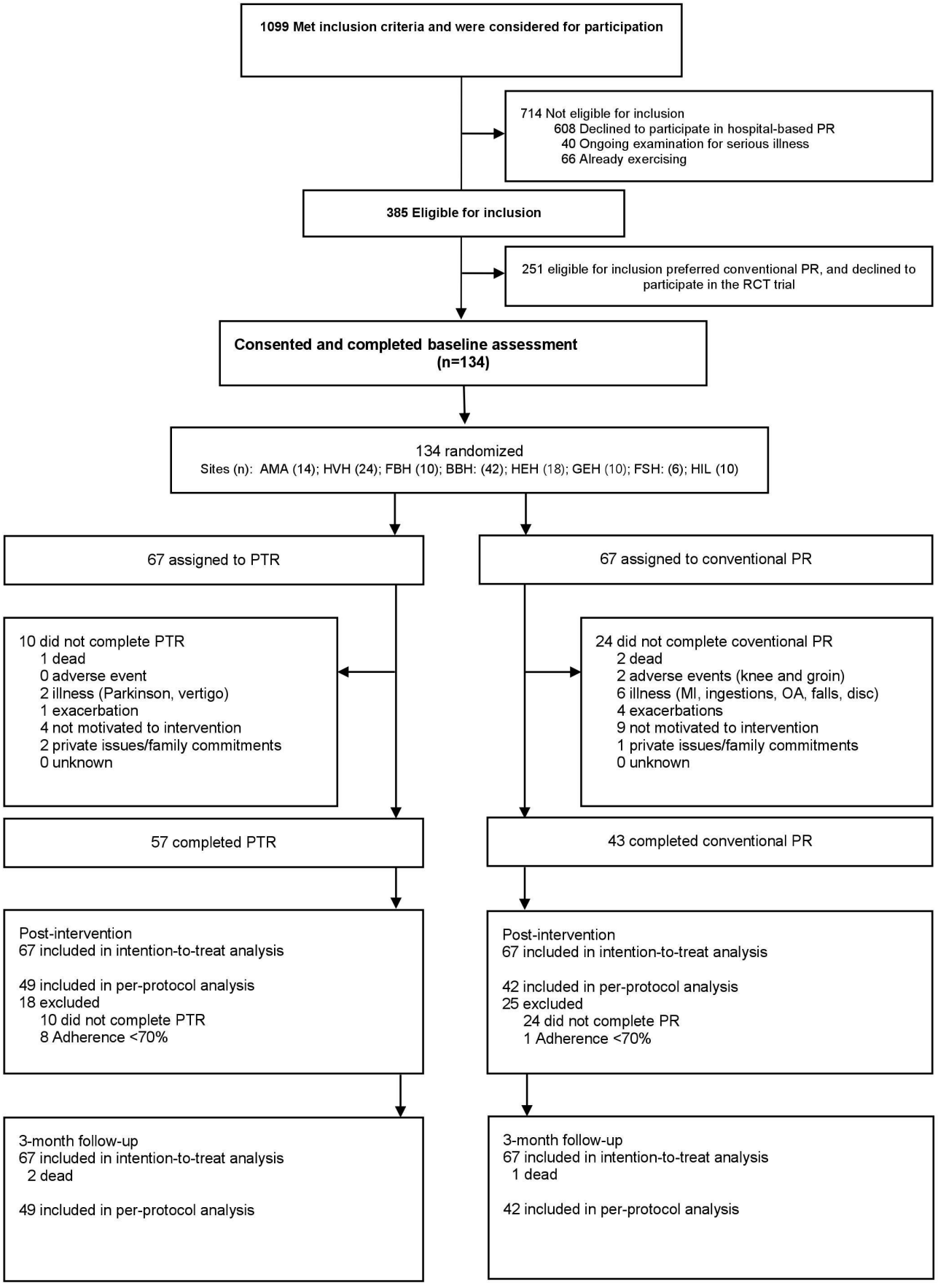

Figure 1 Consolidated Standards of Reporting Trials diagram. AMA, Amager; BBH, Bispebjerg; Disc, discogenic issue; FBH, Frederiksberg; FSH, Frederikssund; GEH, Gentofte; HEH, Herlev; HIL, Hillerød; HVH, Hvidovre; MI, myocardial infarction; OA, osteoarthritis; PR, pulmonary rehabilitation; PTR, pulmonary tele-rehabilitation, RCT, randomisedcontrolled trial.

Table 3 Within-group changes in primary and secondary outcomes in PTR and PR groups. Intention-to-treat principle

	Within-group changes from baseline (95% CI)			
	PTR (n=67)		PR (n=67)	
	End rehabilitation†	22 weeks from baseline‡	End rehabilitation†	22 weeks from baseline‡
Primary outcome				
6MWD, min	17.2 (5.8 to 28.5)*	22.0 (5.0 to 39.1)*	23.5 (12.1 to 35.0)*	11.0 (–5.2 to 27.2)
Secondary outcomes				
30sec-STS, reps	1.3 (0.4 to 2.0)*	1.1 (0.1 to 2.0)*	1.7 (0.9 to 2.5)*	1.5 (0.5 to 2.3)*
CAT, points	–1.7 (–3.2 to –0.2)*	–0.5 (–1.9 to 1.1)	–0.3 (–1.8 to 1.2)	–1.0 (–2.5 to 0.6)
HADS				
Anxiety, points	–1.0 (–1.7 to –0.2)*	–0.5 (–1.4 to 0.5)	0.1 (–0.6 to 0.8)	–0.3 (–1.2 to 0.7)
Depression, points	–0.4 (–1.1 to 0.3)	0.5 (–0.4 to 1.5)	0.3 (–0.4 to 1.0)	0.3 (–0.6 to 1.4)
EQ5D-VAS, points	3.2 (–1.2 to 7.6)	3.5 (–1.2 to 8.2)	2.9 (–1.4 to 7.2)	4.2 (–0.4 to 9.0)
CCQ				
Function, points	–0.3 (–0.5 to –0.1)*	0.1 (–0.1 to 0.4)	–0.1 (–0.4 to 0.1)	0.1 (–0.2 to 0.5)
Mental, points	–0.2 (–0.6 to 0.1)	–0.1 (–0.5 to 0.3)	–0.1 (–0.4 to 0.2)	–0.1 (–0.4 to 0.3)
Symptoms, points	–0.3 (–0.6 to –0.1)*	–0.2 (–0.5 to 0.1)	–0.2 (–0.4 to 0.1)	0.1 (–0.3 to 0.5)
Total, points	–0.3 (–0.4 to –0.1)*	0.0 (–0.2 to 0.2)	–0.1 (–0.3 to 0.1)	0.1 (–0.2 to 0.3)
PAL				
Steps per day	–116 (–503 to 270)	–292 (–852 to 307)	–400 (–803 to –2.3)*	–594 (–1164 to –57)*
Sedentary, min	29.0 (–29.9 to 95.4)	18.8 (–11.8 to 49.3)	38.3 (–21.7 to 107.3)	10.1 (–21.0 to 41.3)
Active, min	–29.0 (–95.4 to 29.9)	–18.8 (–49.3 to 11.8)	–38.3 (–107.3 to 21.7)	–10.1 (–41.3 to 21.0)

Data are mean difference (95% CI). Estimates adjusted for baseline outcome measure. Estimates calculated for baseline measure equal to the mean baseline measure for study population.

*P value within group changes <0.05.

†Complete observations (n) used for the likelihood estimate from end of rehabilitation to baseline (PTR/PR): 6MWD: (56/59); 30-sec STS: (56/59); CAT: (59/62); HADS: (53/57); EQ5d-VAS: (57/62); CCQ: (57/62); PAL: (30/29).

‡Complete observations (n) used for the likelihood estimate from 22 weeks' follow-up from baseline to baseline (PTR/PR): 6MWD: (44/51); 30sec-STS: (44/51); CAT: (53/53); HADS: (50/50); EQ5d-VAS: (51/53); CCQ: (53/53); PAL: (28/27).

CAT, COPD Assessment Test; CCQ, COPD Clinical Questionnaire; EQ-5D, EuroQol 5-Dimension Questionnaire; HADS, Hospital Anxiety and Depression Scale; 6MWD, 6 min walk distance; PAL, physical activity level; PR, pulmonary rehabilitation; PTR, pulmonary tele-rehabilitation; 30sec-STS, 30 s sit-to-stand test; VAS, Visual Analogue Scale.

group session (49/360). Individual patient cancellation caused by technical problems was 12 of 1902 individual connections.

DISCUSSION

The main finding of this multicentre, single-blinded, randomised clinical trial was that supervised PTR was not superior to conventional hospital-based PR regarding walking capacity (6MWD). More patients completed PTR than PR, whereas, contrary to our pre-hypothesis, there was no between-group difference in adherence rate (attending ≥70% of the planned sessions).

To our knowledge, the effects of a supervised PTR programme compared with a supervised conventional PR programme have not been previously investigated. Tsai *et al* found a clinically relevant effect on 6MWD and endurance shuttle walk test (ESWT) from supervised PTR compared with no intervention.[16] The study by Bernocchi *et al*[15] including patients with both COPD and heart failure reported superiority on 6MWD from an individual home-monitored exercise programme with a weekly phone call compared with no intervention; the intervention group exceeded the MCID and maintained the gain at the 2-month follow-up.[15] The studies by Bourne *et al*[13] and Chaplin *et al*[14] compared the effect of unsupervised web-based or video-demonstrated individual exercise and education with conventional group PR and found comparable between-group effects on walking tests and within-group changes that exceeded the MCID for 6MWD and ESWT but not for incremental shuttle walk test.[13 14]

By contrast, we found that neither conventional PR nor PTR improved the 6MWD above the MCID. Differences in population characteristics could in part explain our negative result. Compared with the above-mentioned studies, patients in our cohort had lower FEV_1, higher symptom burden, more exacerbations, lower walking capacity and most likely more locomotor disadvantages because in our study, 34% used a walking aid. Use of a walking aid or other indications of frailty have not been reported in the previous PTR studies.[13–16] We recruited patients with identical real-world inclusion criteria for hospital-based PR, which could limit the consistency and efficacy of the results; however, our study reflects routine practice. Recently, two large RCTs by Holland *et al*[27] and Horton *et al*[28] including in total 453 patients with COPD, compared home-based PR with supervised centre-based PR, using a pragmatic trial design, also failed to achieve the expected MCID on walking capacity from both interventions. Finally, a retrospective cohort study of 2068 patients with COPD of differing severity and with different characteristics receiving gold standard outpatient or inpatient PR in the Netherlands reported that only 40% to 50% of all patients exceeded the MCID for 6MWD, HADS-A, HADS-D and St George's Respiratory Questionnaire, while the group average improvement almost exceeded the MCID.[29] In this study, Spruit and colleagues demonstrated that patients respond

very heterogeneously on both the physical and self-reported clinical outcomes. This suggests the need for reconsideration of the assumption that all patients with COPD are likely to respond similarly and sufficiently to specific and restricted primary outcomes in either conventional PR programs[29] or alternative home-based programs.[27 28]

From the Cochrane review it appears that 43% of the larger studies (including more than 30 participants in each group) did not exceed the MCID for the 6MWD[1] and, importantly, meta-epidemiological studies have shown that single-centre trials yield 14% to 27% larger effect sizes than do multicentre trials even when analyses are adjusted for sample size and bias.[30]

The completion rate in our study was significantly higher in the PTR group than in the PR group; however, we did not find a significant higher adherence rate in the PTR group (73%) compared with the PR group (62%). The drop-out rate of 36% in the PR group was anticipated and comparable to other studies reporting drop-out rates from 10% to 50%.[6 7 11 27 28 31] The annual 2018 data audit from the Danish Regional Quality Database in COPD revealed that 45% of all participants in Danish outpatient hospital PR adhere to less than 50% of the PR program.[32] The real-world data from this quality database reflect the challenges with adherence in a conventional hospital-based real-world PR programme and should be contrasted with the distinctly higher adherence in the PTR programme, where 73% of patients attended ≥70% of the sessions. Thus, PTR seemingly has the potential to overcome some barriers to adherence and completion. It should be noted that only one-third of patients eligible for this study were willing to participate in this RCT as they stated 'preferring conventional PR', thus limiting the external validity (figure 1). Patient preferences and motivation have a potential impact on the outcomes achieved in different settings. This indicates that PTR could be an alternative for some patients eligible for outpatient hospital-based PR. As the 134 patients who agreed to participate may be particularly motivated, the 608 patients who declined participation in conventional PR would be an important group of interest for future research in the field of exploring the relevance and effects of PTR as an alternative delivery model.

There were also a number of important secondary findings in the present study. We investigated a cohort of patients with an extremely low level of physical activity, with average steps per day corresponding to basal and limited activity, for example, getting out of bed, making a meal and infrequent walks outside the home. This low and unchanged PAL throughout the study could affect the outcome and explain why the MCID in 6MWD was not exceeded since PAL and steps above 7500 per day are considered essential for physical functioning and overall health.[33]

We found that the PTR group had a significant reduction in CAT, anxiety and depression scores (HADS-A and HADS-D) compared with the PR group after intervention; however, the reduction did not exceed the MCID and the difference was not persistent at the 22-week follow-up. The higher completion rate in the PTR group, where patients continued to receive real-time attention and care, could be a plausible explanation of the differences after intervention. The previously mentioned PTR studies by Chaplin *et al*[14] and Bourne *et al*[13] did not find any between-group differences in HADS after intervention, while Tsai *et al*[16] found differences identical to ours with supervised PTR compared with no intervention. The impact of real-time supervision versus the web-based PTR, including the means of communication, is not possible to quantify but could potentially explain some of these inconsistent findings between the PTR studies.

We are not aware of any studies comparing non-supervised PTR with supervised PTR. Ability to navigate and interact independently on a tablet and a webpage was required in the non-supervised PTR studies, whereas for the patients in our study, it was sufficient to have naive technical ability and skills.[13 14 17] Essentially, future tele-rehabilitation designs must include specific considerations regarding delivery form and content and technical skills of the targeted population, particularly if PTR is to be considered as an extended offer specifically to those who live remotely and to those who lack energy and resources to join a conventional PR programme.

The strengths of this study include the multicentre design, rigorous methodology, powering for an adequate sample size to test our *a priori* hypothesis and the intention-to-treat analysis, which limits the risk of bias. We recruited patients with severely progressed COPD using national inclusion and exclusion criteria identical to routine clinical practice for conventional outpatient hospital-based PR. Blinding was also a strength of the present study. Our assessment of outcomes was performed with documented small and acceptable measurement errors.[21] A limitation of the study concerns the small but real variation in exercise content and volume among the seven hospitals delivering conventional PR, which was not possible to monitor and align. However, this is a true reflection of the real-world setting and thereby a real-world comparison. Different practical challenges to modelling, staffing and structuring PTR and differing patient acceptance of PTR in different countries, geographical regions and different types of healthcare system are limitations of the generalisability of our findings.

Proper organisation of PTR remains a challenge. It is a delicate balance in terms of decision-makers not limiting access to outpatient conventional PR and replacing it with PTR to save the costs related to buildings, equipment, transportation, etc, while endeavouring to provide an option for patients who are unable to attend the outpatient programme. From our perspective, many research questions remain unanswered regarding PTR. Future research should address subjects such as which patients are best suited to PTR and how we accommodate the increasing focus on personalised training. We need to find ways to enhance digital literacy among elderly, frail patients and discover whether the supervised or web-based tele-model is more effective as well as cost-effective. Furthermore, it is not yet known if applications will be as as good as online groups with videoconferencing. Other aspects include the role of monitoring PTR and the long-term health-related and QoL-related outcomes. Another issue regarding future studies of both PR and PTR concerns the measured outcomes of interest. As results to date regarding the traditional exercise and QoL outcomes are not convincing in patients with severe disease status, it is necessary to try a different approach. Outcomes that embrace activities of daily living and/or reduce symptoms such as dyspnoea and fatigue are warranted. In the study by Spruit *et al*[29] a composite endpoint for response to a 40-session PR programme was constructed and patients were clustered according to response profile. Interestingly, those in the 'very good responder' cluster were characterised by a worse baseline health status in comparison with the other clusters. However, it was unclear whether this multidimensional response was driven by a single outcome measure or several measures, thus calling for further research in the context of composite outcomes.

CONCLUSION

In conclusion, supervised PTR was not superior to supervised conventional PR in increasing 6MWD. Improvements in completion of PTR compared with PR were found; however, future non-inferiority studies of the 6MWD for PTR and PR are needed to justify recommending PTR based on better adherence to the programme.

Author affiliations
[1]Respiratory Research Unit, Department of Respiratory Medicine, Hvidovre Hospital, Hvidovre, Denmark
[2]Department of Physical and Occupational Therapy, Bispebjerg Hospital, Copenhagen, Denmark
[3]Institute for Clinical Medicine, University of Copenhagen Faculty of Health and Medical Sciences, Copenhagen, Denmark
[4]Clinical Research Center, Copenhagen University Hospital Amager and Hvidovre, Hvidovre, Denmark
[5]Department of Pulmonary Medicine, Gentofte Hospital, Hellerup, Denmark
[6]Department of Respiratory Medicine, Bispebjerg Hospital, Copenhagen, Denmark
[7]Department of Respiratory Medicine, Hvidovre Hospital, Hvidovre, Denmark
[8]Department of Respiratory Medicine and Infectious Diseases, Hillerød Hospital, Hillerød, Denmark
[9]Department of Public Health, University of Copenhagen Faculty of Health Sciences, Copenhagen, Denmark

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Data availability statement Data are available upon reasonable request. Data sharing plan: Supervised pulmonary tele-rehabilitation versus pulmonary rehabilitation in severe COPD: a randomised multicentre trial. (1) Will individual, de-identified participant data (including data dictionaries) will be shared? Yes. (2) What data in particular will be shared? Participant data that underlie the results reported in this article, after de-identification (text, tabes, figures and appendices). (3) Whether additional, related documents will be made available? Published study protocol, statistical analytics coding used in R, consent form (in Danish). (4) When and for how long the data will become/be available? Data available until 31 December 2021. (5) The criteria to access the data (including who can request access and for what types of analyses, and the name of the data repository). Proposal for data use should be addressed to Henrik.hansen.09@regionh.dk. Data access in Denmark are under very strict juristic data protection law. Any possible access or sharing demands a part application to; (1) Danish Data Protection Agency, (2) Ethics Committee of the Capital Region, (3) National Health Data Authorities. Only if the applications are approved data will be considered available for sharing. The authors will not be able to support this process and a prolonged process must be expected.

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Supplementary material

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Methods

Study principles

The protocol for this study followed the SPIRIT 2013 (Standard Protocol Items: Recommendations for interventional Trials) and the Template for Interventions Description and Replication (TIDieR) checklist for description of the interventions[1–3].

Study design

The study is a randomized controlled, assessor- and statistician-blinded, superiority, multicenter trial with two parallel groups. The trial investigates the effect of supervised pulmonary tele-rehabilitation in groups, delivered by health professionals in the patients' own homes via a computer, in patients with severe and very severe (stage III-IV) COPD (ClinicalTrial.gov-identifier: NCT02667171). Patients from the university hospitals in the Capital Region of Denmark were randomized 1:1 to the supervised group-based pulmonary tele-rehabilitation (PTR) or to a conventional, supervised group-based pulmonary rehabilitation program (PR).

Study setting and study population

The trial was conducted at the Respiratory and Physiotherapy Departments of eight hospitals in the capital region of Denmark. The participating hospitals were Amager, Hvidovre, Bispebjerg, Frederiksberg, Herlev, Gentofte, Frederikssund and Hillerød University Hospitals, University of Copenhagen. Recruitment of eligible patients and collection of data started March 18, 2016 and all data collection was finalized December 31, 2018 (clinicaltrial.gov registration January 12, 2016). The participating hospitals provided monthly reports on patients who accepted participation, and those who declined with reasons for their lack of participation. The recruitment was facilitated by a

steering committee with members from the departments of the participating hospitals. The investigator (HH) provided quarterly updates on the recruitment progress and participated in meetings with the clinical staff when requested.

Eligibility criteria

Potentially eligible patients were identified and recruited by a chest physician or a respiratory nurse during standard out-patient COPD check-up visits. The eligibility criteria were fully identical with routine criteria for conventional, supervised group-based pulmonary rehabilitation at the hospital. Eligibility was determined according to the inclusion and exclusion criteria listed below.

Inclusion criteria

1. Age 18 years or older
2. Clinical diagnosis of COPD defined as the ratio of forced expiratory volume at one second (FEV1) to forced vital capacity (FVC) < 0.70 and no primary diagnosis of asthma
3. FEV1 <50%, corresponding to severe or very severe airflow limitation
4. Symptoms equivalent to the Medical Research Council dyspnea scale (MRC) from 2 to 5

Exclusion criteria

1. Participation in/or recent completion of pulmonary rehabilitation within the last six months before start of intervention
2. Dementia/ cognitive impairment or symptomatic psychiatric illness
3. Impaired hearing and / or vision leading to inability to understand instructions
4. Unable to understand or speak Danish
5. Unable to read Danish

6. Severe co-morbidity leading to the recommend physical exercise for patients with COPD being contraindicated.

Eligible patients received written information of the study by the healthcare professional and verbal information about the study by the investigator or project staff. The investigator ensured that all questions regarding participation were addressed before the patient was invited to participate in the study. According to the ethical guidelines for medical research in Denmark, all patients were encouraged to consider consent for at least 24 hours before making a decision. Patients who agreed to participate were asked to sign an informed consent form to be included in the study. The patient kept the original document and a copy was archived with the Case Report Form (CRF).

Randomization and blinding

After baseline assessments, patients were randomly allocated 1:1 to receiving PTR or conventional hospital-based PR. The allocation followed a computer-generated randomization list made by a biostatistician for each recruiting hospital; treatment was denoted as A and B to ensure blinding of the biostatistician. A senior manager from an independent research department was responsible for the randomization list and provided the draw to ensure concealment. The investigator or the project staff subsequently informed the patient about the allocation and when to begin. All assessors were blinded to group allocation and previous test results. Patients were not possible to blind for allocation. In the case of failure to keep the assessor blinded, a second assessor was available to conduct the blinded assessment on another day. The biostatistician had the main responsibility for the data analyses (Table S6).

Sample size

The study's primary endpoint was 6-minute walk distance (6MWD). A mean change difference of 26 meters between groups was considered a minimal clinically important difference (MCID) in patients with COPD [4,5]. Based on a two-sample independent t-test with the given MCID of 26 meters, standard deviation of 44.6 meters based on data published by Puhan et al. 2011[5], power of 80% and significance level of 0.05, 47 patients were needed in each group, 94 in total. A drop-out rate of 30% was anticipated, and 134 patients were included in the final study population to reach sufficient power for the per-protocol analysis (Table S8).

Power estimations for secondary outcomes

We performed power estimations for all secondary outcomes based on the decided inclusion of 134 (67 in each group) patients and expected standard deviation (SD) and an existing minimal clinically important difference (MCID) for each outcome (Table S8). The sample of 134 patients provided power to detect clinically relevant differences in secondary outcomes for, respectively, muscle strength and leg endurance, symptoms, anxiety and depression, and health-related quality of life (HRQOL), all corresponding with a power above 80% to reject the null hypothesis (type I error 5%). The outcomes for disease-specific quality of life (Clinical COPD Questionnaire) and physical activity (steps per day) both had a power below 80%.

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Interventions

Warm-up in both groups (PR and PTR)

Warm-up had a duration of five minutes (PTR group) and ten minutes (PR group). The aim was familiarization of movements, increasing range of motion and stimulation of joints, muscles and cardiorespiratory warm-up in accordance with recommendations from the American College of Sports Medicine[6]. The warm-up protocol is presented in (Table S9 and S11).

Comparison group—Conventional pulmonary rehabilitation programme (PR) (Table S9.)

Patients in the comparison group received a supervised, standard pulmonary rehabilitation program (PR) for patients with severe and very severe (stage III-IV) COPD, in groups of 6–12 patients, which followed the Danish Health Authority's National Clinical Guideline and the Regional Guidelines[7–9]. The guidelines allowed minor variations in the duration of the program (from 10 to12 weeks) but not in the program content[7–9]. The rehabilitation program included individually tailored physical exercise and patient education. Exercise sessions lasted 60 minutes twice weekly (weekly exercise volume of 120 minutes) for 10 weeks (in one hospital, for 12 weeks) supervised by two skilled physiotherapists with at least two years of experience with PR. The exercises used in the PR exercise program were well-documented endurance and resistance exercises[10] and are presented in Table S9. The time volume allocated for endurance and resistance training modalities was equal. Endurance training always included 15 minutes of stationary cycling, performed in intervals or as continuous cycling, depending on patient preference, desaturation, hip/knee/back pain and other comorbidities. Another 5–15 minutes of endurance training was performed as functional exercises in, for example, paced walking, stairclimbing or circuit training. Intensity was set to reach dyspnea

corresponding to a Borg score of CR10, 4–7, depending on whether exercises were performed continuously or at intervals.

Resistance training involved large muscle groups with 50/50 % of exercises for upper and lower extremities, respectively [10–17]. Volume, intensity and content specified in the training protocol is in accordance with both national and international exercise recommendations to assure appropriate dosage of exercise and intensity [7–11,18,19]. The exercises were executed in two to three sets of 8 to 25 repetitions (corresponding to 40–80% of 1RM) to achieve peripheral muscle fatigue and muscle strengthening (Table S9). A pause of 1–2 minutes between each set was mandatory. Exercises were done in three strength training machines (leg press, knee extension and chest press or pulldown) supplemented with dumbbells, elastic bands, and weight cuffs. Resistance was readjusted every 2nd to 4th week and depended on training adherence, repetition count, patient feedback and motivation[6,20] A familiarization phase to adapt to exercising, adjust and optimize load and avoid demotivation and musculoskeletal overload injuries spanned 2–4 sessions for each patient. The patient education session of 60–90 minutes took place once a week following the exercise session and was led by a trained respiratory nurse with at least two years' PR experience. A chest physician, a physiotherapist and a dietician separately led one of ten session respectively during the education period. The total number of patient education sessions was 10 (in one hospital 12 lessons). Topics covered in the education program and the didactics are presented in Table S10 and were disseminated as a combination of dialog, reflection exercises and practical exercises[9,21] (Table S10). Overall the topics were similar to those in the PTR group (see Table S14).

Intervention group—Pulmonary tele-rehabilitation program (PTR) (Table S11, S12 and S13)

Patients in the intervention group received a supervised pulmonary tele-rehabilitation program (PTR), which is an intervention that has not been systematically offered in Denmark. The PTR intervention was supervised by skilled physiotherapists and respiratory nurses with at least two years of experience with conventional PR. The physiotherapist and respiratory nurses delivered PTR via a webcam at Bispebjerg Hospital to a group of 4–8 patients who exercised at home and communicated via a videoconference software system installed on a single touch screen. The videoconference software system and single touch screen was installed and delivered by a technician, who also delivered the exercise-equipment consisting of one step-box and dumbbell-pairs of 1–10kg (Figure S1). Each session was 60 minutes, e.g. 35 minutes of exercise (weekly exercise volume 105 minutes) and 20 minutes of patient education (weekly education volume 60 minutes), three times per week for 10 weeks. Exercises was supervised by a physiotherapist and patient education by a respiratory nurse. The exercises used in the PTR exercise program were identified and selected from exercises used in previous exercise intervention studies in patients with severe or very COPD and involved larger muscle groups with 50/50 % exercises for upper and lower extremities, respectively [10–17]. The volume, intensity and content specified in the training protocol are in accordance with both national and international exercise recommendations to assure appropriate dosage of exercise and intensity[7–11,18,19]. The exercises (Table S12) were done in four sets to achieve peripheral muscle fatigue and secondary exercise-induced dyspnea/breathlessness. Each set was carried out in a predefined period of 20 to 40 seconds with a maximum number of repetitions performed until muscle failure, i.e. 8 to 25 repetitions depending on the patients' exercise capacity and motivation[6,20] but with the aim of 12 to 20 repetitions. The pause was predefined from 40 to 20 seconds (see Table S13). The exercise velocity was based on

recommendations applying to high-repetitive exercises (> 15 repetitions)[6], i.e. moderate to high speed equaling 1–2 seconds for both the concentric and the eccentric movements. The exercise load was body weight supplemented with external weight using dumbbells (1 to 20 kg). The intensity was estimated to be equivalent to 40–80% of one repetition maximum (8–25 repetitions), and exercises were performed as high repetitive time-based muscle endurance training at least 80% of the exercise time, corresponding to a weekly volume of 90 minutes (30 minutes x 3 sessions / excluding warm-up of 5 min). In practice, the training intensity was additionally assessed by using the self-rated Borg CR-10 scale (score range 0–10), aiming at a Borg score of 4–7 (moderate to very strong shortness of breath during the exercises).

The first two weeks served as a familiarization phase to adapt to exercising, to adjust and optimize the load and to avoid demotivation and musculoskeletal overload injuries. Thus exercises for the lower extremities (Table S12: exercise # 1, 3, 5) were carried out without dumbbells at the first session. If a patient could perform three consecutive sets without resting during the active period, external load was added at the subsequent training session. The external re-load increase ranged from 2 to 4 kilo (total weight for two dumbbells) when progression adjustments were made. Exercises for the upper extremities (Table S12: exercise # 2, 4, 6) were carried out with the smallest weights (1kg / pcs.) at the first exercise session.

Progression: If the patient could perform three consecutive sets without rest during the active period, external load was added at the subsequent training session. The external load increase ranged from 2 to 4 kilo (total weight for two dumbbells) when progression adjustments were made. Progressions were assessed individually from session to session[12–15]. In addition, patients were asked to count their repetitions in each set every 6th sessions (every 2nd week), and if the number of repetitions exceeded 25, the external load was increased at the next training session.

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Exercise log

Each patient had an exercise log completed by the supervisor who instructed the sessions on-screen. The exercise log contained the number of completed sets, loads in kilo, customized additions and non-completed sets for each participant for all sessions.

Patient education

The education topics were disseminated as a combination of dialog, reflection exercises and practical exercises[9,21] (Table S14). Overall, the topics were similar to those in PR but delivered as 20-minute sessions three times per week in total 30 sessions. The medical and nutrition topics were provided by a respiratory nurse in the PTR education sessions.

The dissemination focused in particular on

- Participation and dialog to facilitate sustainable knowledge related to COPD
- Creation of space for reflection and for patients to develop their own action plan for dealing with the disease
- Awareness and acceptance of patients' different ways of understanding and acquiring knowledge
- Promotion of the positive aspects and opportunities of life with COPD

Statistical analysis

Descriptive data for the PTR and conventional PR are presented as mean and SD except where otherwise indicated. Differences between the intervention groups in change of primary and secondary outcomes (end of intervention–baseline and 22 weeks' follow-up from baseline–baseline) were analyzed by mixed effect models. The models included adjustment for treatment group, age, sex, BMI, FEV_1, Charlson Comorbidity Index, smoking status, and a random effect for hospital allocation. To account for possible regression to the mean effect, the baseline measure for the outcome was also included as a fixed effect variable in the models. Normal distribution of the

model residuals was evaluated by Q-Q plots. All data are considered missing at random and because of this, the ignorability assumption for the likelihood estimator is used to account for missing data (number of datasets is stated in the Manuscript Table 1 and 2 and Supplement Table S2 and S3). Group differences on number of patients remaining in their programs for the full intervention period, adherence, hospitalization and death were analyzed with chi-squared test. Per-protocol analysis included patients attending ≥70% of the planned session. Statistical analyses were carried out using R 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). P-values of less than 0.05 were considered statistically significant.

Health economic analysis

Costs related to the interventions are calculated based on the expenses associated with exercise instruction and support, the time used by participants and relatives, transportation costs and the participants' use of healthcare services. Cost-effectiveness (cost per quality-adjusted life year) is estimated from the cost calculations combined with changes in EQ-5D-3L scores over time during the observation period. Costs related to COPD treatment and the use of healthcare services by patients and relatives are estimated from national administrative health registries.

The health economic analysis will be published in a separate publication and a potential business case conducted by an independent research company when the clinical outcomes are published.

Compliance

In addition to the intention-to-treat analysis, a per-protocol analysis was performed. The participants in both groups had to completed 70% of the COPD rehabilitation program to be included in the per-protocol analysis.

Hansen H, *et al. Thorax* 2020;0:1–9. doi: 10.1136/thoraxjnl-2019-214246

Data collection

Blinded assessors performed pre- post- and follow-up tests and collected data in CRFs at five locations (Bispebjerg-, Hvidovre-, Gentofte-, Herlev- and Frederikssund University Hospitals) to cover the whole Capital Region. For practical reasons, all locations had two to three assessors available. All assessors completed a four-hour assessor course to ensure they followed the same testing protocol and that test procedures and recording of results were standardized. In addition, assessors had observed at least four live tests before being accredited as blinded assessors. All raters were familiar with the 6MWT and 30-sec-STS from clinical practice. The median years of experience after graduation as a therapist was 11.5 years (10 years [n=3]; 10–20 years [n=4]; and >20 years [n=3]). The therapists had experience in areas relating to geriatrics, cancer, heart and lung diseases, neurology, and orthopedics as well as in the intensive care unit.

All assessments followed the same procedures (Figure S15) and were conducted under the same conditions, including the same location and a time frame from 10am to 2pm, Monday–Friday. Patients were instructed not to do any vigorous activities three hours prior to assessments and to take their prescribed medication as usual. The assessment/test procedure reflects the conditions in everyday clinical practice, where several performance tests and questionnaires are conducted within a narrow time frame (Figure S15).

Data management

All CRFs and questionnaires were checked for errors and missing data before being entered in a log-protected spreadsheet database. All entered data were double checked against the CRF, and range checked. The principal investigator had blinded access to the full dataset, and co-investigators and the steering committee had blinded access as needed for random auditing. All paper-based

CRFs and questionnaire versions were anonymized and locked in a filing cabinet to ensure data confidentiality. Data management complied with the rules of the Danish Data Protection Agency.

Adverse event reporting

Adverse events were recorded in the CRF. The protocol distinguishes between adverse events arising from the study interventions and those not attributable to the study. Serious adverse events were reported within 24 h to the principal investigator. The steering committee, consisting of a pulmonologist, respiratory nurse and clinical physiotherapist, surveyed the study and evaluated serious adverse events.

Technical hardware and software used in the pulmonary tele-rehabilitation program

Hardware/software

The screen solution used was called Homecare. The screen for patients was a 511 x 309 x 38mm single touch interface with a power on/off and one touch button. The healthcare professional (HCP) screen was 930 x 523 x 38mm. The patient and HCP screens were connected to a professional video conference system that allowed professionals and patients to see, hear and talk to single or multiple persons at one time and supported group sessions.

The conference took place via an encrypted connection that met data protection standards in Denmark. Data were transmitted via IPSEC VPN connection. Patient data were transferred via OIOXML and prepared in HL7 standards.

The technical equipment and support were rented for 67 patient set-ups in the pulmonary tele-rehabilitation program**.**

Outcomes *(see Table S7)*

Physical performance outcome measure

The 6-minute walk test (6MWT) measured endurance and walking capacity. The 6MWT is widely used for measurement of endurance walking capacity in patients with COPD [10,22]. The walking course was 20 meter due to walking space shortage at some locations and to ensure the same standard walking length at all five locations[23]. Apart from corridor length, the 6MWT test was conducted in accordance with standardized guidelines [22]: patients were instructed to walk as far as possible in 6 minutes, receiving recommended standardized encouragement; two tests were performed to eliminate a potential learning effect and the highest value was recorded; a 30-minute rest was mandatory between the first and second 6MWT.

The 30-second sit-to-stand test (30sec-STS) was used as an indirect assessment of lower limb muscle endurance strength [24,25]. A standardized chair with a seat height of 45–47 cm was used at the five test sites for all assessments; patients were asked to stand up fully and sit down as many times as possible in 30 seconds with their arms across the chest. The number of full stands was recorded. A score zero was recorded if a patient was unable to rise from the chair without using his or her arms. Two tests were performed to eliminate a potential learning effect; the best result was recorded. A 30-minute rest was mandatory between the first and second 30sec-STS.

24-hour physical activity was measured with an *active*PAL ™ triaxial accelerometer (PAL Technologies Ltd., Glascow, UK). Patients were asked to wear an *active*PAL™ on the thigh 24 hours a day for five days prior to randomization; five days during the intervention period (after 5–7 weeks); five days after completion of intervention period; and for five days 22-weeks from baseline. Due to limited staff resources and geographical transportation issues, activity level was measured

only in the first 68 patients (approximately 50% of the population) who lived within a radius of 25 kilometers of Bispebjerg University hospital. The *active*PAL™ accelerometer is attached on the front of the thigh and measures the number of steps, time spent lying/sitting (thigh in horizontal position), and time spent standing and walking (thigh in a vertical position), cadence, and the number of sit-to-stand and stand-to-sit transitions. The *active*PAL™ is a valid and reliable measure of posture and transitions in mobility-limited older adults and adults with severe and very severe COPD[26–28]. However, a*ctive*PAL™ underestimates step rate at slow walking speeds compared with observed step counts, whereas step rate with the use of walking aids, such as rollator and crutches does not differ from observed step rate counts[28]. A walking speed between 2.4 and 5.6 km/h is preferable to obtain valid data on time spent walking[26,29]; consequently, walking time could potentially be categorized as standing in those with a walking speed slower than 2.4km/h[26,29]. Accordingly, we dichotomized position data into time spent sedentary (lying/sitting) and upright (standing/walking).

Patient reported outcome measures (PROMS)

The PROMS, COPD Assessment Test (CAT), Hospital Anxiety and Depressions Scale (HADS), EuroQol 5-Dimension Questionnaire (EQ-5D), and Clinical COPD Questionnaire (CCQ) were completed in a quiet room during a scheduled mandatory rest period between the two sessions of physical performance outcome measures. The questionnaires were completed without inference from the blinded assessor.

Figure S1. Pictures of technical and exercise equipment

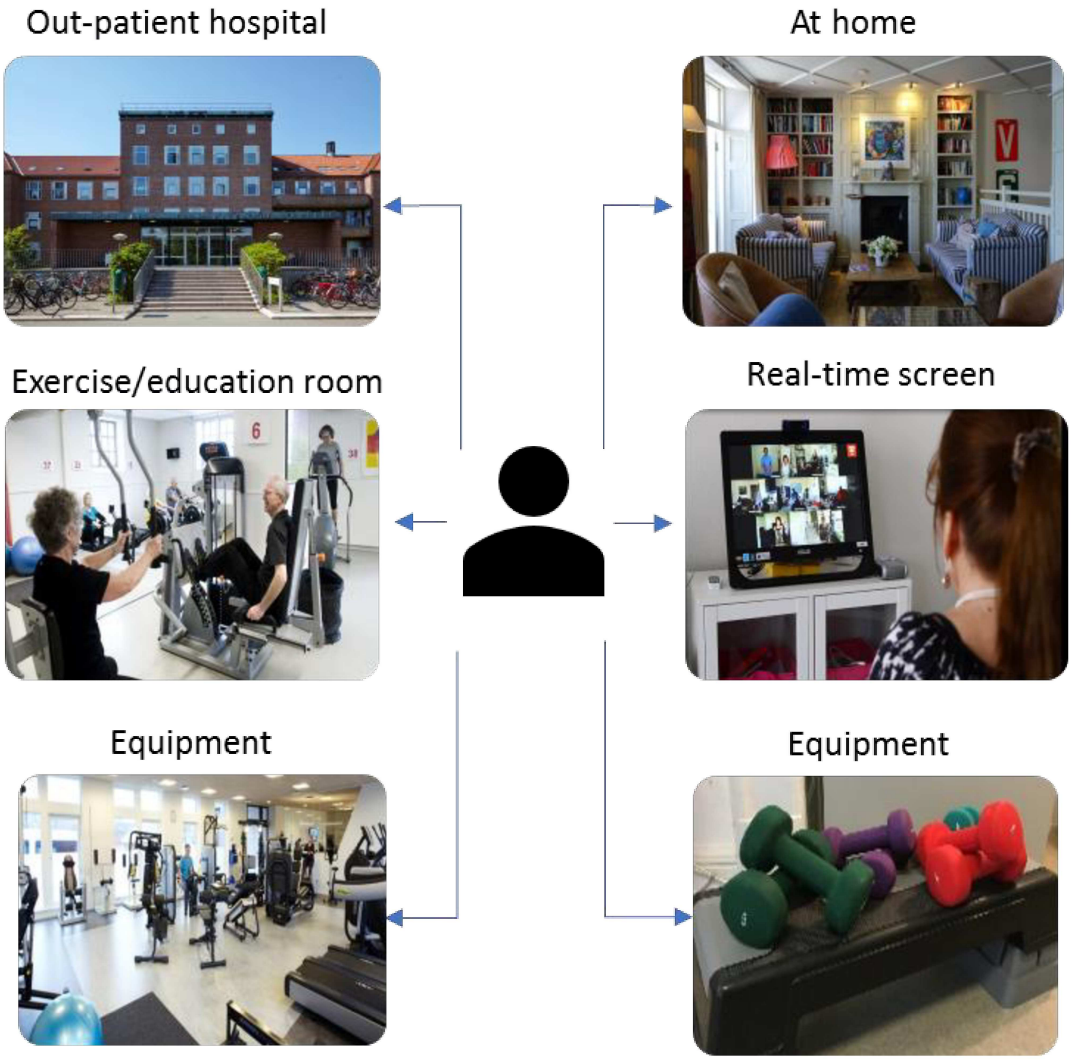

Table S2. Between-group differences in primary and secondary outcomes in PTR and PR groups. Per protocol analysis

	Between-group changes from baseline (95% CI)			
	PR- PTR (Unadjusted)		PR- PTR (Adjusted)	
	End rehabilitation[#]	22-weeks from baseline[##]	End rehabilitation[#]	22-weeks from baseline[##]
Primary outcome				
6MWD, m	5.0 (-11.2; 21.2)	-11.3 (-36.0; 13.4)	7.4 (-9.5; 23.9)	-6.1 (-31.4; 19.1)
Secondary outcomes				
30sec-STS, reps	0.5 (-0.6; 1.7)	0.3 (-0.9; 1.5)	0.7 (-0.5; 1.9)	0.4 (-0.8; 1.6)
CAT, points	1.2 (-0.6; 3.0)	-0.8 (-3.2; 1.6)	1.0 (-0.8; 2.8)	-0.9 (-3.1; 1.3)
HADS				
Anxiety, points	0.6 (-0.6; 1.7)	-0.5 (-1.7; 0.7)	0.5 (-0.7; 1.7)	-0.6 (-1.8; 0.6)
Depression, points	0.4 (-0.5; 1.3)	-0.3 (-1.6; 0.9)	0.4 (-0.5; 1.3)	-0.2 (-1.6; 1.1)
EQ5D-VAS, points	0.3 (-6.8; 7.3)	1.9 (-5.4; 9.1)	1.8 (-4.8; 8.4)	2.2 (-5.1; 9.5)
CCQ				
Function, points	0.0 (-0.3; 0.4)	0.1 (-0.3; 0.5)	-0.1 (-0.4; 0.3)	0.1 (-0.3; 0.5)
Mental, points	0.1 (-0.3; 0.6)	-0.2 (-0.6; 0.3)	0.2 (-0.3; 0.7)	-0.1 (-0.5; 0.3)
Symptoms, points	0.2 (-0.2; 0.5)	0.1 (-0.4; 0.5)	0.1 (-0.2; 0.5)	0.1 (-0.3; 0.4)
Total, points	0.1 (-0.2; 0.4)	0.0 (-0.3; 0.3)	0.1 (-0.2; 0.4)	0.0 (-0.3; 0.3)
PAL				
Steps per day	-361 (-1084; 361)	-559 (-1345; 227)	-464 (-1211; 283)	-232 (-1083; 619)
Sedentary, minutes	5.9 (--26.1; 37.2)	18.0 (-26.6; 62.5)	5.8 (-26.1; 37.3)	3.4 (-44.6; 47.8)
Active, minutes	-5.9 (-37.2; 26.1)	-18.0 (-62.5; 26.6)	-5.8 (-37.3; 26.1)	-3.4 (-47.8; 44.6)

Definition of abbreviations: 6MWD: 6-minute walk distance; 30sec-STS: 30-second sit-to-stand test; CAT: COPD Assessment Test; CCQ: COPD Clinical Questionnaire; HADS: Hospital Anxiety and Depression Scale; EQ5d-VAS: EuroQol 5-Dimension Questionnaire; PAL: Physical Activity Level; Data are mean difference (95% confidence interval); * p-value within group changes <0.05; ✝ p-value for group mean change differences <0.05.

[#]*Complete observations (n) used for the likelihood estimate from end of rehabilitation to baseline (total): 6MWD: (88);* 30sec-STS: (88); CAT: (89); HADS: (80); EQ5d-VAS: (89); CCQ: (89); PAL: (43).

[##]*Complete observations (n) used for the likelihood estimate from 22-weeks follow-up from baseline to baseline (total): 6MWD: (79);* 30sec-STS: (79); CAT: (86); HADS: (80); EQ5d-VAS: (85); CCQ: (86); PAL: (43).

Table S3. Within-group changes in primary and secondary outcomes in PTR and PR groups. Per protocol analysis

	Within-group changes from baseline (95% CI)			
	PTR (n=67)		PR (n=67)	
	End rehabilitation[###]	22-weeks from baseline[####]	End rehabilitation[###]	22-weeks from baseline[####]
Primary outcome				
6MWD, m	19.4 (8.5; 30.3)*	27.9 (10.2; 45.6)*	24.4 (12.4; 36.3)*	16.6 (-1.0; 33.8)
Secondary outcomes				
30sec-STS, reps	1.3 (0.5; 2.1)*	1.4 (0.3; 2.4)*	1.9 (1.0; 2.7)*	1.6 (0.6; 2.6)*
CAT, points	-1.5 (-2.7; -0.3)*	0.1 (-1.5; 1.8)	-0.3 (-1.6; 1.1)	-0.7 (-2.4; 1.1)
HADS				
Anxiety, points	-0.8 (-1.5; -0.1)*	-0.1 (-1.0; 0.7)	-0.2 (-1.0; 0.6)	-0.7 (-1.5; 0.2)
Depression, points	-0.2 (-0.9; 0.4)	1.0 (-0.1; 2.2)	0.2 (-0.5; 0.9)	0.7 (-0.5; 2.0)
EQ5D-VAS, points	4.6 (-0.2; 9.4)	4.0 (-1.0; 9.0)	4.9 (-0.3; 10.0)	5.9 (0.6; 11.1)*
CCQ				
Function, points	-0.2 (-0.4; 0.1)	0.1 (-0.2; 0.3)	-0.1 (-0.4; 0.1)	0.2 (-0.1; 0.5)
Mental, points	-0.3 (-0.6; 0.1)	0.1 (-0.3; 0.4)	-0.1 (-0.5; 0.2)	-0.1 (-0.5; 0.3)
Symptoms, points	-0.3 (-0.6; -0.1)*	-0.3 (-0.6; 0.1)	-0.1 (-0.4; 0.2)	-0.2 (-0.5; 0.1)
Total, points	-0.2 (-0.4; -0.1)*	0.0 (-0.2; 0.2)	-0.1 (-0.3; 0.1)	0.0 (-0.2; 0.2)
PAL				
Steps per day	-139 (-634; 329)	-188 (-712; 334)	-500 (-1063; -41)*	-748 (-1325; -171)*
Sedentary, minutes	15.3 (-14.1; 48.1)	9.1 (-22.4; 38.3)	9.3 (-22.3; 44.5)	27.1 (-9.1; 58.4)
Active, minutes	-15.3 (-48.1; 14.1)	-9.1 (-38.3; 22.4)	-9.3 (-44.5; 22.3)	-27.1 (-58.4; 9.19)

Definition of abbreviations: 6MWD: 6-minute walk distance; 30sec-STS: 30-second sit-to-stand test; CAT: COPD Assessment Test; CCQ: COPD Clinical Questionnaire; HADS: Hospital Anxiety and Depression Scale; EQ5d-VAS: EuroQol 5-Dimension Questionnaire; PAL: Physical Activity Level.

Data are mean difference (95% confidence interval). Estimates adjusted for baseline outcome measure. Estimates calculated for baseline measure equal to the mean baseline measure for study population.

* p-value within group changes <0.05; † p-value for group mean change differences <0.05.

[###]Complete observations (n) used for the likelihood estimate from end of rehabilitation to baseline (PTR/PR): 6MWD: (47/41); 30sec-STS: (47/42); CAT: (47/42); HADS: (43/37); EQ5d-VAS: (47/42); CCQ: (47/42); PAL: (24/19).

[####]Complete observations (n) used for the likelihood estimate from 22-weeks follow-up from baseline to baseline (PTR/PR): 6MWD: (38/41); 30sec-STS: (38/41); CAT: (45/41); HADS: (43/38); EQ5d-VAS: (44/41); CCQ: (45/41); PAL: (23/20).

Supplements S4. Admission and action diagnosis coding for respiratory-related hospital admissions.

Respiratory hospitalizations were defined based on admission with an action diagnosis DJ44 alone, or

DJ13, DJ14, DJ15, DJ16, DJ17, DJ18 or DJ96 but these must all include DJ44 as secondary diagnosis.

Supplements S5. hospital days and out-patient visits.

	PTR	PR
Hospital days per admission per patient All-cause, median [IQR]	2.3 [1.3; 3.4]	2.2 [1.1; 4.7]
Hospital days total admission per patient All-cause, median [IQR]	11.8 [3.4; 27.8]	5.2 [3.2; 13.8]
Hospital days per admission per patient Respiratory, median [IQR]	2.4 [1.6; 3.7]	2.5 [1.2; 5.2]
Hospital days total admission per patient Respiratory, median [IQR]	7.5 [3.1; 14.4]	5.2 [2.6; 10.0]
Out-patient visits 10-weeks from baseline, number	113	744
Out-patient visits 22-weeks from baseline, number	270	899

Table S6. Study blinding of patients, personnel and researchers according to the CONSORT recommendations for non-pharmacological trials

	Blinded to:			
	Study hypotheses and objectives	**Intervention details**	**Random assignment**	**Outcome measures**
Study participants	Yes	Partially[1]	Yes	Partially[3]
Hospital staff	Yes	Yes	Yes	Partially[2,3]
Blinded assessors	Yes	Yes	Yes	No
Intervention staff (PT, RN, MD, Dietician)	No	No	Yes	Yes
Researchers, steering committee	No	No	Yes	Partially[4]
Statistician	No	Yes	Yes	Partially[5]
Allocation senior manager	Yes	Yes	No	Yes

[1] Patients were aware of the existence of two interventions and the overall content as a mandatory requirement from the Ethics Committee.
[2] Health professionals taking care of the patients were blinded, except where a member of the research team was the physician of a patient involved and the patient revealed the intervention content. According to the physician (n=1), this situation happened in 0 (0%) patients.
[3] Outcome information was given to patients if they requested it and was sent to their physicians if patients requested. No information of the intervention or study objectives was included.
[4] Outcome information was available for mandatory audit. Available but blinded for allocation.
[5] Outcome information was not available until the analysis phase. Available but blinded for allocation.

Table S7. Study measures and outcomes to be collected

Variable	Baseline	10/12 weeks (post)	22-weeks from baseline
Primary outcomes			
6-min walk distance (6MWD)	X	X	X
Secondary outcomes			
30sec sit-to-stand test (30STS)	X	X	X
Clinical COPD Questionnaire (CCQ)	X	X	X
COPD Assessment Test (CAT)	X	X	X
Hospital Anxiety Depression Scale	X	X	X
EuroQol 5D (3-L)	X	X	X
24h-mobility (ActivePAL3tm; 5 days)	X	X	X
Other variables and outcomes		X	
Attendance of rehabilitation	X	X	X
Number of COPD-related hospital admissions	X	X	X
Number of COPD hospital days	X	X	X
COPD-related outpatient visits	X	X	X
Number of COPD exacerbations	X	X	X
Mortality		X	X
Descriptive variables			
Lung function	X		
FVC	X		
FEV1	X		
FEV1/FVC%	X		
FEV1% expected	X		
Charlson Comorbidity Index	X		
Anthropometric measures			
Gender	X		
Age	X		
Weight	X	X	X
Height	X	X	X
Body Mass Index (BMI)	X	X	X
Self-reported measures			
Smoking status	X	X	X
Pharmacologic treatment	X	X	X

Table S8. Anticipated power on secondary outcomes

Variables	Instrument	Subscales	Cronbach's alpha	Hypothesized Difference/ SD (anticipated power)
Muscle strength and endurance legs	30 seconds sit-to-stand test	Total number of repetitions	NR (not reported)	2.0/2.5 (0.99)
Symptoms	COPD Assessment Test (CAT)	Eight symptom questions (0-5 points) Total score 0-40 points	0.88	3.0/5.5 (0.88)
Disease-specific quality of life	Clinical COPD Questionnaire (CCQ)	Ten items, three domain scores (symptoms, functional and mental) and overall score. Items score ranges 0–6	Overall score 0.91 Symptom score 0.78 Functional score 0.89 Mental score 0.80	Overall score 0.4/1.1 (0.55)
Anxiety and depression	Hospital Anxiety and Depressions Scale (HADS)	HADS-A scale (0-21) HADS-D scale (0-21)	HADS-A 0.83 HADS-D 0.82	HADS-A 1.5/2.5 (0.93) HADS-D 1.5/2.5 (0.93)
Health-Related Quality of Life	EuroQol 5-Dimension Questionnaire (EQ-5D)	EQ5D-questionnaire (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) Norm based utility score (-0.624-1.000) EQ5D-VAS (0-100 millimeters)	Not relevant–only one question in each dimension	EQ5D-VAS 8/16 (0.82)
Physical activity	*active*PAL™ activity monitor (PAL Technologies Ltd., Glasgow, UK)	Steps per day Minutes lying/sitting Minutes standing/walking Number of body transitions per day	NR (not reported)	Steps per day 1100/2262 (0.50)

Table S9. Exercise content comparison group—conventional pulmonary rehabilitation

Exercise type	Exercises	Intensity	Progression
Warm-up (duration 5-10min)	Sitting or standing: -heel uprisings (uni- or bilateral), - knee extension - rear deltoid row - chest press movement - vertical shoulder press (uni- or bilateral). Standing: -walking various - leg curl - leg swing - squats	Non-specific intensity Purpose: -increase body temperature - cardiorespiratory warm-up -muscle and tendon tissue warm-up	none
Endurance training (duration 20-30min)	-Walking or -Cycle or - Treadmill or - Circuit training or - Activity games	Borg CR-10 dyspnea 4-7 Exercises performed in intervals or continuously	Every 2nd to 4th week load adjustment individualized
Resistance training Duration 20-30min)	Machine: -leg press -knee extension Pull down and/or chestpress (vertical) Other equipment for strength circuit training elastic band dumbbells weight cuff	40-80% of 1RM corresponding to 8-25 repetitions 2-3 sets	Every 2nd to 4th week load adjustment individualized (repetition counting by supervisor)
Cool-down (duration 5-10min)	Breathing exercises Pursed lip breathing Relaxation exercises Yoga exercises	Non-specific intensity	Non-specific

Health professional responsible: Physiotherapist
Monitoring of intensity may vary, but it is expected that hospitals use either objective (pulse or Watt monitoring) or subjective (CR Borg scale for dyspnea) measurements for intensity monitoring.
Resistance training will be evaluated for progression by counting the maximum repetitions and estimating a new optional weight/resistance within 8-25 repetitions.
Workout logs from every training session are recommended to be registered by the authorization law.

Table S10. Patient education topics control group—conventional pulmonary rehabilitation	
Topics/themes	**Communication/ learning form**
• COPD and the treatment • The importance of smoking cessation • The importance of daily activity and exercise • The importance of nutrition • Medication and use of devices and inhalation techniques • Early signs of exacerbation and action plan • Use of nebulizer apparatus and oxygen apparatus. Individual smoking cessation and dietary advice will be offered to the individual COPD patient if assessed relevant.	Topics are promoted as a combination of • Information • Dialog • Reflection exercises • Practical exercises • Focusing on increasing the individual's self-competence • Networking and exchange of experience.
Health professional responsible: Respiratory nurse	

Table S11. Warm-up protocol—pulmonary tele-rehabilitation

Time	Exercises	Intensity	Progression
Warm-up (duration 5min)	Sitting or standing: -heel uprisings (uni- or bilateral), - knee extension - rear deltoid row - chest press movement - vertical shoulder press (uni- or bilateral). Standing: -Walking on site - side to side walking - leg curl - leg swing - squats	Non-specific intensity Purpose: -increase body temperature - cardiorespiratory warm-up -muscle and tendon tissue warm-up	none

Table S12. Exercise protocol intervention group pulmonary tele-rehabilitation (Chronological order)

Exercise #	Exercise name	Extremities	Uni/bilateral execution	Body position	Time/volume	Exercise load
1	Sit-to-stand	Lower extremities	Bilateral	Sitting and standing	Active: 80-160sec. Rest:160-80sec. Total: 240sec.	Bodyweight and dumbbells
2	Biceps curl - shoulder press	Upper extremities	Bilateral	Standing	Active: 80-160sec. Rest:160-80sec. Total: 240sec.	Dumbbells
3	Step-up	Lower extremities	Bilateral	Standing	Active: 80-160sec. Rest:160-80sec. Total: 240sec.	Bodyweight, dumbbells and stepbox
4	Bent Over Rowing	Upper extremities	Unilateral	Standing Upper body bent slightly forward	Active: 80-160sec. Rest:160-80sec. Total: 240sec.	Dumbbells
5	Static-dynamic Squat	Lower extremities	Bilateral	Standing	Active: 80-160sec. Rest:160-80sec. Total: 240sec.	Bodyweight and dumbbells
6	Front Raise Dumbbells	Upper extremities	Bilateral	Standing	Active: 80-160sec. Rest:160-80sec. Total: 240sec.	Dumbbells

Table S13. Progression model—intervention group pulmonary tele-rehabilitation (Chronological order)

Phase	Week number	Working volume in seconds	Rest volume in seconds	Number of sets for each exercise
Familiarization	1-2	20	40	4
Progression 1	3-6	30	30	4
Progression 2	7-10	40	20	4

Table S14. Patient education protocol—intervention group pulmonary tele-rehabilitation

Topic/themes	Communication/ learning form	Week	Duration	Number of sessions
Welcome and individual presentation	Information, dialog	1	20min	3
COPD and the treatment	Information, dialog	2	20min	3
Early signs of exacerbation and action plan	Information, dialog, reflection	3	20min	3
Medication and use of devices and inhalation techniques. Use of nebulizer apparatus and oxygen apparatus.	Information, dialog, reflection, practical exercises	4	20min	3
Physical activity and exercise	Information, dialog, reflection	5	20min	3
Food, importance of food in COPD	Information, dialog, reflection, practical exercises	6	20min	3
Smoking, cessation, substitution	Information, dialog, reflection	7	20min	3
Anxiety management, relaxation	Information, dialog, reflection, practical exercises	8	20min	3
Repetition		9	20min	3
Group needs		10	20min	3

Table S15 Assessment procedures at baseline, post-rehab and at 22-weeks' follow up

Assessment and progression procedure
1. Subject history/introduction, while seated: resting blood pressure, resting heart rate, resting SpO_2, resting dyspnea. Standing: anthropometric measures (weight and height), (until 30 minutes)
2. Instruction and performing 6MWT, end-heart rate, end-SpO_2, end-dyspnea (10 minutes)
3. Seated rest (5 minutes)
4. Instruction and performing 30sec-STS (5 minutes)
5. Four questionnaires: completion order CAT, CCQ, HADS, EQ5D-3L, quiet room no interference (30 minutes)
6. Seated: resting blood pressure, resting heart rate, resting SpO_2, resting dyspnea (5 minutes)
7. Instruction and performing 6MWT, end-heart rate, end-SpO_2, end-dyspnea (10 minutes)
8. Seated rest for (5 minutes)
9. Instruction and performing 30sec-STS (5 minutes)
10. Assessment session completed. Total time 145 minutes.

Abbreviations: SpO_2, arterial oxygen saturation as measured by pulse oximetry (%); dyspnea, perceived dyspnea (Borg cr-10); 6MWT, six-minute walk test; 30sec-STS, 30 seconds sit-to-stand test (repetitions); end-, immediately measure after test completion; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; HADS-A and P, Hospital Anxiety and Depressions Scale (HADS); EQ-5D-3L, EuroQol 5-Dimension 3-likert utility score and VAS score.

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