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

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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).

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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

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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.

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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

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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**.**

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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.

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Figure S1. Pictures of technical and exercise equipment

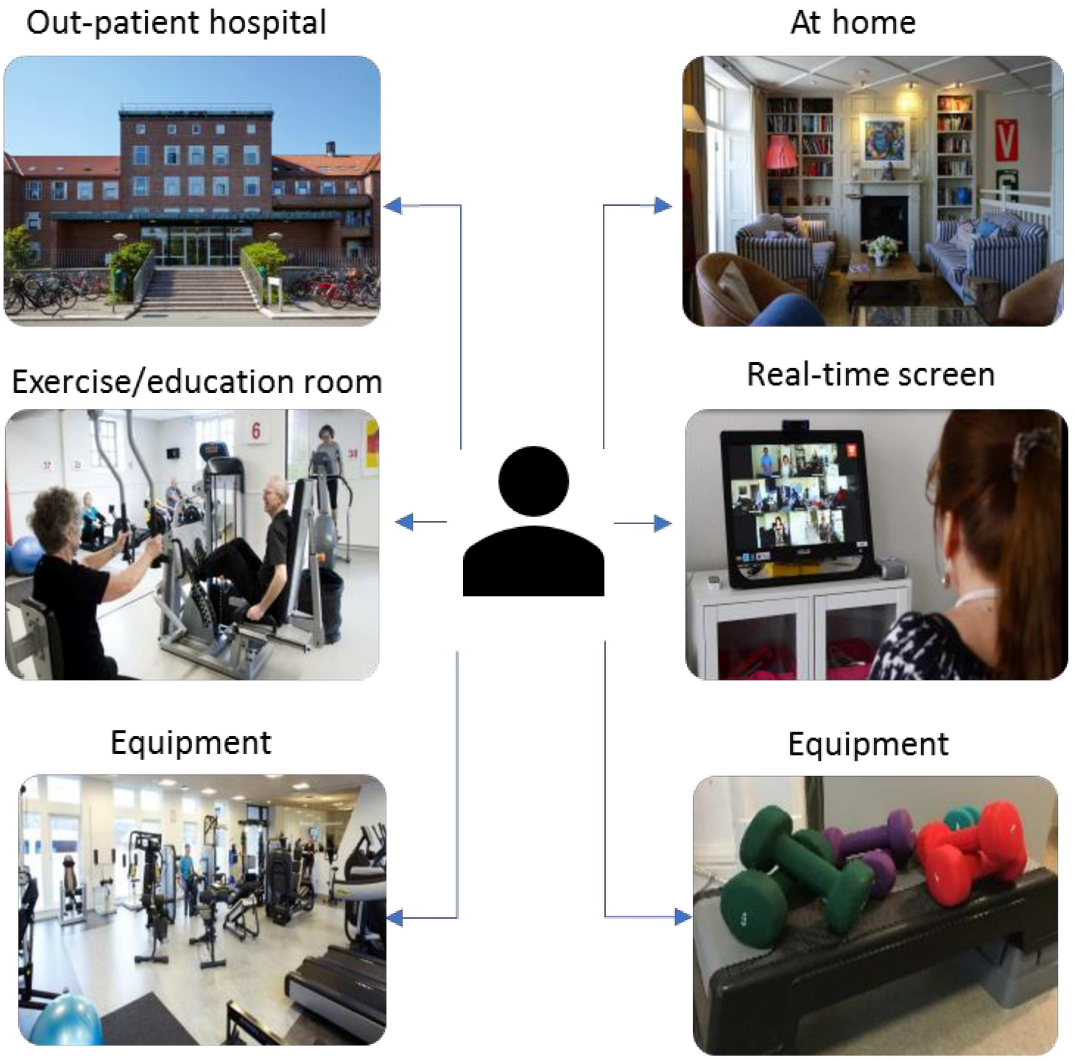

Table S2. Between-group differences in primary and secondary outcomes in PTR and PR groups. Per protocol analysis

	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).

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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).

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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

Hansen H, *et al. Thorax* 2020; 75:413–421. doi: 10.1136/thoraxjnl-2019-214246

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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