American Journal of Physical Medicine & Rehabilitation Articles Ahead of Print
DOI: 10.1097/PHM.0000000000002441

An Educational, Exercise and Occupational Therapy-Based Telerehabilitation Program versus 'Wait-and-See' for Improving Self-Perceived Exertion in Patients with post-COVID Fatigue and Dyspnea: A Randomized Clinical Trial

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Study Registration: This study was prospectively registered at https://clinicaltrials.gov (NCT05121688).

Disclosures

Conflicts of Interest: The authors declare no conflict of interest.

Funding: This research received no funding.

Informed Consent Statement: Written informed consent was obtained from all subjects involved in the study.

Ethical Statement: The protocol described in this research was supervised and approved by the local Ethics Committee of Hospital Clínico San Carlos (21/734-EC_X)

Author Contributions: Conceptualization, J.C.-P., M.J.D.-A. and G.P.-M.; methodology, all authors; investigation, all authors; resources, J.C.-P. and M.I.G.-V.; data curation, J.A.V.-C.; writing—original draft preparation, J.A.V-C; C.F.d.l.P; writing-review and editing, all authors; visualization, all authors; supervision, M.J.D.-A. and G.P.-M.; project administration, J.C.-P.; funding acquisition, J.C.-P.. All authors have read and agreed to the published version of the manuscript.

Registration: The study protocol was prospectively registered in the ClinicalTrials.gov International Registry (Identification Number: NCT05121688).

Data Availability: The data that support the findings of this study are available on request from the corresponding author.

JosÃ© Calvo-Paniagua is in training.

Abstract

Objective: To compare the effectiveness of a tele-rehabilitation exercise program versus 'wait-and-see' on physical exertion, quality of life, dyspnea severity, heart rate and oxygen saturation in patients with post-COVID fatigue and dyspnea.

Design: Sixty-four patients were enrolled in this randomized clinical trial. A tele-rehabilitation program based on patient education, physical activity, airway clearing, and breathing exercise interventions was conducted. Self-perceived physical exertion during daily living activities, dyspnea severity, health-related quality of life and physiological outcomes and the 6-minute walking test (6MWT) were assessed at baseline, after the program and at 1- and 3-months follow-up periods.

Results: The experimental group experienced greater improvements in self-perceived physical exertion during daily living activities, dyspnea severity, health-related quality of life and 6MWT (all, $p<0.001$). Additionally, patients undergoing the tele-rehabilitation program reported lower exertion scores at rest and after the 6MWT (both, $p<0.001$). Between-group oxygen saturation differences were found at rest ($p<0.001$), but not after the 6MWT ($p=0.024$). Finally, significant between-group differences were found for heart rate after the 6MWT ($p<0.001$).

Conclusion: Although both groups showed a significant improvement after 3 months of follow-up, the group receiving the tele-rehabilitation program described a greater improvement compared with the group receiving no intervention.

Keywords: COVID-19; Physical Exertion; Physiotherapy; Primary Care

What is known

Previous research demonstrated the efficacy of tele-rehabilitation programs compared with no treatment or usual care and observed the superiority of telerehabilitation strategies for improving dyspnea, lower limb muscle strength, ambulation capacity or depressive symptoms.

What is new

Although the applied telerehabilitation intervention was previously tested in a previous quasi-experimental study, this study included patients with long-lasting symptoms (>12 months) and a control group to analyze the symptoms natural course. This tele-rehabilitation program had greater improvements on perceived physical exertion, oxygen saturation, dyspnea severity, quality of life and physical conditioning compared with no intervention.

Introduction

From the end of 2019 until June 2023, more than 760 million subjects worldwide have been infected by the SARS-CoV-2[1]. The acute manifestations of COVID-19 affect different systems in the body, including the pulmonary, cardiovascular, neurologic, hematologic and gastrointestinal systems[2]. However, recent research has focused on the post-acute phase, referred to as acute post-COVID (2- 5 weeks after onset), long post-COVID (12 to 24 weeks after onset) and persistent post-COVID (>24 weeks after onset)[3,4], as a significant number of individuals who have had survived to COVID-19 continue to experience health issues and complications even after the acute phase has passed[5,6].

Up to 60% of COVID-19 survivors who were previously hospitalized due to SARS-CoV-2 infection experience symptoms such as fatigue, shortness of breath, cognitive difficulties, muscle weakness, joint pain, chest pain, or gastrointestinal disturbances the following months after the infection[7,8]. Among this plethora of symptoms[9], fatigue and dyspnea are reported as the most common post-COVID symptoms, reaching a prevalence about 32% and 25% respectively 3-to-6 months after the onset, 36% and 25% 6-to-9 months, 37% and 21% 9-to-12 months and 41% and 31% >12 months[10].

Tele-rehabilitation strategies have been shown to be effective for improving post-COVID symptoms in COVID-19 survivors[11-13] while reducing the economic burden as a high number of patients can be reached in primary health care[14,15]. A recent study assessed the effectiveness of a tele-rehabilitation program for improving physical exertion, quality of life and physiological variables[16]. However, this study did not include a control group for ethical reasons as patients were recruited during the COVID-19 outbreak and, therefore, there is a potential risk of bias (i.e., changes observed may not be totally attributable to the program,

having the natural course of the disease a direct impact on these changes). Furthermore, participants included in this previous study were in the acute post-COVID stage[16], but, as the number of infections has decreased in the last year, therapeutic strategies should be now tested on patients with long-lasting post-COVID symptoms.

A meta-analysis investigated the efficacy of tele-rehabilitation programs compared with no treatment or usual care and observed the superiority of telerehabilitation strategies for dyspnea (moderate-quality evidence), lower limb muscle strength (moderate-quality evidence), ambulation capacity (moderate-quality evidence) or depressive symptom (very low-quality evidence); however, no evidence found tele-rehabilitation to be superior to usual care for improving anxiety or quality of life[17].

Accordingly, the aim of this randomized clinical trial was to compare the effects of a tele-rehabilitation primary health program based on exercise versus no intervention ('wait-and-see' with conventional medical care recommendations) on quality of life, self-sufficiency, fatigue and dyspnea in persistent patients with long-COVID and to compare the score of these exertion metrics at a 3-months follow-up.

Methods

Study Design

A prospective, multicenter, randomized clinical trial with two parallel groups was conducted between November 2021 and May 2022. The protocol was developed by four Primary Health Care centers in Madrid (Spain) listed in the GAAP (Gerencia Asistencial de Atención Primaria). All procedures considered the rights of the participants, and the protocol

of this study was supervised and approved by the local Ethics Committee of Hospital Clínico San Carlos (21/734-EC_X).

The trial was conducted following the Consolidated Standards of Reporting Trials (CONSORT)[18] (see supplementary content, http://links.lww.com/PHM/C304) and the Enhancing the QUAlity and Transparency of health Research (EQUATOR)[19] guidelines. The study protocol was prospectively registered in the ClinicalTrials.gov International Registry (Identification Number: NCT05121688). Once all the participants signed the written informed consent, the group allocation was conducted using the online random allocation website www.randomizer.org.

Participants

Patients who had survived from SARS-CoV-2 infection (confirmed by a positive nasopharyngeal or throat swab) presenting respiratory post-COVID symptoms and linked to one of the four GAAP centers participating in this study were screened for eligibility. To be included, they should be aged between 25 and 70 years old and present moderate respiratory and/or functional impairments starting after the acute SARS-CoV-2 infection, at least 93% of oxygen saturation by pulse oximetry at rest on room air and owning a smart phone, tablet, or computer to access on-line sessions. Exclusion criteria included: 1, reporting other post-COVID symptoms different from fatigue and dyspnea requiring particular medical attention (e.g., diarrhea, vomiting, anosmia or ageusia); 2, presence of multimorbidity (diagnosis of >2 diseases e.g., diabetes, dyslipidemia, cardiovascular diseases, osteoarthritis, respiratory diseases, digestive diseases, or tumors); 3, previous history of ischemic heart disease, lung failure, lung cancer, cystic fibrosis, pulmonary fibrosis, chronic kidney failure, liver diseases, myocardial arrhythmias, deep vein thrombosis, severe aortic stenosis or liver diseases; 4,

immune system disease; 5, cognitive problems; 6, active bleeding, or, 7, any other condition associated with physical exertion.

Sample size calculation

For detecting between-groups differences (2 groups) and within groups (4 follow-up measurements), an a priori analysis was conducted by running an ANOVA with repeated measures test using the G*Power v.3.1. The input parameters were set at α=0.05, β=0.05 (95% power). According to the criteria established by Cohen[20], an effect size of moderate magnitude (0.25) was fixed as is required to detect clinically relevant differences. This calculation led to a minimum sample size of 36 participants (n=18 per group). Since a follow-up period of three months was planned, an additional 10% was considered for potential losses. Therefore, for ensuring appropriate statistical power, the participation of at least 40 participants was required.

Tele-rehabilitation program

The experimental group received a tele-rehabilitation protocol detailed and tested in a previous study[16] and implemented by videoconference using Zoom (Zoom Video Communications, Inc). Although the control group did not receive this intervention (in order to understand the natural progression of the post-COVID fatigue and dyspnea), this treatment was offered to all patients once the study was completed. The 7-week program consisted of 18 sessions (40 minutes per session) in alternate days. It was structured on sanitary education sessions (basic concepts of anatomy, physiology, primary COVID-19 prevention, use of facemasks and social distance, smoking cessation, weight control, nutrition, and active attitudes), respiratory therapy, physical conditioning with aerobic exercise, active mobilizations and motor control exercises. In this program, physiotherapists conducted the

theoretical sessions, the breathing exercises, the functional exercises and the physical conditioning and body balance training while occupational therapists focused on exercises for daily living activities. The schedule and intervention details are available in Supplementary Materials, http://links.lww.com/PHM/C305.

Primary outcome: Perceived physical exertion

The level of physical exertion experienced by the participants during their daily activities was evaluated using the Modified Borg Dyspnea Scale (MBDS) before and after the intervention, and at 1- and 3- months after. This scale is a valid tool for assessing breathlessness in people with respiratory conditions[21]. The participants were asked to rate their perceived exertion on a vertical scale from 0 to 10, where each number was linked to a verbal expression indicating the intensity of breathlessness experienced during daily tasks[21].

Secondary outcomes

Dyspnea severity

The severity of dyspnea was evaluated before and after the intervention, and at 1- and 3- months after by using the modified Medical Research Council (mMRC) scale, which is widely recognized and validated scale for assessing breathlessness during daily activities in people with chronic respiratory conditions[22]. Participants were categorized into different grades based on their level of dyspnea. Grade 0 indicates being breathless only with strenuous exercise; Grade 1 represents experiencing shortness of breath while hurrying on level ground or walking uphill; Grade 2 denotes walking slower than peers of the same age on level ground and experiencing breathlessness or the need to stop; Grade 3 indicates needing to stop to catch their breath after walking for a few minutes on level ground; and,

Grade 4 refers to being too breathless to leave the house or carry out non-strenuous activities like dressing or undressing[22].

Quality of life

Health-related quality of life was assessed by using the St George's Respiratory Questionnaire (SGRQ). A questionnaire designed for patients with asthma and chronic obstructive pulmonary disease, the SGRQ consists of 50 items that are categorized into three domains: symptoms, activity limitations, and psychosocial impact[23]. The final score on the questionnaire ranges from 0 (the best health status) to 100 (the poorest health status)[23]. Measurements were taken before and after the intervention, and at 1- and 3- months after.

Endurance capacity

To assess the impact of physical exertion on various parameters, the 6-Minute Walking Test (6MWT) was used[24]. Participants were instructed to walk for a duration of 6 minutes in a flat, long, and covered corridor (approximately 30 meters in length) that was marked at each meter to facilitate distance measurements[24], indicating the level of exertion before and after the test (using the MBDS). The objective of the test was that participants covered the greatest possible distance within the given time frame of 6min[24]. Meanwhile, oxygen (O_2) saturation and heart rate were registered every minute by using a pulse oximeter NANOXμ® for measuring oxygen saturation and an OMRON M3® device for measuring heart rate.

Statistical Analysis

All statistical analyses were conducted with in the SPSS Statistics software v.25 (IBM Corporation, Armonk, NY, USA). Normal data distribution was verified using the Saphiro-

Wilk test and histograms and Levene tests were used for variance homogeneity. Continuous variables were reported providing central tendency and dispersion data for group scores and mean differences with 95% Confidence Interval (95% CI) and p values for reporting between-groups baseline difference. Categorical data were reported as frequency and percentage for each group. Between-group comparisons were calculated using Chi-Square tests.

Between-group differences were assessed by using multivariate lineal general models including the outcomes as dependent variables and group (experimental and control) and measurement time (baseline, after intervention, 1 month and 3 months after) as fix factors. As multiple comparisons were calculated, post-hoc tests were run (time* group) by using the Bonferroni correction with baseline scores as covariates. The effect size was estimated using the η_p^2 (a score of 0.01 was considered small, 0.06 medium and 0.14 large). P values were assumed to be significant at <0.00625 (0.05/8).

Results

Participant flow chart recommended by the CONSORT guidelines is illustrated in **Figure 1**. Initially, 67 volunteers were screened for eligibility; however, three participants were excluded since they had <93% of oxygen saturation at rest at baseline. Finally, none of the participants withdrawn during the study and therefore 64 patients were analyzed (**Figure 1**). The mean duration of long-COVID symptoms of the total sample was 14.8 ± 1.7 months after the infection (14.8±1.5 experimental group vs. 14.8±1.9 control group). **Table 1** summarizes the sociodemographic characteristics of both groups.

Table 2 provides self-perceived physical exertion during daily living activities, dyspnoea severity, and quality of life data. At baseline, both groups were comparable for all these clinical indicators (all, p>0.05). The lineal general model revealed significant group * time interactions for MBDS (F=391.371, p<0.001, η^2_p=0.826), mMRC scale (F= 58.821, p<0.001, η^2_p=0.416) and the SGRQ **(**F=103.063, p<0.001, η^2_p=0.555): patients with long-COVID assigned to telerehabilitation program reported higher improvements in all outcomes at all follow-ups than those assigned to the control group (**Table 2**).

Table 3 summarizes the perceived exertion changes during the 6MWT. At baseline, both groups showed comparable exertion scores before and after the 6MWT and also for the change before/after (all, p>0.05). The lineal general model showed a significant group * time interaction for perceived exertion before (F=248.532, p<0.001, η^2_p=0.750) and after (F=107.446, p<0.001, η^2_p=0.565) the 6MWT but no differences for changes between rest and exertion (F=2.779, p=0.042, η^2_p=0.033). Individuals with long-COVID assigned to the telerehabilitation program reported decreased perceived exertion at rest and after the 6MWT than those who did not receive the telerehabilitation program as shown in **Table 3**.

The lineal general model revealed no significant group*time interaction in heart rate at rest (F=3.627, p=0.014, η^2_p=0.042), but significant interactions after the 6MWT (F=24.700, p<0.001, η^2_p=0.230) and for the change score (F=7.294, p<0.001, η^2_p=0.081). After the 6MWT test, the experimental group experienced significantly higher heart rate values in comparison with controls (**Table 3**).

Regarding the O_2 saturation, the experimental group had a worst baseline score (p<0.001) at rest, but similar after the 6MWT (p=0.86). The lineal general model revealed

showed time*group interactions for O_2 saturation before (F=11.441, p<0.001, η^2_p=0.122) and in the change score between before/after (F=12.881, p<0.001, η^2_p=0.135) but not after (F=3.186, p=0.025, η^2_p=0.037) the 6MWT (**Table 4)**. Between-groups differences in O_2 saturation were significant after the 6MWT in favor of the experimental group, but results were comparable during the follow-up. The O_2 saturation and heart rate every minute during the 6MWT is illustrated in **Figure 2** for the experimental group and **Figure 3** for the control group.

Finally, the distance walked during the 6MWT is detailed in **Table 4**. Both groups walked a similar distance at baseline (p=0.614). The lineal general model revealed a significant time*group interaction (F=10.708, p<0.001, η^2_p=0.115): the experimental group significantly increased the distance walked compared with the control group (**Table 4**).

Discussion

This clinical trial contrasted the benefits of a 7-week tele-rehabilitation exercise program for improving physical exertion symptoms in patients with long-COVID fatigue and dyspnea versus a cohort who did not receive any intervention. No adverse events were reported during the study. Fatigue is probably the most common post-COVID symptom and is hypothesized to be attributed to brain glymphatic system dysfunctions (causing cerebrospinal fluid congestion and therefore toxic build-up in the central nervous system) and local processes of inflammation of myofibers and neuromuscular junctions and mitochondrial dysfunctions[25].

On the other hand, dyspnea (closely associated with fatigue as reported in network analyses)[26] is suggested to be the consequence from substantial pulmonary injuries caused by

viral replication, endothelial cell dysfunction, immune responses and micro-vessel damage[25]. However, recent hypotheses suggest a potential role of brain glymphatic system dysfunction among other mechanisms, warranting a more cautious, exploratory framing of these theories. Notably, fatigue in cases of minor post-COVID severity appears less directly linked to pulmonary injuries[27]. The use of Cardiopulmonary Exercise Testing (CPET) emerges as a vital tool for differential diagnosis. CPET can identify distinct patterns of limitations in patients, informing targeted therapies and rehabilitation strategies. Moreover, the assessment of dysfunctional breathing and deconditioning is critical in evaluating post-COVID-19 patients. These factors help distinguish between dysfunctional syndromes and organic diseases, underscoring the importance of dynamic, rather than static, investigations in understanding and managing post-COVID-19 conditions[28].

Although the applied telerehabilitation intervention was described and tested in a previous quasi-experimental study[16], there are two important differences between both studies. First, the participants of this study were patients with long-lasting symptoms >12 months after the onset while the previous quasi-experimental study included patients with symptoms 3 months after the infection. Although the clinical course of long-COVID is unclear, fatigue is the only symptom which its prevalence increases over the months (from 35–57% at 2-3 months after the onset to 44-63% at 6-12 months after the infection[25].

Second, this trial included a control group to analyze whether the natural course of the symptoms may influence the results of this quasi-experimental study[16]. In fact, the results obtained in this study revealed that patients who did not receive any intervention improved significantly the perceived exertion during daily living activities and after walking after one month, dyspnea after one month and quality of life after 3 months (attributable to the natural

course of the post-COVID dyspnea and fatigue). In addition, we found these participants to develop cardiovascular adaptations during the follow-up decreasing their heart rate at rest and after a physical demand and increasing their oxygen saturation after walking. However, it should be noted that even if the natural course is relatively favorable, the tele-rehabilitation program resulted in better perceived exertion, dyspnea severity and quality of life and also had a favorable effect on the distance walked in a 6-minute time-lapse (while the control group did not improve the distance walked) as support the statistically significant differences found in this study.

Although heart rate data at rest and after the physical demand were provided and analyzed, the heart rate change is the metric which should be consider for interpreting the sample adaptations to submaximal exercise (e.g., lower differences indicate greater cardiovascular efficiency and better physical condition). Heart rate changes comparison during the intervention are substantially different in this study compared with the quasi-experimental study[16]. While patients with post-COVID symptoms of less than 3 months of duration showed a significant heart rate reduction at rest after the intervention and during the follow up, the sample of patients with long-lasting symptoms longer than 12 months of duration included in this study showed no significant changes. It should be noted that experience a higher heart rate during submaximal exercise cannot be interpreted negatively (as it is a normal body response to effort), but a very high heart rate may indicate that the exercise is too intense for their current fitness level[29]. However, the oxygen saturation increased significantly after the intervention and during the follow-up. These findings could be attributed to the fatigue and dyspnea severity differences between both samples (at baseline and during the studies).

Based on the results obtained in this clinical trial, the implementation of this tele-rehabilitation program could be recommended for improving the natural course of post-COVID fatigue and dyspnea as large effect sizes were obtained in the experimental group. In addition to the clinical improvements, this intervention has several advantages such as the feasibility to manage and follow a larger number of patients and its cost-effectiveness in comparison with traditional face-to-face strategies[12-16]. Although to the authors' knowledge no previous studies assessing similar samples with post-COVID fatigue reported the minimal clinically important difference (MCID) for the outcomes analyzed in this study, other articles including samples with different conditions (e.g., asthma and chronic obstructive pulmonary disease) and similar baseline conditions reported these metrics. For instance, the MCIDs of O_2 saturation, mMRC, distance walked in the 6MWT and SGRQ reported for samples with asthma and baseline scores of 94.0%, 1.0 points, 450m and 50 points respectively were 1.5%, 0.6 points, 26m and 10.3 points[30-32]. The MCID cut-off proposed for the mMRC and Borg scale at submaximal exercise capacity was stated in a recent review and were established between -0.5 and -1.0 points and -1 point, respectively[33].

Although the current clinical trial overcome previous limitations in comparison with the quasi-experimental study[16], it also has some potential limitations. First, this therapeutic approach is designed for patients with mild-to-moderate post-COVID fatigue and dyspnea. Thus, caution with patients reporting moderate-to-severe symptoms (i.e., respiratory distress with respiratory rate>30, O_2 saturation<93% or PaO_2/FiO_2<300 mm Hg) which approximately represent 20% of individuals suffering from long-COVID[34], is encouraged as these patients require hospitalization and monitoring[35]. Secondly, even if tele-rehabilitation strategies are cost-effective when compared with face-to-face interventions, further research comparing both interventions to clarify the impact of both alternatives on the natural course

of the disease is clearly needed[36]. In addition, the results of this clinical trial can be potentially biased as no control on essential aspects of the intervention such as the intensity of the aerobic exercise or a correct performance of motor control exercises was conducted.

Conclusion

This clinical trial found that patients with post-COVID fatigue and dyspnea who received a tele-rehabilitation program had greater improvements on perceived physical exertion at rest and after physical activity, oxygen saturation at rest and after walking, dyspnea severity, quality of life and distance walked in a 6-minute time-lapse compared with no intervention. No significant changes in heart rate were observed. Importantly, we also found a favorable clinical course of patients with post-COVID fatigue and dyspnea if no interventions are applied since perceived exertion at rest and after walking, dyspnea severity, quality of life and oxygen saturation improved 3 months after.

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Legends of Figures

Figure 1. CONSORT flowchart diagram.

Figure 2. Analysis of oxygen saturation (%) changes during the 6-Minute Walking Test for both groups (experimental and control groups) at baseline, after the intervention and during the follow-up periods (1 and 3 months).

Figure 3. Analysis of heart rate (beats per minute) changes during the 6-Minute Walking Test for both groups (experimental and control groups) at baseline, after the intervention and during the follow-up periods (1 and 3 months).

Figure 1

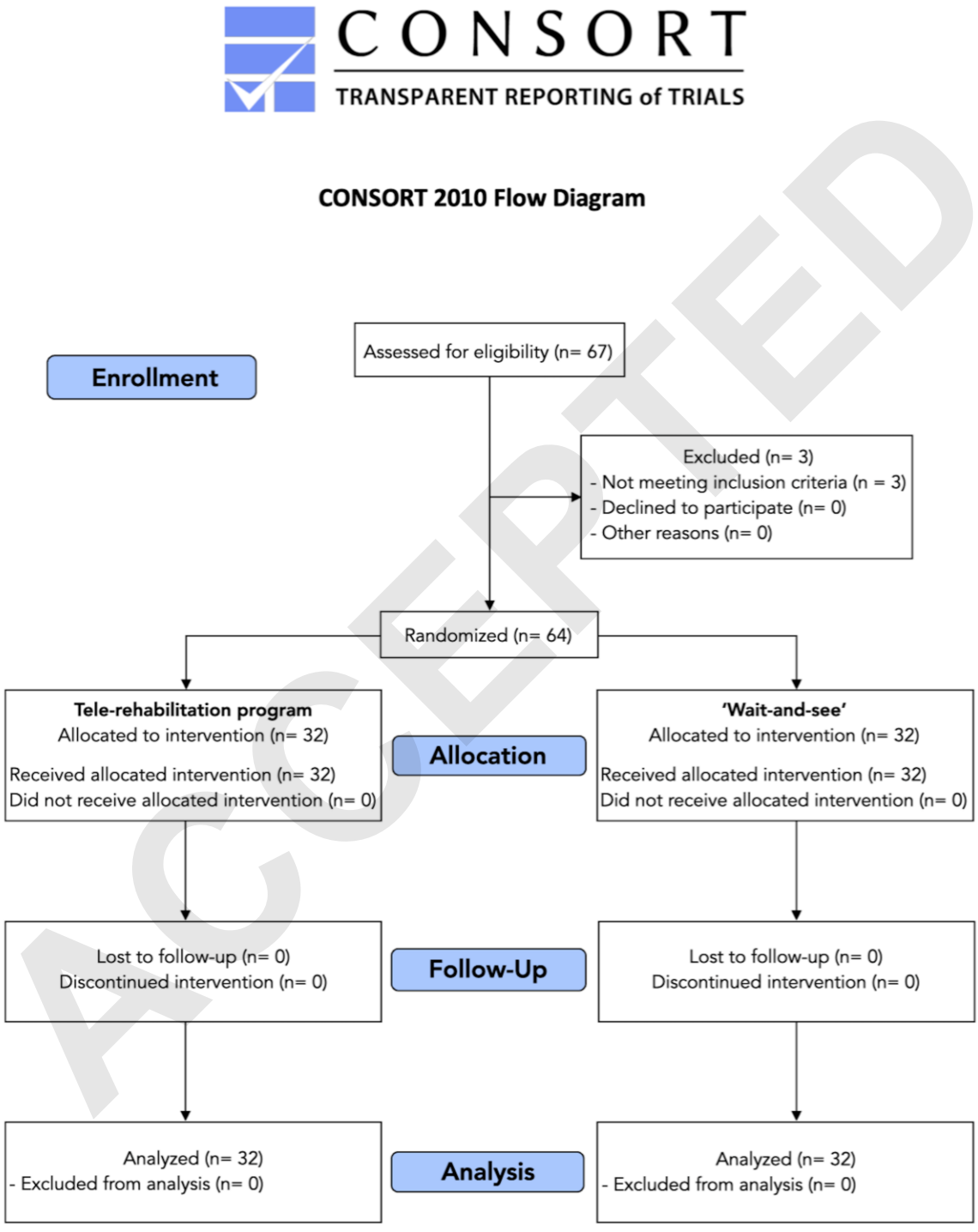

Figure 2

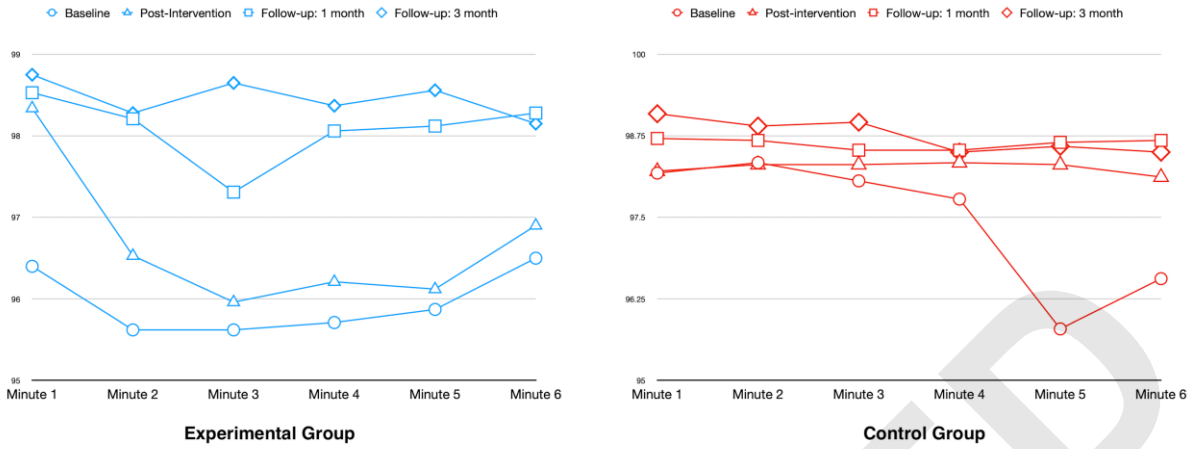

Figure 3

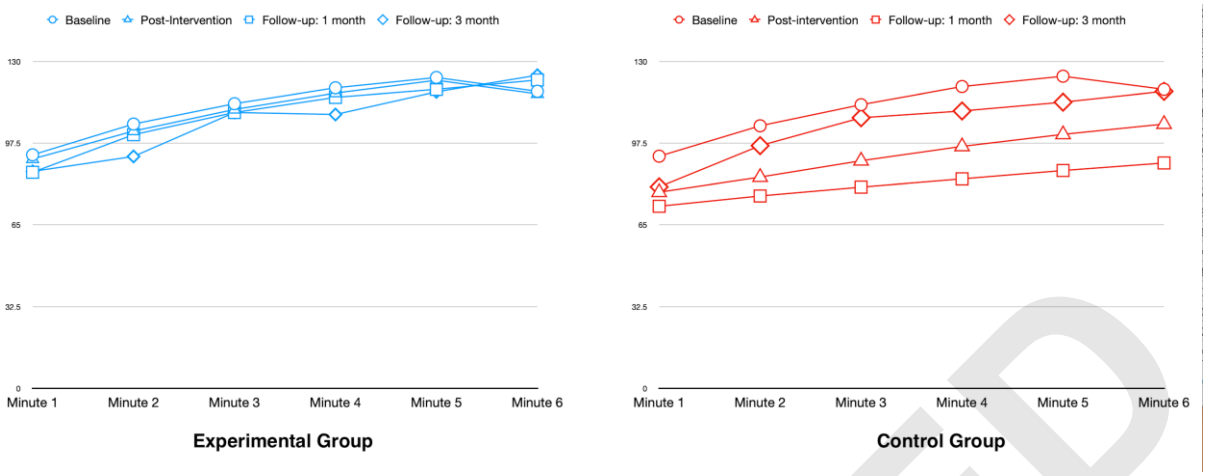

Table 1: Sociodemographic data of the sample at baseline (n=64)

	Experimental Group (n=32)	**Control Group (n=32)**	**Difference**
Age, mean ± SD, years	50.8 ± 8.4	49.4 ± 10.0	1.4 (-3.2; 6.0), p=0.554
Gender, male/female, n (%)	14 (43.8) / 18 (56.3)	10 (31.3) / 22 (68.8)	χ^2=1.067, p=0.302
Weight, mean ± SD, kg	80.9 ± 17.2	82.3 ± 17.3	1.4 (-7.3; 10.0), p=0.751
Height, mean ± SD, m	1.73 ± 0.09	1.71 ± 0.11	0.01 (-0.03; 0.06), p=0.588
Body Mass Index, mean ± SD, kg/m^2	27.0 ± 5.4	27.9 ± 5.7	1.0 (-1.8; 3.7), p=0.493
Smoking, yes/no, n (%)	4 (12.5) / 28 (87.5)	5 (15.6) / 27 (84.4)	χ^2=0.129, p=0.719

Table 2: Perceived physical exertion during daily living activities, dyspnea severity and health-related quality of life.

	Modified Borg Scale (0-10)		mMRC Scale (0-5)		SGRQ (0-100)	
	Experimental Group	Control Group	Experimental Group	Control Group	Experimental Group	Control Group
Baseline	7.9 ± 1.1	8.2 ± 0.8	2.6 ± 0.7	2.8 ± 0.6	62.7 ± 14.6	68.8 ± 9.5
Post-Intervention	0.3 ± 0.5	8.2 ± 0.7	0.2 ± 0.4	2.3 ± 0.5	11.7 ± 4.8	69.8 ± 9.6
1 Month After	0.1 ± 0.3	7.4 ± 0.6	0.2 ± 0.4	2.1 ± 0.5	9.8 ± 4.0	64.5 ± 9.6
3 Months After	0.0 ± 0.2	6.5 ± 1.0	0.0 ± 0.2	1.9 ± 0.5	8.1 ± 3.9	55.0 ± 11.4
	Within-Group Differences #					
Post-intervention	-7.6 (-8.1; -7.2) p<0.001	0.0 (-0.6; 0.5) p=0.999	-2.5 (-2.8; -2.2) p<0.001	-0.5 (-0.9; -0.2) p<0.001	-51.0 (-56.5; -45.6) p<0.001	1.0 (-6.1; 8.0) p=0.998
1 Month After	-7.8 (-8.2; -7.4) p<0.001	-0.8 (-1.4; -0.3) p<0.001	-2.5 (-2.8; -2.2) p<0.001	-0.8 (-1.1; -0.4) p<0.001	-52.9 (-58.4; -47.4) p<0.001	-4.4 (-11.5; 2.7) p=0.595
3 Months After	-7.9 (-8.3; -7.5) p<0.001	-1.8 (-2.3; -1.2) p<0.001	-2.6 (-2.9; -2.3) p<0.001	-0.9 (-1.2; -0.6) p<0.001	-54.6 (-60.0; -49.1) p<0.001	-13.9 (-21.0; -6.8) p<0.001

mMRC: Modified British Medical Research Council; SGRQ: Saint George's Respiratory Questionnaire
Compared with baseline scores

Table 3: Perceived exertion and heart rate during the 6-Minute Walking Test (6MWT)

	Perceived Exertion during the 6MWT					
	Experimental Group			**Control Group**		
	Pre-Test	Post-Test	Change	Pre-Test	Post-Test	Change
Baseline	7.6 ± 1.7	9.1 ± 0.7	1.6 ± 1.8	8.3 ± 0.8	9.1 ± 0.7	0.9 ± 0.9
Post-Intervention	0.3 ± 0.5	2.7 ± 1.5	2.3 ± 1.3	8.2 ± 0.7	8.8 ± 0.8	0.6 ± 0.8
1 Month After	0.1 ± 0.3	2.4 ± 1.5	2.3 ± 1.4	7.4 ± 0.6	7.8 ± 0.7	0.4 ± 0.9
3 Months After	0.0 ± 0.0	2.4 ± 1.5	2.4 ± 1.5	6.5 ± 1.0	7.5 ± 0.7	1.0 ± 1.0
	Within-Group Differences #					
Post-intervention	-7.3 (-7.9; -6.6) *	-6.5 (-7.4; -5.6) *	-0.8 (-1.8; 0.3)	-0.0 (-0.6; 0.5)	-0.3 (-0.8; 0.1)	-0.3 (-0.9; 0.3)
1 Month After	-7.5 (-8.1; -6.9) *	-6.8 (-7.7; -5.6) *	-0.7 (-1.7; 0.3)	-0.8 (-1.4; -0.3) *	-1.3 (-1.8; -0.8) *	-0.4 (-1.0; 0.2)
3 Months After	-7.6 (-8.2; -7.0) *	-6.8 (-7.7; -5.9) *	-0.8 (-1.8; 0.2)	-1.8 (-2.3; -1.2) *	-1.7 (-2.1; -1.2) *	0.1 (-0.5;0.7)
	Heart Rate during the 6MWT					
	Experimental Group			**Control Group**		
	Pre-Test	Post-Test	Change	Pre-Test	Post-Test	Change
Baseline	92.8 ± 15.6	118.1 ± 13.6	25.3 ± 17.5	92.4 ± 16.2	118.9 ± 11.8	26.5 ± 16.9
Post-Intervention	91.3 ± 16.8	117.1 ± 13.5	25.8 ± 16.7	78.0 ± 9.5	105.1 ± 14.3	27.1 ± 12.1
1 Month After	85.9 ± 13.9	122.6 ± 10.1	36.6 ± 17.6	72.4 ± 7.7	89.6 ± 12.2	17.2 ± 9.6
3 Months After	86.3 ± 13.4	124.5 ± 7.5	38.3 ± 15.2	80.1 ± 8.9	118.1 ± 7.6	38.1 ± 12.0
	Within-Group Differences #					
Post-intervention	-1.6 (-11.6; 8.5)	-1.0 (-8.8; 6.8)	0.6 (-10.7; 11.8)	-14.4 (-21.8; -7.0) *	-13.8 (-21.7; -5.9) *	0.6 (-8.1; 9.2)
1 Month	-6.9 (-17.0; 3.1)	4.4 (-3.3; 12.2)	11.3 (0.1; 22.6)	-20.0 (-27. 4; -12.5) *	-29.3 (-37.2; -21.4) *	-9.3 (-18.0; -1.2)
3 Months	-6.6 (-16.6; 3.4)	6.4 (-1.3; 14.2)	13.0 (1.8; 24.2)	-12.3 (-21.9; -2.7) *	-0.7 (-8.2; 6.7)	11.6 (0.9; 22.3)

* Statistical significance between groups (lineal general model, P<0.001)
# Compared with baseline scores

Table 4: Oxygen saturation and distance walked during the 6-Minute Walking Test (6MWT)

Oxigen saturation during the 6MWT						
	Experimental Group			Control Group		
	Pre-Test	Post-Test	Change	Pre-Test	Post-Test	Change
Baseline	96.4 ± 1.5	96.5 ± 1.4	0.1 ± 1.9	98.2 ± 1.1	96.6 ± 1.5	-1.6 ± 1.7
Post-Intervention	98.3 ± 0.9	96.9 ± 1.3	-1.4 ± 1.2	98.2 ± 1.2	98.1 ± 1.1	-0.1 ± 1.7
Follow-up: 1 Month	98.5 ± 0.9	98.3 ± 1.1	-0.3 ± 1.3	98.7 ± 0.6	98.7 ± 0.6	0.0 ± 0.7
Follow-up: 3 Months	98.8 ± 0.7	98.2 ± 0.8	-0.6 ± 1.2	99.1 ± 0.8	98.3 ± 0.8	-0.6 ± 1.1
	Within-Group Differences #					
Post-intervention	1.9 (1.2; 2.6) *	0.4 (-0.4; 1.2)	-1.5 (-2.5; -0.6) *	0.0 (-0.6; 0.7)	1.6 (0.9; 2.3) *	1.5 (0.6; 2.5) *
1 Month	2.1 (1.4; 2.8) *	1.8 (1.0; 2.6) *	-0.3 (-1.3;0.6)	0.5 (-0.1; 1.2)	2.1 (1.4; 2.8) *	1.6 (0.7; 2.5) *
3 Months	2.4 (1.6; 3.1) *	1.7 (0.9; 2.4) *	-0.7 (-1.7;0.3)	0.9 (0.2 ;1.5)	1.9 (1.1; 2.7) *	1.1 (0.2; 2.0)
Distance Walked (m) during the 6MWT						
	Experimental Group			Control Group		
Baseline	533.9 ± 95.6			546.7 ± 106.9		
Post-Intervention	660.4 ± 140.7			506.6 ± 94.7		
Follow-up: 1 Month	687.8 ± 145.9			513.3 ± 99.7		
Follow-up: 3 Months	710.1 ± 135.6			518.3 ± 87.2		
	Within-Group Differences #					
Post-intervention	126.5 (38.7; 214.3) *			-40.1 (-105.4; 25.1)		
1 Month	154.0 (66.2; 241.8) *			-33.4 (-98.7; 31.8)		
3 Months	176.2 (88.4; 264.0) *			-28.4 (-93.7; 36.8)		

* Statistical significance between groups (lineal general model, P<0.001)
# Compared with baseline scores