Minimal clinically important differences for patient-reported outcome measures of fatigue in patients with COPD after pulmonary rehabilitation.

Journal:	*CHEST*
Manuscript ID	CHEST-19-2122.R1
Article Type:	Original Research
Date Submitted by the Author:	n/a
Complete List of Authors:	Rebelo, Patricia; University of Aveiro, Lab 3R – Respiratory Research and Rehabilitation Laboratory, School of Health Sciences (ESSUA); University of Aveiro, iBiMED – Institute of Biomedicine, Department of Medical Sciences Oliveira, Ana; West Park Healthcare Centre, Respiratory Medicine; McMaster University, School of Rehabilitation Science; University of Aveiro, Lab3R – Respiratory Research and Rehabilitation Laboratory, School of Health Sciences (ESSUA); University of Aveiro, iBiMED – Institute of Biomedicine, Department of Medical Sciences Andrade, Lília; Centro Hospitalar do Baixo Vouga EPE, Pulmonology Department Valente, Carla; Centro Hospitalar do Baixo Vouga EPE, Pulmonology Department Marques, Alda; University of Aveiro, Lab 3R – Respiratory Research and Rehabilitation Laboratory, School of Health Sciences (ESSUA); University of Aveiro, iBiMED – Institute of Biomedicine, Department of Medical Sciences
Keywords:	EXERCISE, Interpretability, Outcome measurement, Health Status, Clinical decision-making

Abbreviations list

AECOPD – Acute exacerbation of Chronic Obstructive Pulmonary Disease

AUC – Area under the curve

CAT – COPD Assessment Test

CI – Confidence interval

CIS-FS – Checklist of individual strength fatigue subscale

COPD – Chronic Obstructive Pulmonary Disease

ES – Effect size

FACIT-FS – Functional assessment of chronic illness therapy fatigue subscale

GRC – Global Rating of Change Scale

LR – Likelihood ratio

MCID – Minimal clinically important difference

MDC – Minimal detectable change

PR – Pulmonary rehabilitation

PROM - Patient-reported outcome measure

ROC – Receiver operating characteristic

SD – Standard deviation

SEM – Standard error of measure

SGRQ – St. George's Respiratory Questionnaire

Text word count (max 2500): 3027
Abstract word count (max 250): 239
Running head (of 50 characters or less): Fatigue in COPD: quantifying improvement

Minimal clinically important differences for patient-reported outcome measures of fatigue in patients with COPD after pulmonary rehabilitation.

Patrícia Rebelo, MSc[1,2], Ana Oliveira, PhD[1-4], Lília Andrade[5], Carla Valente[5], Alda Marques, PhD[1,2]

[1]Lab3R – Respiratory Research and Rehabilitation Laboratory, School of Health Sciences, University of Aveiro (ESSUA), Aveiro, Portugal

[2]iBiMED – Institute of Biomedicine, Department of Medical Sciences, University of Aveiro, Aveiro, Portugal

[3]West Park Healthcare Centre, Toronto, ON, Canada

[4]School of Rehabilitation Science, McMaster University, Hamilton, ON, Canada

[5]Pulmonology Department, Centro Hospitalar do Baixo Vouga, Aveiro

Corresponding author information: Alda Marques, [1]Lab3R - Respiratory Research and Rehabilitation Laboratory, School of Health Sciences (ESSUA) and [2]Institute of Biomedicine (iBiMED), University of Aveiro, Agras do Crasto - Campus Universitário de Santiago, Edifício 30, 3810-193 Aveiro, Portugal
Tel +351 234372462
Email amarques@ua.pt

Conflict of interests' statement: The authors report no financial, or non-financial, conflicts of interest in this work.

Funding information: This work, was funded by Fundo Europeu de Desenvolvimento Regional (FEDER) - Comissão Diretiva do Programa Operacional Regional do Centro, by Fundação para a Ciência e Tecnologia - FCT (SAICT-POL/23926/2016, PTDC/DTP-PIC/2284/2014, PTDC/SAU-SER/28806/2017, UID/BIM/04501/2019) and by Programa Operacional Competitividade e Internacionalização (COMPETE), through COMPETE 2020 (POCI-01-0145-FEDER-016701, POCI-01-0145-FEDER-007628, POCI-01-0145-FEDER-028806).

Notation of prior abstract publication/presentation:

- European Respiratory Society (ERS) International Congress, 28th September – 2nd October 2019, Madrid, Spain
- World Confederation of Physical Therapy Congress, 10th -13th May 2019, Genève, Switzerland

ABSTRACT:

Background: Fatigue is a burdensome and prevailing symptom in patients with chronic obstructive pulmonary disease (COPD). Pulmonary rehabilitation (PR) improves fatigue however, interpreting when such improvement is clinically relevant is challenging. Minimal clinically important differences (MCIDs) for instruments assessing fatigue are warranted to better tailor PR and guide clinical decisions. We estimated MCIDs for the functional assessment of chronic illness therapy-fatigue subscale (FACIT-FS), the modified-FACIT-FS and the checklist of individual strength-fatigue subscale (CIS-FS), in patients with COPD after PR.

Methods: Data from patients with COPD who completed a 12-weeks community-based PR programme were used to compute the MCIDs. The pooled MCID was estimated by calculating the arithmetic weighted mean, resulting from the combination of anchor (weight-2/3) and distribution-based (weight-1/3) methods. Anchors were patients' and physiotherapists' global rating of change scale, COPD assessment test, St. George's respiratory questionnaire (SGRQ) and exacerbations. To estimate MCIDs we used mean change, receiver operating characteristic curves and linear regression analysis for anchor-based approaches, and 0.5*standard deviation, standard error of measurement (SEM),1.96*SEM and minimal detectable change for distribution-based approaches.

Results: Fifty-three patients with COPD (79%male, 68.4±7.6years, $FEV_1$48.7±17.4$_{\%predicted}$) were used in the analysis. Exacerbations, the SGRQ-impact and the SGRQ-total scores fulfilled the requirements to be used as anchors. Pooled MCIDs were 4.7 for FACIT-FS, 3.8 for the modified-FACIT-FS and 9.3 for the CIS-FS.

Conclusion: The MCIDs proposed in this study can be used by different stakeholders to interpret PR effectiveness.

Clinical trial registration: NCT03799666 on ClinicalTrials.gov

Keywords: *Exercise *Interpretability *Outcome measurement *Health status * clinical decision-making

INTRODUCTION:

Chronic obstructive pulmonary disease (COPD) is highly symptomatic.[1] Although dyspnoea is the symptom most commonly reported,[1] fatigue has been recognised to affect around 50 to 70% of patients with COPD.[2,3] Fatigue is a multi-dimensional and disabling symptom defined as an overwhelming feeling of tiredness and drain of energy.[4,5] It negatively influences patients' physical, cognitive, psychological and social functioning,[4,6-8] leads to limited daily functioning and reduced health-related quality of life.[3,8-10] Fatigue severely impacts on COPD prognosis, being closely associated to exacerbations rate and an independent predictor of mortality.[10-13]

Pulmonary rehabilitation (PR) is a fundamental intervention to manage COPD, with known cost-effectiveness in fatigue reduction.[1,8,14-18] However, the interpretation of PR effects on fatigue remains a challenge due to the lack of well-established minimal clinically important differences (MCID) of patient-reported outcome measures (PROMs) that assess fatigue.[19-21] MCIDs establish thresholds for clinical meaningfulness, i.e., determine which is the smallest change in a PROM score that will be perceived as an important improvement for the patient.[19,21,22] MCIDs for fatigue-related PROMs will establish a therapeutic threshold for PR effectiveness and guide clinical decision-making in the management of patients with COPD.[23-25] A wide variety of methods can be used to estimate MCIDs,[23,24,26-28] among which the following two are distinguished: anchor-based methods, which use an external criterion (e.g., self-reported opinion or clinicians judgements) to provide clinical meaning;[27,29] and distribution-based methods, that add statistical significance by expressing change scores according to the sample variability and measurement precision.[27,30] Although the importance of anchor-based approaches in comparison to distribution methods has been advocated,[23,27] both methodologies present limitations, thus, the recommendation is to triangulate both methods.[27,28]

We determined the MCID of three PROMs commonly used to assess fatigue in patients with COPD, the functional assessment of chronic illness therapy fatigue subscale (FACIT-FS),[31] the modified-FACIT-FS[32] and the checklist of individual strength fatigue subscale (CIS-FS).[4]

MATERIALS AND METHODS:

Study design and population

This observational prospective study is integrated into a larger trial (NCT03799666), with ethical approval from the Ethics Committee for Health of the *Administração Regional de Saúde do Centro* (Ref. 73/2016) and from the National Committee for Data Protection (no. 7295/2016). All participants signed an informed consent.

Patients diagnosed with COPD,[1] who completed a 12-weeks community-based PR programme, between January and July 2019, in 6 primary healthcare centres and in the Respiratory Research and Rehabilitation laboratory (Lab3R) at the School of Health Sciences, University of Aveiro, were included. Exclusion criteria included the presence of other respiratory diseases or significant cardiovascular, neurological or musculoskeletal disease which limited patients' participation in PR. The PR programme consisted of exercise training sessions twice a week and education and psychosocial sessions once every two weeks, with two of them targeting specifically the management of fatigue: i) management of symptoms and strategies of energy conservation and ii) sleep disorders and management of stress and anxiety. Further information regarding the intervention and education and psychosocial contents has been previously published.[33,34] Only participants who attended at least 8 of the 12-weeks of PR were included.[1]

A sample size of at least 50 participants is required to determine the MCID of a PROM.[35,36] Since the drop-out rates during PR programmes range from 20 to 30%,[37,38] we aimed to recruit 65 participants.

Data collection

Sociodemographic, anthropometric and clinical data were obtained to characterise the sample. The Charlson Comorbidity Index[39] was used to score the severity of comorbid conditions. The remaining outcome measures were assessed before (T0) and after PR (T1). Impact of the disease was assessed with the COPD assessment test (CAT)[40] and health-related quality of life with the St. George's respiratory questionnaire (SGRQ).[41]

The FACIT-FS is a multi-dimensional 13-item questionnaire assessing tiredness, weakness and difficulty in handling daily activities due to fatigue, over the previous 7 days.[12,31] Each item has a 5-points Likert scale (from "not at all" to "very much"), and scores range from 0 to 52, with higher scores indicating less fatigue.[31,42] Patients scoring below the cut-off point of 43 points were considered to have clinically relevant fatigue.[43] The FACIT-FS has shown high internal consistency[32] and test-retest reliability,[44] and good concurrent and discriminating validity[32,45] in patients with COPD. A modified version of FACIT-FS,

adapted to patients with COPD, has been proposed.[32] The modified-FACIT-FS has 9 items and scores range from 0 to 36 points.[32]

The CIS-FS[4] was used to evaluate the fatigue experience. The CIS-FS is an 8-statements self-reported measure, with a period recall of two weeks, where each item is scored on a 7-point Likert scale.[4] Total scores range from 8 to 56, and 3 subgroups can be categorised: normal fatigue (≤26 points), mild fatigue (27-35 points) and severe fatigue (≥36 points).[46] The CIS-FS has shown high internal consistency and test-retest reliability, good concurrent and criterion validity[46] and ability to detect change in subjective fatigue.[2,47-49]

The global rating of change scale (GRC) is a simple, retrospective and numerical analogue scale[50] that asks patients to make a judgement regarding their perceived fatigue after PR and to compare it with the initial assessment. It was administered only after PR, using an 11-point Likert scale ranging from -5 (much worse) to +5 (much better) (supplementary material).[50]

Statistical analysis

Data analysis was performed with IBM SPSS Statistics 24, and plots were designed with GraphPad Prism 7 and MetaXL 5.3. Paired t-test were used to test significance of changes in PROMs from T0 to T1. Floor and ceiling effects were checked and deemed inexistent if less than 15% of the patients scored at the bottom or top of the questionnaires.[51] Outliers were checked, i.e., inspection of extreme points in plotted graphs from the studied variables, and excluded if present.[52]

MCIDs were established through the combination of anchor-based and distribution-based methods for the FACIT-FS, modified-FACIT-FS and CIS-FS. [24,27]

Anchor-based methods

The following measures were explored for their adequacy to be used as anchors:

i) Patients referencing: the GRC was used to classify patients' perception of change in fatigue. Significant changes were considered for the GRC higher than 2.[50]

ii) Physiotherapists referencing: the GRC was used to ask the physiotherapists running the PR programmes about their perception regarding patients' changes in fatigue. Significant changes were considered for the GRC higher than 2.[50]

iii) Questionnaire referencing: changes in CAT and SGRQ were used as external criterions to determine the CIS-FS and FACIT-FS MCIDs. The MCIDs for the CAT (2 points)[53] and for the SGRQ (4 points)[54] were used to distinguish between patients who improved from those who did not improve their fatigue symptoms.

iv) Criterion referencing: AECOPD are considered major health events[1] and are correlated to worse PROM scores, thus, their occurrence during PR was used as an anchor.[25]

Correlations between the potential anchors and each fatigue-related PROM were explored using Pearson or point-biserial correlation coefficients. For patients, physiotherapists and questionnaire referencing, significant and moderate correlations ($r \geq 0.3$) were established as criteria to proceed with the calculation of the MCIDs using anchor-based methods.[27] Then, three statistical methods were used to compute the MCID: i) mean change in the PROM score (between T1 and T0) for patients who reached the anchor MCID;[22,24] ii) receiver operating characteristic (ROC) curves and the corresponding likelihood ratio (LR) (interpreted according to McGee),[55] calculated with the dichotomous variable, i.e., those who achieved or not the MCID of the anchor [an area under the curve (AUC) was considered adequate if statistically significant and greater than 0.7; the optimal cut-off point was set as the point where specificity and sensitivity were both optimised, i.e., the closest point to the left corner][55] and iii) linear regression analysis, using the Enter method, where the change in the fatigue PROMs was used as the dependent variable, and the change score of the anchor was considered the independent variable.

Regarding criterion referencing, the presence of significant differences in fatigue baseline scores between patients who experienced an exacerbation and those who did not was the criteria to proceed with the MCID calculation. Independent t-tests were used to explore differences and when present, the absolute difference was considered the MCID[25,56] Afterwards, ROC statistics were used to test the PROMs discriminating ability to anticipate the occurrence of an AECOPD.

Distribution-based methods

The distribution-based methods used to determine the MCID were:

i) 0.5 times standard deviation (SD) at the baseline;[26]

ii) standard error of measurement (SEM), calculated as $SEM=SD_{baseline}\sqrt{(1-r)}$, where r is the test-retest reliability coefficient;[21]

iii) 1.96 times SEM;[23,28]

iv) minimal detectable change (MDC),[26,57] calculated as $MDC=1.96*SEM*\sqrt{2}$;

v) effect size (ES) through $ES=(mean_{afterPR}-mean_{baseline})/\sqrt{(SD^2_{afterPR}+SD^2_{baseline})/2}$. The ES thresholds were ≥0.2 for small, ≥0.5 for medium and ≥0.8 for large.[57]

Pooled MCID

There are no guidelines on how to weight anchor- and distribution-based approaches, therefore, based on the authors' best judgement and on previous work,[58,59] we decided to attribute 2/3 to anchor-based and 1/3 to distribution-based methods. To pool the final MCID we calculated the arithmetic weighted mean. The MCIDs generated from the different methods were entered into the MetaXL 5.3 to create the MCIDs' plots. The percentage of change of the pooled MCID in relation to the fatigue-related PROMs was also calculated. Previous studies have suggested that MCIDs which fell within the range of 6 to 10% of the total score,[24] correspond to the desirable ES for MCID, i.e., 0.2 to 0.5.[24,27,57] The ES derived from the pooled MCID were calculated using the ESformula: $MCID_{ES} = MCID_{pooled}/\sqrt{(SD^2_{afterPR}+SD^2_{baseline})/2}$.

RESULTS:

A flow diagram of the recruited and included patients is provided in Figure 1.

(Please insert Figure 1 here)

After outliers' assessment, five participants were excluded since in boxplot analysis, they presented extreme scores in FACIT-FS and SGRQ-total change scores. Baseline characteristics of the included sample and of the outliers were not statistically different ($p>0.05$). Included patients and drop-outs presented similar baseline characteristics (Table 1).

(Please insert Table 1 here)

After PR, significant improvements were found in all PROMs (Table 2): 86.8% of participants perceived improvements in their fatigue (GRC: 3.0 [2.0-4.0]) and

physiotherapists also considered that 86.8% of patients improved (3.0, [2.0-4.0]). No ceiling/floor effects were found for the FACIT-FS, modified-FACIT-FS and CIS-FS.

(Please insert Table 2 here)

Minimal clinically important differences

Anchor-based methods

Changes in the FACIT-FS and modified-FACIT-FS correlated significantly and moderatly with changes in the SGRQ-total (r=-0.330; r=-0.439), -impact scores (r=-0.409; r=-0.474) and with AECOPD (r_{pb}=-0.277; r_{pb}=-0.274). A significant correlation between changes in modified-FACIT-FS and SGRQ-ativities scores was also present, however, it was not considered since it was inferior to 0.3 (r=-0.288). Changes in the CIS-20 FS correlated only with AECOPD (r_{pb}=0.323), therefore, the remaining anchors were not further analysed. All correlations are presented in e-Table 1.

Questionnaire referencing

MCIDs for the FACIT-FS derived from the mean change methods were 5.7 points using the SGRQ-impact and 4.9 points using the SGRQ-total whereas for the modified-FACIT-FS were 4.4 points using SGRQ-impact and 3.9 using SGRQ-total (Table 3). Mean change results for all the explored anchors can be found in e-Table 2 and e-Table 3.

The AUCs generated for either FACIT-FS and modified-FACIT-FS using the SGRQ-impact/total did not fulfill the requirements, thus, ROC statistics were not used.

Using linear regression, the estimated MCIDs for the FACIT-FS were 3.4 (SGRQ-impact) and 3.2 (SGRQ-total) points and for the modified-FACIT-FS were 2.3 points using SGRQ-impact and 1.9 points using SGRQ-total (Figure 2).

(Please insert Figure 2 here)

Criterion Referencing

Mean change method applied for criterion referencing yielded a MCID of 6.4 (95%CI 1.2 to 11.6; p=0.044) points for the FACIT-FS; of 4.7 (95%CI 0.1 to 9.3; p=0.047) points for the modified-FACIT-FS; and of 9.6 points (95%CI 2.5 to 16.0; p=0.018) for CIS-FS (e-Table 4).

The AUCs generated for all fatigue PROMs were able to distinguish between patients who experienced an AECOPD and those who did not (FACIT-FS: AUC=0.71; 95%CI 0.58 to 0.85; p=0.021/ modified-FACIT-FS: AUC=0.73; 95%CI 0.59 to 0.86; p=0.015/ CIS-FS: AUC=0.72; 95%CI 0.57 to 0.87; p=0.019)(e-Figure 1). According to the ROC analysis, patients scoring below 32 points on the FACIT-FS or above 43.5 points on the CIS-FS had a LR of 2.2 (sensitivity=68%; specificity=69%). Cut-off point found for the modified-FACIT-FS was 19.5 points, with a LR of 2.5 (sensitivity=73%; specificity=69%).

Distribution-based methods

Distribution-based methods for the FACIT-FS, modified-FACIT-FS and CIS-FS are presented in Table 3.

Pooled MCID

Pooled MCIDs were 4.7 points for the FACIT-FS, 3.8 for the modified-FACIT-FS and 9.3 points for CIS-FS (Figure 3). Overall MCID pooled statistics are presented in Table 3.

(Please insert Figure 3 here)

(Please insert Table 3 here)

DISCUSSION:

This study found pooled MCIDs of 4.7 points for the FACIT-FS, 3.8 points for the modified-FACIT-FS and 9.3 points for CIS-FS, following a PR programme in patients with COPD.

Nearly 80% of our sample reported fatigue symptoms, surpassing the 50 to 70% reported in previous literature.[2,3,11,60] These findings call for attention to the tremendous impact and burden of fatigue in COPD, emphasising the importance of its routine assessment and the need for tailoring therapies to target fatigue. Our results showed significant improvements in FACIT-FS, modified-FACIT-FS and CIS-FS following a community-based-PR programme, highlighting the effectiveness and the key role of this comprehensive intervention in managing fatigue.[2,16,18]

MCIDs are recognised to be disease-specific[23] and, to our best knowledge, this is the first study to establish MCIDs for both FACIT-FS versions and CIS-FS in patients with COPD. For the original-FACIT-FS, the MCID has been previously determined in other populations, with our estimation being similar to the one reported for rheumatoid arthritis (i.e., 3-4 points),[61] but smaller than the estimated for the systemic lupus erythematosus (i.e., 5.9

points).[62] These differences are likely to be explained by the dissimilarities among populations and methodologies (longitudinal and within-patient differences vs. cross-sectional and between patient-differences). Although a MCID of 10 points has been reported for the CIS-FS,[2] no information, or reference, regarding its calculation is provided limiting comparisons between studies.

MCIDs were computed using different approaches and integrating a wide range of anchor- and distribution-based methods. It is known that MDC yield large estimates and tend to overestimate MCIDs.[23,63] Previous research have classified MDC as a benchmark for moderate to large change, warning that MCIDs could be smaller than MDC.[23,63] These discrepancies enhance the need to combine anchor-based methods (weighting 2/3), which provide clinical meaning, and distribution-based methods (weight 1/3), which add statistical significance,[23,27] as previously recommended.[24,27]

Within the multiple anchor-based approaches used, only the SGRQ and the occurrence of AECOPD fulfilled the criterion to proceed with the MCID calculation, with the latter yielding larger estimations. Regarding either patients' or physiotherapists' GRC, it is noticeable that most patients/physiotherapists perceived improvements in fatigue, thus the variability of data was reduced, which is known to limit the power of correlations.[64] Moreover, another hypothetical reason for the lack of correlations is the well-known recall and administration bias associated to the GRC.[24,50,65] Fatigue is a complex, multifaceted and dynamic phenomenon,[5] and PROMs focus specifically on the perceived fatigability, thus, do not fully portray fatigue. This complexity might also have impacted our correlations. Disparities among physiotherapists' GRC and the fatigue PROMs sustain the poor physician-patient concordance previously stated.[66]

The impact of fatigue on health status and quality of life is irrefutable.[2,10,11,32] Previous associations between these outcomes[2,32] highlight the importance of the SGRQ to determine fatigue-related MCIDs. The absence of correlations among the CIS-FS and the SGRQ dimensions might be explained by the conceptual differences between the fatigue PROMs. While the CIS-FS focuses specifically on the subjective experience of fatigue,[4] FACIT-FS integrates two components of fatigue: experience of fatigue and impact of fatigue,[67] probably, the latter is more intimately related to the SGRQ impact-dimension and consequently, to the total-dimension.[32] CAT assesses several respiratory symptoms, and only one item is directly related to fatigue (energy). Instead of the CAT-total score, which

failed to capture changes in fatigue, it would have been interesting to use as an anchor the CAT-energy question. However, this was not possible, as the MCID for single CAT-items is not established.

Similar to previous research,[11,12] our study, further established the role of fatigue as a prognostic measure for AECOPD, showing that patients scoring below 32 points on the FACIT-FS, below 19.5 points on the modified-FACIT-FS and over 43.5 on the CIS-FS have around 15% increased probability of having and exacerbation (LR from 2.2 to 2.5).[55] According to our results, all fatigue PROMs used have similar prediction abilities to distinguish between patients who experienced an AECOPD from those who did not. Thus, these tree questionnaires seem to be equally valuable to predict a patient's exacerbation risk and to adjust the PR programme accordingly (e.g., by further enhancing the education on prevention of exacerbations).[68]

Nevertheless, this study also presents some limitations that should be acknowledged. First, the PROMs used as referencing questionnaires, i.e., CAT and SGRQ, do not assess fatigue specifically. To the authors' best knowledge, the chronic respiratory questionnaire is the only PROM that specifically targets fatigue and has a MCID established for patients with COPD,[69] however it could not be used in this study, as it is not culturally adapted for the Portuguese population. Second, our sample was mainly composed by GOLD B patients, therefore, the external validity of our study might be reduced. MCIDs should correspond to a 6 to 10% change in the PROMs scale and to an ES between 0.2 to 0.5.[24,27,57] The MCID found for CIS-FS corresponded to an ES of 0.7 and 19% change, thus, it may have been overestimated. It is worth noting that, even if nor ceiling or floor effects were present, our sample presented high baseline levels of fatigue, leading to greater room for improvement with treatment, and thus higher MCIDs.[23,24,26,70] The fact that only the criterion anchor and distribution-based methods were used to compute the MCID for CIS-FS, could have also contributed to overestimate the result. Our overall sample size was not enough to perform sub-analysis according to baseline fatigue or disease severity. This study included exclusively the physiotherapists GRC, thus providing a limited insight into patients' fatigue, as PR is a multidisciplinary intervention. Future studies including a Delphi Method would be useful to integrate different stakeholders' perspectives.[27] A consensus between worldwide experts in MCIDs would be extremely helpful to confidently establish the weights assigned to either anchor- and distribution-based approaches. More studies with larger samples are required to control for these factors and further validate our estimations.

CONCLUSIONS:

The present study determined that changes of 4.7 on the FACIT-FS, 3.8 on the modified-FACIT-FS and 9.3 on the CIS-FS represent clinically relevant improvements in fatigue after PR in patients with COPD. These MCIDs should be interpreted accordingly to each patient specificities and incorporated into clinical practice to guide different stakeholders in the decision-making process.

ACKNOWLEDGEMENTS:

Authors' contributions: AM obtained the funding, had full access to all data in the study and takes responsibility for the data and the accuracy of data analysis, including and especially any adverse effects. AM and AO conceived the idea. All authors contributed to the design and interpretation of data. PR, AO, LA and CV contributed to data acquisition. PR performed the analysis and drafted the paper. All authors critically revised the manuscript and approved the final version.

Financial/ nonfinancial disclosures: none declared

Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Other contributions: The authors would like to thank Cátia Paixão, Sara Miranda, Ana Alves and Liliana Santos for their contribution in data collection and implementation of the pulmonary rehabilitation programmes.

REFERENCES (70/75):

1. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2019 Report). 2019.

2. Peters JB, Heijdra YF, Daudey L, Boer LM, Molema J, Dekhuijzen PR, et al. Course of normal and abnormal fatigue in patients with chronic obstructive pulmonary disease, and its relationship with domains of health status. Patient education and counseling. 2011;85(2):281-5.

3. Spruit MA, Vercoulen JH, Sprangers MA, Wouters EF. Fatigue in COPD: an important yet ignored symptom. The Lancet Respiratory Medicine. 2017;5(7):542-4.

4. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. Journal of psychosomatic research. 1994;38(5):383-92.

5. Gruet M. Fatigue in Chronic Respiratory Diseases: Theoretical Framework and Implications For Real-Life Performance and Rehabilitation. Frontiers in physiology. 2018;9.

6. Ream E, Richardson A. Fatigue in patients with cancer and chronic obstructive airways disease: a phenomenological enquiry. International journal of nursing studies. 1997;34(1):44-53.

7. Beurskens AJ, Bültmann U, Kant I, Vercoulen JH, Bleijenberg G, Swaen GM. Fatigue among working people: validity of a questionnaire measure. Occupational and environmental medicine. 2000;57(5):353-7.

8. Kouijzer M, Brusse-Keizer M, Bode C. COPD-related fatigue: Impact on daily life and treatment opportunities from the patient's perspective. Respiratory Medicine. 2018. 141:47-51.

9. Small S, Lamb M. Fatigue in chronic illness: the experience of individuals with chronic obstructive pulmonary disease and with asthma. Journal of advanced nursing. 1999;30(2):469-78.

10. Stridsman C, Skär L, Hedman L, Rˆnmark E, Lindberg A. Fatigue affects health status and predicts mortality among subjects with COPD: report from the population-based OLIN COPD study. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2015;12(2):199-206.

11. Baghai-Ravary R, Quint JK, Goldring JJ, Hurst JR, Donaldson GC, Wedzicha JA. Determinants and impact of fatigue in patients with chronic obstructive pulmonary disease. Respiratory medicine. 2009;103(2):216-23.

12. Antoniu SA, Ungureanu D. Measuring fatigue as a symptom in COPD: from descriptors and questionnaires to the importance of the problem. Chronic respiratory disease. 2015;12(3):179-88.

13. Paddison JS, Effing TW, Quinn S, Frith PA. Fatigue in COPD: association with functional status and hospitalisations. European Respiratory Journal. 2013;41(3):565-70.

14. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews.2015; 23;(2):CD003793.

15. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. American journal of respiratory and critical care medicine. 2013;188(8):e13-e64.

16. Payne C, Wiffen PJ, Martin S. Interventions for fatigue and weight loss in adults with advanced progressive illness. Cochrane Database of Systematic Reviews. 2012;1:CD008427.

17. Lewko A, Bidgood PL, Jewell A, Garrod R. Evaluation of multidimensional COPD-related subjective fatigue following a pulmonary rehabilitation programme. Respiratory medicine. 2014;108(1):95-102.

18. Van Herck M, Antons J, Vercoulen JH, Goërtz YM, Ebadi Z, Burtin C, et al. Pulmonary Rehabilitation Reduces Subjective Fatigue in COPD: A Responder Analysis. Journal of clinical medicine. 2019;8(8):1264.

19. Johnston BC, Ebrahim S, Carrasco-Labra A, Furukawa TA, Patrick DL, Crawford MW, et al. Minimally important difference estimates and methods: a protocol. BMJ open. 2015;5(10):e007953.

20. Cook CE. Clinimetrics corner: the minimal clinically important change score (MCID): a necessary pretense. Journal of Manual & Manipulative Therapy. 2008;16(4):82E-3E.

21. Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR, editors. Methods to explain the clinical significance of health status measures. Mayo Clinic Proceedings. 2002; 77(4):371-83

22. Jaeschke R, Singer J, Guyatt GH. Measurement of health status: ascertaining the minimal clinically important difference. Controlled clinical trials. 1989;10(4):407-15.

23. Wright A, Hannon J, Hegedus EJ, Kavchak AE. Clinimetrics corner: a closer look at the minimal clinically important difference (MCID). Journal of Manual & Manipulative Therapy. 2012;20(3):160-6.

24. Angst F, Aeschlimann A, Angst J. The minimal clinically important difference raised the significance of outcome effects above the statistical level, with methodological implications for future studies. Journal of clinical epidemiology. 2017;82:128-36.

25. Jones P. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. European Respiratory Journal. 2002;19(3):398-404.

26. Copay AG, Subach BR, Glassman SD, Polly DW, Schuler TC. Understanding the minimum clinically important difference: a review of concepts and methods. The Spine Journal. 2007;7(5):541-6.

27. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. Journal of clinical epidemiology. 2008;61(2):102-9.

28. Rai SK, Yazdany J, Fortin PR, Aviña-Zubieta JA. Approaches for estimating minimal clinically important differences in systemic lupus erythematosus. Arthritis research & therapy. 2015;17(1):143.

29. Haley SM, Fragala-Pinkham MA. Interpreting change scores of tests and measures used in physical therapy. Physical therapy. 2006;86(5):735-43.

30. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Medical care. 2003;41(5):582-92.

31. Webster K, Cella D, Yost K. The F unctional A ssessment of C hronic I llness T herapy (FACIT) Measurement System: properties, applications, and interpretation. Health and quality of life outcomes. 2003;1(1):79.

32. Al-Shair K, Muellerova H, Yorke J, Rennard SI, Wouters EF, Hanania NA, et al. Examining fatigue in COPD: development, validity and reliability of a modified version of FACIT-F scale. Health and quality of life outcomes. 2012;10(1):100.

33. Marques A, Jácome C, Rebelo P, Paixão C, Oliveira A, Cruz J, et al. Improving access to community-based pulmonary rehabilitation: 3R protocol for real-world settings with cost-benefit analysis. BMC Public Health. 2019;19(676).

34. Laboratório de Investigação e Reabilitação Respiratória (Lab3R). Plataforma de Reabilitação Respiratória em Rede. 2018. Available from: http://3r.web.ua.pt/.

35. Terwee CB, Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. Journal of clinical epidemiology. 2007;60(1):34-42.

36. Mokkink LB, Prinsen CA, Patrick DL, Alonso J, Bouter LM, de Vet HC, et al. COSMIN Study Design checklist for Patient-reported outcome measurement instruments. 2019.

37. Fischer MJ, Scharloo M, Abbink JJ, van't Hul AJ, van Ranst D, Rudolphus A, et al. Drop-out and attendance in pulmonary rehabilitation: the role of clinical and psychosocial variables. Respiratory medicine. 2009;103(10):1564-71.

38. Keating A, Lee A, Holland AE. What prevents people with chronic obstructive pulmonary disease from attending pulmonary rehabilitation? A systematic review. Chronic respiratory disease. 2011;8(2):89-99.

39. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of chronic diseases. 1987;40(5):373-83.

40. Jones P, Harding G, Berry P, Wiklund I, Chen W, Leidy NK. Development and first validation of the COPD Assessment Test. European Respiratory Journal. 2009;34(3):648-54.

41. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. American Review of Respiratory Disease. 1992;145(6):1321-7.

42. Elbers RG, Rietberg MB, van Wegen EE, Verhoef J, Kramer SF, Terwee CB, et al. Self-report fatigue questionnaires in multiple sclerosis, Parkinson's disease and stroke: a systematic review of measurement properties. Quality of Life Research. 2012;21(6):925-44.

43. Cella D, Lai Js, Chang CH, Peterman A, Slavin M. Fatigue in cancer patients compared with fatigue in the general United States population. Cancer. 2002;94(2):528-38.

44. Anderson WH, Ha JW, Couper DJ, O'Neal WK, Barr RG, Bleecker ER, et al. Variability in objective and subjective measures affects baseline values in studies of patients with COPD. PloS one. 2017;12(9):e0184606.

45. Al-Shair K, Müllerova H, Locantore N, Hanania N, Sharafkhaneh A, Wouters E, et al. Fatigue components in COPD patients and controls using the FACIT-F scale; data from ECLIPSE study. European Respiratory Journal; 2011;38:3624.

46. Worm-Smeitink M, Gielissen M, Bloot L, van Laarhoven H, van Engelen B, van Riel P, et al. The assessment of fatigue: Psychometric qualities and norms for the Checklist individual strength. Journal of psychosomatic research. 2017;98:40-6.

47. van Koulil S, Kraaimaat FW, van Lankveld W, van Riel PL, Evers AW. A patient's perspective on multidisciplinary treatment gain for fibromyalgia: An indicator for pre‐post treatment effects? Arthritis Care & Research. 2009;61(12):1626-32.

48. Panitz S, Kornhuber M, Hanisch F. The checklist individual strength (CIS20‐R) in patients with amyotrophic lateral sclerosis‐A longitudinal study. Acta Neurologica Scandinavica. 2015;131(6):372-80.

49. Evers AW, Kraaimaat FW, van Riel PL, de Jong AJ. Tailored cognitive-behavioral therapy in early rheumatoid arthritis for patients at risk: a randomized controlled trial. Pain. 2002;100(1-2):141-53.

50. Kamper SJ, Maher CG, Mackay G. Global rating of change scales: a review of strengths and weaknesses and considerations for design. Journal of Manual & Manipulative Therapy. 2009;17(3):163-70.

51. McHorney CA, Tarlov AR. Individual-patient monitoring in clinical practice: are available health status surveys adequate? Quality of Life Research. 1995;4(4):293-307.

52. Aggarwal R, Ranganathan P. Common pitfalls in statistical analysis: The use of correlation techniques. Perspectives in clinical research. 2016;7(4):187.

53. Kon SS, Canavan JL, Jones SE, Nolan CM, Clark AL, Dickson MJ, et al. Minimum clinically important difference for the COPD Assessment Test: a prospective analysis. The lancet Respiratory medicine. 2014;2(3):195-203.

54. Jones PW. St. George's respiratory questionnaire: MCID. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2005;2(1):75-9.

55. McGee S. Simplifying likelihood ratios. Journal of general internal medicine. 2002;17(8):647-50.

56. Alma H, De Jong C, Jelusic D, Wittmann M, Schuler M, Flokstra-de Blok B, et al. Health status instruments for patients with COPD in pulmonary rehabilitation: defining a minimal clinically important difference. NPJ primary care respiratory medicine. 2016;26:16041.

57. Cohen J. A power primer. Psychological bulletin. 1992;112(1):155.

58. Oliveira A, Machado A, Marques A. Minimal Important and Detectable Differences of Respiratory Measures in Outpatients with AECOPD. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2018;15(5):479-488

59. Alma H, de Jong C, Tsiligianni I, Sanderman R, Kocks J, van der Molen T. Clinically relevant differences in COPD health status: systematic review and triangulation. European Respiratory Journal. 2018;52(3):1800412.

60. Stridsman C, Müllerova H, Skär L, Lindberg A. Fatigue in COPD and the impact of respiratory symptoms and heart disease—a population-based study. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2013;10(2):125-32.

61. Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. The Journal of Rheumatology. 2005;32(5):811-9.

62. Goligher EC, Pouchot J, Brant R, Kherani RB, Aviña-Zubieta JA, Lacaille D, et al. Minimal clinically important difference for 7 measures of fatigue in patients with systemic lupus erythematosus. The Journal of rheumatology. 2008;35(4):635-42.

63. Turner D, Schünemann HJ, Griffith LE, Beaton DE, Griffiths AM, Critch JN, et al. The minimal detectable change cannot reliably replace the minimal important difference. Journal of clinical epidemiology. 2010;63(1):28-36.

64. Goodwin LD, Leech NL. Understanding correlation: Factors that affect the size of r. The Journal of Experimental Education. 2006;74(3):249-66.

65. Garrison C, Cook C. Clinimetrics corner: the Global Rating of Change Score (GRoC) poorly correlates with functional measures and is not temporally stable. Journal of Manual & Manipulative Therapy. 2012;20(4):178-81.

66. Miravitlles M, Ferrer J, Baró E, Lleonart M, Galera J. Differences between physician and patient in the perception of symptoms and their severity in COPD. Respiratory medicine. 2013;107(12):1977-85.

67. Cella D, Lai J-S, Stone A. Self-reported fatigue: one dimension or more? Lessons from the Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-F) questionnaire. Supportive Care in Cancer. 2011;19(9):1441-50.

68. Criner GJ, Bourbeau J, Diekemper RL, Ouellette DR, Goodridge D, Hernandez P, et al. Prevention of acute exacerbations of COPD: American college of chest physicians and Canadian thoracic society guideline. Chest. 2015;147(4):894-942.

69. Schünemann HJ, Puhan M, Goldstein R, Jaeschke R, Guyatt GH. Measurement properties and interpretability of the Chronic respiratory disease questionnaire (CRQ). COPD: journal of chronic obstructive pulmonary disease. 2005;2(1):81-9.

70. Alma H, de Jong C, Jelusic D, Wittmann M, Schuler M, Kollen B, et al. Baseline health status and setting impacted Minimal Clinically Important Differences in COPD: an explorative study. Journal of clinical epidemiology. 2019;116:49-61.

TABLES:

Table 1: Sample characterisation (n=70).

Characteristics	Patients included n=53 (75.7%)	Drop-outs n=17 (24.3%)	p-value
Age, years	68.4±7.6	67±11.3	0.568
Gender, male n (%)	42 (79.2)	12 (70.6)	0.460
BMI, kg/m²	25.6±4.3	27.2±4.8	0.217
Smoking status, n (%)			0.638
Current	9 (17)	6 (35.3)	
Former	35 (66)	7 (41.2)	
Never	9 (17)	4 (23.5)	
Packs/year	40.5 [26.4-64]	22 [13.3-50.4]	0.057
Exacerbations/year[1], n	1 [0-1]	1 [0-2]	0.139
AECOPD hospitalisations[1], n (%)	4 (7.5)	4 (23.5)	0.072
Duration of hospitalisations, days	8.2±7.1	10.4±9.4	0.606

COPD-related emergencies[1], n (%)	18 (34)	7 (41.2)	0.589
Lung function (post-bronchodilator)			
FEV_1, l	1.3±0.5	1.4±0.5	0.404
FEV_1, %predicted	48.1±17.4	56.5±19.6	0.101
FEV_1/FVC, %	49.1±14.1	55.9±13	0.077
GOLD stages, n (%)			0.905
I	5 (9.4)	2 (11.8)	
II	19 (35.8)	7 (41.2)	
III	23 (43.4)	7 (41.2)	
IV	6 (11.3)	1 (5.9)	
GOLD groups, n (%)			0.106
A	8 (15.1)	4 (23.5)	
B	34 (64.2)	6 (35.3)	
C	0 (0)	0 (0)	
D	11 (20.8)	7 (41.2)	
CCI, n (%)			0.389
Mild (1-2 points)	7 (13.2)	1 (5.9)	
Moderate (3-4 points)	30 (56.6)	8 (47.1)	
Severe (≥5 points)	16 (30.2)	8 (47.1)	
Medication, n (%)			
Bronchodilators			
SABA	7 (13.2)	1 (5.9)	0.360
SAMA	2 (3.8)	0 (0)	0.393
LABA	6 (11.3)	5 (29.4)	0.102
LAMA	16 (30.2)	10 (58.8)	0.065
LAMA/LABA combination	16 (30.2)	4 (23.5)	0.597
ICS	9 (17)	1 (5.9)	0.226
ICS/LABA combination	23 (43.3)	7 (41.2)	0.872
ICS/LABA/LAMAcombination	1 (1.9)	0 (0.0)	0.273
LTRA	2 (3.8)	2 (11.8)	0.217
Xanthines	10 (18.9)	2 (11.8)	0.499

Expectorants	5 (9.4)	1 (5.9)	0.649
Antibiotics	1 (1.9)	0 (0)	0.606
mMRC, points	2 [1-3]	2 [1-3]	0.733
CAT, points	16.9±7.5	16.2±9.2	0.736
SGRQ, points			
Symptoms	55±20.5	45.8±20.1	0.112
Activities	64.8±20.9	50.3±27.8	0.060
Impact	36.6±19.8	27.8±19.1	0.114
Total	48.2±18.6	37.7±19.8	0.050
FACIT-FS, points	33.3±10	37.7±12.8	0.151
No relevant fatigue (>43), n (%)	19 (17)	5 (29.4)	0.214
Relevant fatigue (≤43), n (%)	44 (83)	12 (70.6)	
Modified-FACIT-FS	21.2±7.4	22.7±7.7	0.496
CIS-FS, points	36.9±12.8	32.7±13.9	0.258
Normal fatigue (≤26), n (%)	9 (17)	6 (35.3)	
Mild fatigue, (27-35), n (%)	12 (22.6)	5 (29.4)	0.153
Severe fatigue (≥36), n (%)	32 (60.4)	6 (35.3)	

Notes: Values are presented as mean±standard deviation or median [interquartile range], unless otherwise stated. [1]in the past-year; * p<0.05

Legend: PR – pulmonary rehabilitation; BMI – body mass index; AECOPD – acute exacerbation of chronic obstructive pulmonary disease; FEV_1 – forced expiratory volume in one second; FVC – forced vital capacity; GOLD - Global Initiative for Chronic Obstructive Lung Disease; CCI – Charlson comorbidity index; SABA – short-acting beta-agonists; SAMA – short-acting muscarinic antagonist; LABA – long-acting beta-agonists; LAMA – long-acting muscarinic antagonist; ICS – inhaled corticosteroid; LRTA – leukotriene receptor antagonist; mMRC – modified medical research council questionnaire; CAT – COPD assessment test; SGRQ – St George's Respiratory Questionnaire; FACIT-FS - Functional assessment of chronic illness therapy fatigue subscale; CIS-FS - Checklist of individual strength fatigue subscale.

Table 2: Patient-reported outcome measures before and after the community-based pulmonary rehabilitation programme (n=53).

PROM (points)	Baseline	Post-PR	Δ	95% CI	p-value	ES
CAT	16.9±7.5	13.0±6.9	-3.9±6.7	-5.8 to -2.0	<0.001*	-0.54
SGRQ						
Symptoms	55±20.5	41.1±20.5	-13.9±21.5	-19.8 to -7.9	<0.001*	-0.68
Activities	64.8±20.9	57.8±23.5	-7.0±11.6	-10.2 to -3.8	<0.001*	-0.31
Impact	36.6±19.8	30.4±18.7	-6.2±12.0	-9.5 to -2.8	<0.001*	-0.32
Total	48.2±18.6	40.6±18.1	-7.6±10.4	-10.5 to -4.7	<0.001*	-0.41
FACIT-FS	33.3±10	36.9±8.8	3.7±7.1	1.7 to 5.6	<0.001*	0.38
Modified-FACIT-FS	21.2±7.4	24.0±6.9	2.7±5.5	1.2 to 4.3	0.001	0.38
CIS-20 FS (n=52)	36.9±12.8	31.1±13.4	-5.8±10.2	-8.7 to -3.0	<0.001*	-0.44

Notes: Values are presented as mean±standard deviation. *p<0.05

Legend: PROM – Patient-reported outcome measure**;** PR – pulmonary rehabilitation; Δ – mean change; ES – Effect sizes: 95%CI – 95% confidence interval; CAT – COPD assessment test; SGRQ – St George's Respiratory Questionnaire; FACIT-FS – Functional assessment of chronic illness therapy fatigue subscale; CIS-20 FS – Checklist of individual strength fatigue subscale.

Table 3: Anchor and distribution-based methods used to compute the minimal clinically important difference of fatigue patient-reported outcome measures.

		FACIT-FS	Modified-FACIT-FS	CIS-FS
SGRQ-Impact	Mean change	5.7 (3.3 to 8.1)	4.4 (2.4 to 6.4)	-
	ROC	-	-	-
	Linear regression	3.4 (2.1 to 4.7)	2.3 (1.2 to 3.3)	-
SGRQ-Total	Mean change	4.9 (2.5 to 7.2)	3.9 (2.0 to 5.9)	-
	ROC	-	-	-
	Linear regression	3.2 (1.7 to 4.6)	1.9 (0.7 to 3.1)	-
AECOPD	Mean change	6.4 (1.2 to 11.6)	4.7 (0.1 to 9.3)	9.6 (3.2 to 15.9)
0.5SD		4.3	3.7	6.4
SEM		2.6	2.2	5.0
1.96SEM		5.1	4.4	9.7
MDC		7.2	6.2	13.8
ES		0.42	0.38	-0.44
Pooled MCID		4.7	3.8	9.3
% of change		9.1	10.6	19.3
MCID ES		0.5	0.5	0.7

Notes: Values are presented as mean and 95% confidence intervals. % of change was computed within each scale range. The MCID ES are compute as the MCID value divided by the pooled SD.

Legend: FACIT-FS – Functional assessment of chronic illness therapy fatigue subscale; CIS-20 FS – Checklist of individual strength fatigue subscale; SGRQ – St George's Respiratory Questionnaire; ROC – Receiver operating characteristic curves; SD – standard deviation; SEM – standard error of measurement; MDC – minimal detectable change; ES – effect size; MCID - minimal clinically important difference.

FIGURE LEGEND:

Figure 1: Flow diagram of participants recruited and included in the study. COPD – Chronic obstructive pulmonary disease; PR – pulmonary rehabilitation; AECOPD – acute exacerbation of chronic obstructive pulmonary disease.

Figure 2: Linear regression between changes in the A) Functional Assessment of Chronic Illness Therapy Fatigue Subscale (FACIT-FS) and changes in the St George's Respiratory Questionnaire (SGRQ)-impact; B) FACIT-FS and changes in the SGRQ-total score; C) modified-FACIT-FS and changes in the SGRQ-impact; D) modified-FACIT-FS and changes in the SGRQ-total score (n=53).

Figure 3: Plots of the pooled minimal clinically important differences (MCID) for the: A) Functional Assessment of Chronic Illness Therapy Fatigue Subscale (FACIT-FS); B) modified-FACIT-FS; C - Checklist of individual strength fatigue subscale (CIS-FS). The plots represent the MCID estimates derived in this study, and where appropriated the estimates include the 95% confidence interval (n=53). AECOPD – acute exacerbation of chronic obstructive pulmonary disease; SGRQ – St. George Respiratory Questionnaire; SD – standard deviation; SEM – standard error of measurement; MDC – minimal detectable change.

Text word count (max 2500): 3027
Abstract word count (max 250): 239
Running head (of 50 characters or less): Fatigue in COPD: quantifying improvement

Minimal clinically important differences for patient-reported outcome measures of fatigue in patients with COPD after pulmonary rehabilitation.

Patrícia Rebelo, MSc[1,2], Ana Oliveira, PhD[1-4], Lília Andrade[5], Carla Valente[5], Alda Marques, PhD[1,2]

[1]Lab3R – Respiratory Research and Rehabilitation Laboratory, School of Health Sciences, University of Aveiro (ESSUA), Aveiro, Portugal

[2]iBiMED – Institute of Biomedicine, Department of Medical Sciences, University of Aveiro, Aveiro, Portugal

[3]West Park Healthcare Centre, Toronto, ON, Canada

[4]School of Rehabilitation Science, McMaster University, Hamilton, ON, Canada

[5]Pulmonology Department, Centro Hospitalar do Baixo Vouga, Aveiro

Corresponding author information: Alda Marques, [1]Lab3R - Respiratory Research and Rehabilitation Laboratory, School of Health Sciences (ESSUA) and [2]Institute of Biomedicine (iBiMED), University of Aveiro, Agras do Crasto - Campus Universitário de Santiago, Edifício 30, 3810-193 Aveiro, Portugal
Tel +351 234372462
Email amarques@ua.pt

Conflict of interests' statement: The authors report no financial, or non-financial, conflicts of interest in this work.

Funding information: This work, was funded by Fundo Europeu de Desenvolvimento Regional (FEDER) - Comissão Diretiva do Programa Operacional Regional do Centro, by Fundação para a Ciência e Tecnologia - FCT (SAICT-POL/23926/2016, PTDC/DTP-PIC/2284/2014, PTDC/SAU-SER/28806/2017, UID/BIM/04501/2019) and by Programa Operacional Competitividade e Internacionalização (COMPETE), through COMPETE 2020 (POCI-01-0145-FEDER-016701, POCI-01-0145-FEDER-007628, POCI-01-0145-FEDER-028806).

Notation of prior abstract publication/presentation:

- European Respiratory Society (ERS) International Congress, 28th September – 2nd October 2019, Madrid, Spain
- World Confederation of Physical Therapy Congress, 10th -13th May 2019, Genève, Switzerland

ABSTRACT:

Background: Fatigue is a burdensome and prevailing symptom in patients with chronic obstructive pulmonary disease (COPD). Pulmonary rehabilitation (PR) improves fatigue however, interpreting when such improvement is clinically relevant is challenging. Minimal clinically important differences (MCIDs) for instruments assessing fatigue are warranted to better tailor PR and guide clinical decisions. We estimated MCIDs for the functional assessment of chronic illness therapy-fatigue subscale (FACIT-FS), the modified-FACIT-FS and the checklist of individual strength-fatigue subscale (CIS-FS), in patients with COPD after PR.

Methods: Data from patients with COPD who completed a 12-weeks community-based PR programme were used to compute the MCIDs. The pooled MCID was estimated by calculating the arithmetic weighted mean, resulting from the combination of anchor (weight-2/3) and distribution-based (weight-1/3) methods. Anchors were patients' and physiotherapists' global rating of change scale, COPD assessment test, St. George's respiratory questionnaire (SGRQ) and exacerbations. To estimate MCIDs we used mean change, receiver operating characteristic curves and linear regression analysis for anchor-based approaches, and 0.5*standard deviation, standard error of measurement (SEM),1.96*SEM and minimal detectable change for distribution-based approaches.

Results: Fifty-three patients with COPD (79%male, 68.4±7.6years, $FEV_1$48.7±17.4$_{\%predicted}$) were used in the analysis. Exacerbations, the SGRQ-impact and the SGRQ-total scores fulfilled the requirements to be used as anchors. Pooled MCIDs were 4.7 for FACIT-FS, 3.8 for the modified-FACIT-FS and 9.3 for the CIS-FS.

Conclusion: The MCIDs proposed in this study can be used by different stakeholders to interpret PR effectiveness.

Clinical trial registration: NCT03799666 on ClinicalTrials.gov

Keywords: *Exercise *Interpretability *Outcome measurement *Health status * clinical decision-making

INTRODUCTION:

Chronic obstructive pulmonary disease (COPD) is highly symptomatic.[1] Although dyspnoea is the symptom most commonly reported,[1] fatigue has been recognised to affect around 50 to 70% of patients with COPD.[2,3] Fatigue is a multi-dimensional and disabling symptom defined as an overwhelming feeling of tiredness and drain of energy.[4,5] It negatively influences patients' physical, cognitive, psychological and social functioning,[4,6-8] leads to limited daily functioning and reduced health-related quality of life.[3,8-10] Fatigue severely impacts on COPD prognosis, being closely associated to exacerbations rate and an independent predictor of mortality.[10-13]

Pulmonary rehabilitation (PR) is a fundamental intervention to manage COPD, with known cost-effectiveness in fatigue reduction.[1,8,14-18] However, the interpretation of PR effects on fatigue remains a challenge due to the lack of well-established minimal clinically important differences (MCID) of patient-reported outcome measures (PROMs) that assess fatigue.[19-21] MCIDs establish thresholds for clinical meaningfulness, i.e., determine which is the smallest change in a PROM score that will be perceived as an important improvement for the patient.[19,21,22] MCIDs for fatigue-related PROMs will establish a therapeutic threshold for PR effectiveness and guide clinical decision-making in the management of patients with COPD.[23-25] A wide variety of methods can be used to estimate MCIDs,[23,24,26-28] among which the following two are distinguished: anchor-based methods, which use an external criterion (e.g., self-reported opinion or clinicians judgements) to provide clinical meaning;[27,29] and distribution-based methods, that add statistical significance by expressing change scores according to the sample variability and measurement precision.[27,30] Although the importance of anchor-based approaches in comparison to distribution methods has been advocated,[23,27] both methodologies present limitations, thus, the recommendation is to triangulate both methods.[27,28]

We determined the MCID of three PROMs commonly used to assess fatigue in patients with COPD, the functional assessment of chronic illness therapy fatigue subscale (FACIT-FS),[31] the modified-FACIT-FS[32] and the checklist of individual strength fatigue subscale (CIS-FS).[4]

MATERIALS AND METHODS:

Study design and population

This observational prospective study is integrated into a larger trial (NCT03799666), with ethical approval from the Ethics Committee for Health of the *Administração Regional de Saúde do Centro* (Ref. 73/2016) and from the National Committee for Data Protection (no. 7295/2016). All participants signed an informed consent.

Patients diagnosed with COPD,[1] who completed a 12-weeks community-based PR programme, between January and July 2019, in 6 primary healthcare centres and in the Respiratory Research and Rehabilitation laboratory (Lab3R) at the School of Health Sciences, University of Aveiro, were included. Exclusion criteria included the presence of other respiratory diseases or significant cardiovascular, neurological or musculoskeletal disease which limited patients' participation in PR. The PR programme consisted of exercise training sessions twice a week and education and psychosocial sessions once every two weeks, with two of them targeting specifically the management of fatigue: i) management of symptoms and strategies of energy conservation and ii) sleep disorders and management of stress and anxiety. Further information regarding the intervention and education and psychosocial contents has been previously published.[33,34] Only participants who attended at least 8 of the 12-weeks of PR were included.[1]

A sample size of at least 50 participants is required to determine the MCID of a PROM.[35,36] Since the drop-out rates during PR programmes range from 20 to 30%,[37,38] we aimed to recruit 65 participants.

Data collection

Sociodemographic, anthropometric and clinical data were obtained to characterise the sample. The Charlson Comorbidity Index[39] was used to score the severity of comorbid conditions. The remaining outcome measures were assessed before (T0) and after PR (T1). Impact of the disease was assessed with the COPD assessment test (CAT)[40] and health-related quality of life with the St. George's respiratory questionnaire (SGRQ).[41]

The FACIT-FS is a multi-dimensional 13-item questionnaire assessing tiredness, weakness and difficulty in handling daily activities due to fatigue, over the previous 7 days.[12,31] Each item has a 5-points Likert scale (from "not at all" to "very much"), and scores range from 0 to 52, with higher scores indicating less fatigue.[31,42] Patients scoring below the cut-off point of 43 points were considered to have clinically relevant fatigue.[43] The FACIT-FS has shown high internal consistency[32] and test-retest reliability,[44] and good concurrent and discriminating validity[32,45] in patients with COPD. A modified version of FACIT-FS,

adapted to patients with COPD, has been proposed.[32] The modified-FACIT-FS has 9 items and scores range from 0 to 36 points.[32]

The CIS-FS[4] was used to evaluate the fatigue experience. The CIS-FS is an 8-statements self-reported measure, with a period recall of two weeks, where each item is scored on a 7-point Likert scale.[4] Total scores range from 8 to 56, and 3 subgroups can be categorised: normal fatigue (≤26 points), mild fatigue (27-35 points) and severe fatigue (≥36 points).[46] The CIS-FS has shown high internal consistency and test-retest reliability, good concurrent and criterion validity[46] and ability to detect change in subjective fatigue.[2,47-49]

The global rating of change scale (GRC) is a simple, retrospective and numerical analogue scale[50] that asks patients to make a judgement regarding their perceived fatigue after PR and to compare it with the initial assessment. It was administered only after PR, using an 11-point Likert scale ranging from -5 (much worse) to +5 (much better) (supplementary material).[50]

Statistical analysis

Data analysis was performed with IBM SPSS Statistics 24, and plots were designed with GraphPad Prism 7 and MetaXL 5.3. Paired t-test were used to test significance of changes in PROMs from T0 to T1. Floor and ceiling effects were checked and deemed inexistent if less than 15% of the patients scored at the bottom or top of the questionnaires.[51] Outliers were checked, i.e., inspection of extreme points in plotted graphs from the studied variables, and excluded if present.[52]

MCIDs were established through the combination of anchor-based and distribution-based methods for the FACIT-FS, modified-FACIT-FS and CIS-FS. [24,27]

Anchor-based methods

The following measures were explored for their adequacy to be used as anchors:

i) Patients referencing: the GRC was used to classify patients' perception of change in fatigue. Significant changes were considered for the GRC higher than 2.[50]

ii) Physiotherapists referencing: the GRC was used to ask the physiotherapists running the PR programmes about their perception regarding patients' changes in fatigue. Significant changes were considered for the GRC higher than 2.[50]

iii) Questionnaire referencing: changes in CAT and SGRQ were used as external criterions to determine the CIS-FS and FACIT-FS MCIDs. The MCIDs for the CAT (2 points)[53] and for the SGRQ (4 points)[54] were used to distinguish between patients who improved from those who did not improve their fatigue symptoms.

iv) Criterion referencing: AECOPD are considered major health events[1] and are correlated to worse PROM scores, thus, their occurrence during PR was used as an anchor.[25]

Correlations between the potential anchors and each fatigue-related PROM were explored using Pearson or point-biserial correlation coefficients. For patients, physiotherapists and questionnaire referencing, significant and moderate correlations ($r \geq 0.3$) were established as criteria to proceed with the calculation of the MCIDs using anchor-based methods.[27] Then, three statistical methods were used to compute the MCID: i) mean change in the PROM score (between T1 and T0) for patients who reached the anchor MCID;[22,24] ii) receiver operating characteristic (ROC) curves and the corresponding likelihood ratio (LR) (interpreted according to McGee),[55] calculated with the dichotomous variable, i.e., those who achieved or not the MCID of the anchor [an area under the curve (AUC) was considered adequate if statistically significant and greater than 0.7; the optimal cut-off point was set as the point where specificity and sensitivity were both optimised, i.e., the closest point to the left corner][55] and iii) linear regression analysis, using the Enter method, where the change in the fatigue PROMs was used as the dependent variable, and the change score of the anchor was considered the independent variable.

Regarding criterion referencing, the presence of significant differences in fatigue baseline scores between patients who experienced an exacerbation and those who did not was the criteria to proceed with the MCID calculation. Independent t-tests were used to explore differences and when present, the absolute difference was considered the MCID[25,56] Afterwards, ROC statistics were used to test the PROMs discriminating ability to anticipate the occurrence of an AECOPD.

Distribution-based methods

The distribution-based methods used to determine the MCID were:

i) 0.5 times standard deviation (SD) at the baseline;[26]

ii) standard error of measurement (SEM), calculated as $SEM=SD_{baseline}\sqrt{(1-r)}$, where r is the test-retest reliability coefficient;[21]

iii) 1.96 times SEM;[23,28]

iv) minimal detectable change (MDC),[26,57] calculated as $MDC=1.96*SEM*\sqrt{2}$;

v) effect size (ES) through $ES=(mean_{afterPR}-mean_{baseline})/\sqrt{(SD^2_{afterPR}+SD^2_{baseline})/2}$. The ES thresholds were ≥0.2 for small, ≥0.5 for medium and ≥0.8 for large.[57]

Pooled MCID

There are no guidelines on how to weight anchor- and distribution-based approaches, therefore, based on the authors' best judgement and on previous work,[58,59] we decided to attribute 2/3 to anchor-based and 1/3 to distribution-based methods. To pool the final MCID we calculated the arithmetic weighted mean. The MCIDs generated from the different methods were entered into the MetaXL 5.3 to create the MCIDs' plots. The percentage of change of the pooled MCID in relation to the fatigue-related PROMs was also calculated. Previous studies have suggested that MCIDs which fell within the range of 6 to 10% of the total score,[24] correspond to the desirable ES for MCID, i.e., 0.2 to 0.5.[24,27,57] The ES derived from the pooled MCID were calculated using the ESformula: $MCID_{ES} = MCID_{pooled}/\sqrt{(SD^2_{afterPR}+SD^2_{baseline})/2}$.

RESULTS:

A flow diagram of the recruited and included patients is provided in Figure 1.

(Please insert Figure 1 here)

After outliers' assessment, five participants were excluded since in boxplot analysis, they presented extreme scores in FACIT-FS and SGRQ-total change scores. Baseline characteristics of the included sample and of the outliers were not statistically different ($p>0.05$). Included patients and drop-outs presented similar baseline characteristics (Table 1).

(Please insert Table 1 here)

After PR, significant improvements were found in all PROMs (Table 2): 86.8% of participants perceived improvements in their fatigue (GRC: 3.0 [2.0-4.0]) and

physiotherapists also considered that 86.8% of patients improved (3.0, [2.0-4.0]). No ceiling/floor effects were found for the FACIT-FS, modified-FACIT-FS and CIS-FS.

(Please insert Table 2 here)

Minimal clinically important differences

Anchor-based methods

Changes in the FACIT-FS and modified-FACIT-FS correlated significantly and moderatly with changes in the SGRQ-total (r=-0.330; r=-0.439), -impact scores (r=-0.409; r=-0.474) and with AECOPD (r_{pb}=-0.277; r_{pb}=-0.274). A significant correlation between changes in modified-FACIT-FS and SGRQ-ativities scores was also present, however, it was not considered since it was inferior to 0.3 (r=-0.288). Changes in the CIS-20 FS correlated only with AECOPD (r_{pb}=0.323), therefore, the remaining anchors were not further analysed. All correlations are presented in e-Table 1.

Questionnaire referencing

MCIDs for the FACIT-FS derived from the mean change methods were 5.7 points using the SGRQ-impact and 4.9 points using the SGRQ-total whereas for the modified-FACIT-FS were 4.4 points using SGRQ-impact and 3.9 using SGRQ-total (Table 3). Mean change results for all the explored anchors can be found in e-Table 2 and e-Table 3.

The AUCs generated for either FACIT-FS and modified-FACIT-FS using the SGRQ-impact/total did not fulfill the requirements, thus, ROC statistics were not used.

Using linear regression, the estimated MCIDs for the FACIT-FS were 3.4 (SGRQ-impact) and 3.2 (SGRQ-total) points and for the modified-FACIT-FS were 2.3 points using SGRQ-impact and 1.9 points using SGRQ-total (Figure 2).

(Please insert Figure 2 here)

Criterion Referencing

Mean change method applied for criterion referencing yielded a MCID of 6.4 (95%CI 1.2 to 11.6; p=0.044) points for the FACIT-FS; of 4.7 (95%CI 0.1 to 9.3; p=0.047) points for the modified-FACIT-FS; and of 9.6 points (95%CI 2.5 to 16.0; p=0.018) for CIS-FS (e-Table 4).

The AUCs generated for all fatigue PROMs were able to distinguish between patients who experienced an AECOPD and those who did not (FACIT-FS: AUC=0.71; 95%CI 0.58 to 0.85; p=0.021/ modified-FACIT-FS: AUC=0.73; 95%CI 0.59 to 0.86; p=0.015/ CIS-FS: AUC=0.72; 95%CI 0.57 to 0.87; p=0.019)(e-Figure 1). According to the ROC analysis, patients scoring below 32 points on the FACIT-FS or above 43.5 points on the CIS-FS had a LR of 2.2 (sensitivity=68%; specificity=69%). Cut-off point found for the modified-FACIT-FS was 19.5 points, with a LR of 2.5 (sensitivity=73%; specificity=69%).

Distribution-based methods

Distribution-based methods for the FACIT-FS, modified-FACIT-FS and CIS-FS are presented in Table 3.

Pooled MCID

Pooled MCIDs were 4.7 points for the FACIT-FS, 3.8 for the modified-FACIT-FS and 9.3 points for CIS-FS (Figure 3). Overall MCID pooled statistics are presented in Table 3.

(Please insert Figure 3 here)

(Please insert Table 3 here)

DISCUSSION:

This study found pooled MCIDs of 4.7 points for the FACIT-FS, 3.8 points for the modified-FACIT-FS and 9.3 points for CIS-FS, following a PR programme in patients with COPD.

Nearly 80% of our sample reported fatigue symptoms, surpassing the 50 to 70% reported in previous literature.[2,3,11,60] These findings call for attention to the tremendous impact and burden of fatigue in COPD, emphasising the importance of its routine assessment and the need for tailoring therapies to target fatigue. Our results showed significant improvements in FACIT-FS, modified-FACIT-FS and CIS-FS following a community-based-PR programme, highlighting the effectiveness and the key role of this comprehensive intervention in managing fatigue.[2,16,18]

MCIDs are recognised to be disease-specific[23] and, to our best knowledge, this is the first study to establish MCIDs for both FACIT-FS versions and CIS-FS in patients with COPD. For the original-FACIT-FS, the MCID has been previously determined in other populations, with our estimation being similar to the one reported for rheumatoid arthritis (i.e., 3-4 points),[61] but smaller than the estimated for the systemic lupus erythematosus (i.e., 5.9

points).[62] These differences are likely to be explained by the dissimilarities among populations and methodologies (longitudinal and within-patient differences vs. cross-sectional and between patient-differences). Although a MCID of 10 points has been reported for the CIS-FS,[2] no information, or reference, regarding its calculation is provided limiting comparisons between studies.

MCIDs were computed using different approaches and integrating a wide range of anchor- and distribution-based methods. It is known that MDC yield large estimates and tend to overestimate MCIDs.[23,63] Previous research have classified MDC as a benchmark for moderate to large change, warning that MCIDs could be smaller than MDC.[23,63] These discrepancies enhance the need to combine anchor-based methods (weighting 2/3), which provide clinical meaning, and distribution-based methods (weight 1/3), which add statistical significance,[23,27] as previously recommended.[24,27]

Within the multiple anchor-based approaches used, only the SGRQ and the occurrence of AECOPD fulfilled the criterion to proceed with the MCID calculation, with the latter yielding larger estimations. Regarding either patients' or physiotherapists' GRC, it is noticeable that most patients/physiotherapists perceived improvements in fatigue, thus the variability of data was reduced, which is known to limit the power of correlations.[64] Moreover, another hypothetical reason for the lack of correlations is the well-known recall and administration bias associated to the GRC.[24,50,65] Fatigue is a complex, multifaceted and dynamic phenomenon,[5] and PROMs focus specifically on the perceived fatigability, thus, do not fully portray fatigue. This complexity might also have impacted our correlations. Disparities among physiotherapists' GRC and the fatigue PROMs sustain the poor physician-patient concordance previously stated.[66]

The impact of fatigue on health status and quality of life is irrefutable.[2,10,11,32] Previous associations between these outcomes[2,32] highlight the importance of the SGRQ to determine fatigue-related MCIDs. The absence of correlations among the CIS-FS and the SGRQ dimensions might be explained by the conceptual differences between the fatigue PROMs. While the CIS-FS focuses specifically on the subjective experience of fatigue,[4] FACIT-FS integrates two components of fatigue: experience of fatigue and impact of fatigue,[67] probably, the latter is more intimately related to the SGRQ impact-dimension and consequently, to the total-dimension.[32] CAT assesses several respiratory symptoms, and only one item is directly related to fatigue (energy). Instead of the CAT-total score, which

failed to capture changes in fatigue, it would have been interesting to use as an anchor the CAT-energy question. However, this was not possible, as the MCID for single CAT-items is not established.

Similar to previous research,[11,12] our study, further established the role of fatigue as a prognostic measure for AECOPD, showing that patients scoring below 32 points on the FACIT-FS, below 19.5 points on the modified-FACIT-FS and over 43.5 on the CIS-FS have around 15% increased probability of having and exacerbation (LR from 2.2 to 2.5).[55] According to our results, all fatigue PROMs used have similar prediction abilities to distinguish between patients who experienced an AECOPD from those who did not. Thus, these tree questionnaires seem to be equally valuable to predict a patient's exacerbation risk and to adjust the PR programme accordingly (e.g., by further enhancing the education on prevention of exacerbations).[68]

Nevertheless, this study also presents some limitations that should be acknowledged. First, the PROMs used as referencing questionnaires, i.e., CAT and SGRQ, do not assess fatigue specifically. To the authors' best knowledge, the chronic respiratory questionnaire is the only PROM that specifically targets fatigue and has a MCID established for patients with COPD,[69] however it could not be used in this study, as it is not culturally adapted for the Portuguese population. Second, our sample was mainly composed by GOLD B patients, therefore, the external validity of our study might be reduced. MCIDs should correspond to a 6 to 10% change in the PROMs scale and to an ES between 0.2 to 0.5.[24,27,57] The MCID found for CIS-FS corresponded to an ES of 0.7 and 19% change, thus, it may have been overestimated. It is worth noting that, even if nor ceiling or floor effects were present, our sample presented high baseline levels of fatigue, leading to greater room for improvement with treatment, and thus higher MCIDs.[23,24,26,70] The fact that only the criterion anchor and distribution-based methods were used to compute the MCID for CIS-FS, could have also contributed to overestimate the result. Our overall sample size was not enough to perform sub-analysis according to baseline fatigue or disease severity. This study included exclusively the physiotherapists GRC, thus providing a limited insight into patients' fatigue, as PR is a multidisciplinary intervention. Future studies including a Delphi Method would be useful to integrate different stakeholders' perspectives.[27] A consensus between worldwide experts in MCIDs would be extremely helpful to confidently establish the weights assigned to either anchor- and distribution-based approaches. More studies with larger samples are required to control for these factors and further validate our estimations.

CONCLUSIONS:

The present study determined that changes of 4.7 on the FACIT-FS, 3.8 on the modified-FACIT-FS and 9.3 on the CIS-FS represent clinically relevant improvements in fatigue after PR in patients with COPD. These MCIDs should be interpreted accordingly to each patient specificities and incorporated into clinical practice to guide different stakeholders in the decision-making process.

ACKNOWLEDGEMENTS:

Authors' contributions: AM obtained the funding, had full access to all data in the study and takes responsibility for the data and the accuracy of data analysis, including and especially any adverse effects. AM and AO conceived the idea. All authors contributed to the design and interpretation of data. PR, AO, LA and CV contributed to data acquisition. PR performed the analysis and drafted the paper. All authors critically revised the manuscript and approved the final version.

Financial/ nonfinancial disclosures: none declared

Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Other contributions: The authors would like to thank Cátia Paixão, Sara Miranda, Ana Alves and Liliana Santos for their contribution in data collection and implementation of the pulmonary rehabilitation programmes.

REFERENCES (70/75):

1. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2019 Report). 2019.

2. Peters JB, Heijdra YF, Daudey L, Boer LM, Molema J, Dekhuijzen PR, et al. Course of normal and abnormal fatigue in patients with chronic obstructive pulmonary disease, and its relationship with domains of health status. Patient education and counseling. 2011;85(2):281-5.

3. Spruit MA, Vercoulen JH, Sprangers MA, Wouters EF. Fatigue in COPD: an important yet ignored symptom. The Lancet Respiratory Medicine. 2017;5(7):542-4.

4. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. Journal of psychosomatic research. 1994;38(5):383-92.

5. Gruet M. Fatigue in Chronic Respiratory Diseases: Theoretical Framework and Implications For Real-Life Performance and Rehabilitation. Frontiers in physiology. 2018;9.

6. Ream E, Richardson A. Fatigue in patients with cancer and chronic obstructive airways disease: a phenomenological enquiry. International journal of nursing studies. 1997;34(1):44-53.

7. Beurskens AJ, Bültmann U, Kant I, Vercoulen JH, Bleijenberg G, Swaen GM. Fatigue among working people: validity of a questionnaire measure. Occupational and environmental medicine. 2000;57(5):353-7.

8. Kouijzer M, Brusse-Keizer M, Bode C. COPD-related fatigue: Impact on daily life and treatment opportunities from the patient's perspective. Respiratory Medicine. 2018. 141:47-51.

9. Small S, Lamb M. Fatigue in chronic illness: the experience of individuals with chronic obstructive pulmonary disease and with asthma. Journal of advanced nursing. 1999;30(2):469-78.

10. Stridsman C, Skär L, Hedman L, Rˆnmark E, Lindberg A. Fatigue affects health status and predicts mortality among subjects with COPD: report from the population-based OLIN COPD study. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2015;12(2):199-206.

11. Baghai-Ravary R, Quint JK, Goldring JJ, Hurst JR, Donaldson GC, Wedzicha JA. Determinants and impact of fatigue in patients with chronic obstructive pulmonary disease. Respiratory medicine. 2009;103(2):216-23.

12. Antoniu SA, Ungureanu D. Measuring fatigue as a symptom in COPD: from descriptors and questionnaires to the importance of the problem. Chronic respiratory disease. 2015;12(3):179-88.

13. Paddison JS, Effing TW, Quinn S, Frith PA. Fatigue in COPD: association with functional status and hospitalisations. European Respiratory Journal. 2013;41(3):565-70.

14. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews.2015; 23;(2):CD003793.

15. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. American journal of respiratory and critical care medicine. 2013;188(8):e13-e64.

16. Payne C, Wiffen PJ, Martin S. Interventions for fatigue and weight loss in adults with advanced progressive illness. Cochrane Database of Systematic Reviews. 2012;1:CD008427.

17. Lewko A, Bidgood PL, Jewell A, Garrod R. Evaluation of multidimensional COPD-related subjective fatigue following a pulmonary rehabilitation programme. Respiratory medicine. 2014;108(1):95-102.

18. Van Herck M, Antons J, Vercoulen JH, Goërtz YM, Ebadi Z, Burtin C, et al. Pulmonary Rehabilitation Reduces Subjective Fatigue in COPD: A Responder Analysis. Journal of clinical medicine. 2019;8(8):1264.

19. Johnston BC, Ebrahim S, Carrasco-Labra A, Furukawa TA, Patrick DL, Crawford MW, et al. Minimally important difference estimates and methods: a protocol. BMJ open. 2015;5(10):e007953.

20. Cook CE. Clinimetrics corner: the minimal clinically important change score (MCID): a necessary pretense. Journal of Manual & Manipulative Therapy. 2008;16(4):82E-3E.

21. Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR, editors. Methods to explain the clinical significance of health status measures. Mayo Clinic Proceedings. 2002; 77(4):371-83

22. Jaeschke R, Singer J, Guyatt GH. Measurement of health status: ascertaining the minimal clinically important difference. Controlled clinical trials. 1989;10(4):407-15.

23. Wright A, Hannon J, Hegedus EJ, Kavchak AE. Clinimetrics corner: a closer look at the minimal clinically important difference (MCID). Journal of Manual & Manipulative Therapy. 2012;20(3):160-6.

24. Angst F, Aeschlimann A, Angst J. The minimal clinically important difference raised the significance of outcome effects above the statistical level, with methodological implications for future studies. Journal of clinical epidemiology. 2017;82:128-36.

25. Jones P. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. European Respiratory Journal. 2002;19(3):398-404.

26. Copay AG, Subach BR, Glassman SD, Polly DW, Schuler TC. Understanding the minimum clinically important difference: a review of concepts and methods. The Spine Journal. 2007;7(5):541-6.

27. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. Journal of clinical epidemiology. 2008;61(2):102-9.

28. Rai SK, Yazdany J, Fortin PR, Aviña-Zubieta JA. Approaches for estimating minimal clinically important differences in systemic lupus erythematosus. Arthritis research & therapy. 2015;17(1):143.

29. Haley SM, Fragala-Pinkham MA. Interpreting change scores of tests and measures used in physical therapy. Physical therapy. 2006;86(5):735-43.

30. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Medical care. 2003;41(5):582-92.

31. Webster K, Cella D, Yost K. The F unctional A ssessment of C hronic I llness T herapy (FACIT) Measurement System: properties, applications, and interpretation. Health and quality of life outcomes. 2003;1(1):79.

32. Al-Shair K, Muellerova H, Yorke J, Rennard SI, Wouters EF, Hanania NA, et al. Examining fatigue in COPD: development, validity and reliability of a modified version of FACIT-F scale. Health and quality of life outcomes. 2012;10(1):100.

33. Marques A, Jácome C, Rebelo P, Paixão C, Oliveira A, Cruz J, et al. Improving access to community-based pulmonary rehabilitation: 3R protocol for real-world settings with cost-benefit analysis. BMC Public Health. 2019;19(676).

34. Laboratório de Investigação e Reabilitação Respiratória (Lab3R). Plataforma de Reabilitação Respiratória em Rede. 2018. Available from: http://3r.web.ua.pt/.

35. Terwee CB, Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. Journal of clinical epidemiology. 2007;60(1):34-42.

36. Mokkink LB, Prinsen CA, Patrick DL, Alonso J, Bouter LM, de Vet HC, et al. COSMIN Study Design checklist for Patient-reported outcome measurement instruments. 2019.

37. Fischer MJ, Scharloo M, Abbink JJ, van't Hul AJ, van Ranst D, Rudolphus A, et al. Drop-out and attendance in pulmonary rehabilitation: the role of clinical and psychosocial variables. Respiratory medicine. 2009;103(10):1564-71.

38. Keating A, Lee A, Holland AE. What prevents people with chronic obstructive pulmonary disease from attending pulmonary rehabilitation? A systematic review. Chronic respiratory disease. 2011;8(2):89-99.

39. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of chronic diseases. 1987;40(5):373-83.

40. Jones P, Harding G, Berry P, Wiklund I, Chen W, Leidy NK. Development and first validation of the COPD Assessment Test. European Respiratory Journal. 2009;34(3):648-54.

41. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. American Review of Respiratory Disease. 1992;145(6):1321-7.

42. Elbers RG, Rietberg MB, van Wegen EE, Verhoef J, Kramer SF, Terwee CB, et al. Self-report fatigue questionnaires in multiple sclerosis, Parkinson's disease and stroke: a systematic review of measurement properties. Quality of Life Research. 2012;21(6):925-44.

43. Cella D, Lai Js, Chang CH, Peterman A, Slavin M. Fatigue in cancer patients compared with fatigue in the general United States population. Cancer. 2002;94(2):528-38.

44. Anderson WH, Ha JW, Couper DJ, O'Neal WK, Barr RG, Bleecker ER, et al. Variability in objective and subjective measures affects baseline values in studies of patients with COPD. PloS one. 2017;12(9):e0184606.

45. Al-Shair K, Müllerova H, Locantore N, Hanania N, Sharafkhaneh A, Wouters E, et al. Fatigue components in COPD patients and controls using the FACIT-F scale; data from ECLIPSE study. European Respiratory Journal; 2011;38:3624.

46. Worm-Smeitink M, Gielissen M, Bloot L, van Laarhoven H, van Engelen B, van Riel P, et al. The assessment of fatigue: Psychometric qualities and norms for the Checklist individual strength. Journal of psychosomatic research. 2017;98:40-6.

47. van Koulil S, Kraaimaat FW, van Lankveld W, van Riel PL, Evers AW. A patient's perspective on multidisciplinary treatment gain for fibromyalgia: An indicator for pre‐post treatment effects? Arthritis Care & Research. 2009;61(12):1626-32.

48. Panitz S, Kornhuber M, Hanisch F. The checklist individual strength (CIS20‐R) in patients with amyotrophic lateral sclerosis‐A longitudinal study. Acta Neurologica Scandinavica. 2015;131(6):372-80.

49. Evers AW, Kraaimaat FW, van Riel PL, de Jong AJ. Tailored cognitive-behavioral therapy in early rheumatoid arthritis for patients at risk: a randomized controlled trial. Pain. 2002;100(1-2):141-53.

50. Kamper SJ, Maher CG, Mackay G. Global rating of change scales: a review of strengths and weaknesses and considerations for design. Journal of Manual & Manipulative Therapy. 2009;17(3):163-70.

51. McHorney CA, Tarlov AR. Individual-patient monitoring in clinical practice: are available health status surveys adequate? Quality of Life Research. 1995;4(4):293-307.

52. Aggarwal R, Ranganathan P. Common pitfalls in statistical analysis: The use of correlation techniques. Perspectives in clinical research. 2016;7(4):187.

53. Kon SS, Canavan JL, Jones SE, Nolan CM, Clark AL, Dickson MJ, et al. Minimum clinically important difference for the COPD Assessment Test: a prospective analysis. The lancet Respiratory medicine. 2014;2(3):195-203.

54. Jones PW. St. George's respiratory questionnaire: MCID. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2005;2(1):75-9.

55. McGee S. Simplifying likelihood ratios. Journal of general internal medicine. 2002;17(8):647-50.

56. Alma H, De Jong C, Jelusic D, Wittmann M, Schuler M, Flokstra-de Blok B, et al. Health status instruments for patients with COPD in pulmonary rehabilitation: defining a minimal clinically important difference. NPJ primary care respiratory medicine. 2016;26:16041.

57. Cohen J. A power primer. Psychological bulletin. 1992;112(1):155.

58. Oliveira A, Machado A, Marques A. Minimal Important and Detectable Differences of Respiratory Measures in Outpatients with AECOPD. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2018;15(5):479-488

59. Alma H, de Jong C, Tsiligianni I, Sanderman R, Kocks J, van der Molen T. Clinically relevant differences in COPD health status: systematic review and triangulation. European Respiratory Journal. 2018;52(3):1800412.

60. Stridsman C, Müllerova H, Skär L, Lindberg A. Fatigue in COPD and the impact of respiratory symptoms and heart disease—a population-based study. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2013;10(2):125-32.

61. Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. The Journal of Rheumatology. 2005;32(5):811-9.

62. Goligher EC, Pouchot J, Brant R, Kherani RB, Aviña-Zubieta JA, Lacaille D, et al. Minimal clinically important difference for 7 measures of fatigue in patients with systemic lupus erythematosus. The Journal of rheumatology. 2008;35(4):635-42.

63. Turner D, Schünemann HJ, Griffith LE, Beaton DE, Griffiths AM, Critch JN, et al. The minimal detectable change cannot reliably replace the minimal important difference. Journal of clinical epidemiology. 2010;63(1):28-36.

64. Goodwin LD, Leech NL. Understanding correlation: Factors that affect the size of r. The Journal of Experimental Education. 2006;74(3):249-66.

65. Garrison C, Cook C. Clinimetrics corner: the Global Rating of Change Score (GRoC) poorly correlates with functional measures and is not temporally stable. Journal of Manual & Manipulative Therapy. 2012;20(4):178-81.

66. Miravitlles M, Ferrer J, Baró E, Lleonart M, Galera J. Differences between physician and patient in the perception of symptoms and their severity in COPD. Respiratory medicine. 2013;107(12):1977-85.

67. Cella D, Lai J-S, Stone A. Self-reported fatigue: one dimension or more? Lessons from the Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-F) questionnaire. Supportive Care in Cancer. 2011;19(9):1441-50.

68. Criner GJ, Bourbeau J, Diekemper RL, Ouellette DR, Goodridge D, Hernandez P, et al. Prevention of acute exacerbations of COPD: American college of chest physicians and Canadian thoracic society guideline. Chest. 2015;147(4):894-942.

69. Schünemann HJ, Puhan M, Goldstein R, Jaeschke R, Guyatt GH. Measurement properties and interpretability of the Chronic respiratory disease questionnaire (CRQ). COPD: journal of chronic obstructive pulmonary disease. 2005;2(1):81-9.

70. Alma H, de Jong C, Jelusic D, Wittmann M, Schuler M, Kollen B, et al. Baseline health status and setting impacted Minimal Clinically Important Differences in COPD: an explorative study. Journal of clinical epidemiology. 2019;116:49-61.

TABLES:

Table 1: Sample characterisation (n=70).

Characteristics	Patients included n=53 (75.7%)	Drop-outs n=17 (24.3%)	p-value
Age, years	68.4±7.6	67±11.3	0.568
Gender, male n (%)	42 (79.2)	12 (70.6)	0.460
BMI, kg/m²	25.6±4.3	27.2±4.8	0.217
Smoking status, n (%)			0.638
Current	9 (17)	6 (35.3)	
Former	35 (66)	7 (41.2)	
Never	9 (17)	4 (23.5)	
Packs/year	40.5 [26.4-64]	22 [13.3-50.4]	0.057
Exacerbations/year[1], n	1 [0-1]	1 [0-2]	0.139
AECOPD hospitalisations[1], n (%)	4 (7.5)	4 (23.5)	0.072
Duration of hospitalisations, days	8.2±7.1	10.4±9.4	0.606

COPD-related emergencies[1], n (%)	18 (34)	7 (41.2)	0.589
Lung function (post-bronchodilator)			
FEV_1, l	1.3±0.5	1.4±0.5	0.404
FEV_1, %predicted	48.1±17.4	56.5±19.6	0.101
FEV_1/FVC, %	49.1±14.1	55.9±13	0.077
GOLD stages, n (%)			0.905
I	5 (9.4)	2 (11.8)	
II	19 (35.8)	7 (41.2)	
III	23 (43.4)	7 (41.2)	
IV	6 (11.3)	1 (5.9)	
GOLD groups, n (%)			0.106
A	8 (15.1)	4 (23.5)	
B	34 (64.2)	6 (35.3)	
C	0 (0)	0 (0)	
D	11 (20.8)	7 (41.2)	
CCI, n (%)			0.389
Mild (1-2 points)	7 (13.2)	1 (5.9)	
Moderate (3-4 points)	30 (56.6)	8 (47.1)	
Severe (≥5 points)	16 (30.2)	8 (47.1)	
Medication, n (%)			
Bronchodilators			
SABA	7 (13.2)	1 (5.9)	0.360
SAMA	2 (3.8)	0 (0)	0.393
LABA	6 (11.3)	5 (29.4)	0.102
LAMA	16 (30.2)	10 (58.8)	0.065
LAMA/LABA combination	16 (30.2)	4 (23.5)	0.597
ICS	9 (17)	1 (5.9)	0.226
ICS/LABA combination	23 (43.3)	7 (41.2)	0.872
ICS/LABA/LAMAcombination	1 (1.9)	0 (0.0)	0.273
LTRA	2 (3.8)	2 (11.8)	0.217
Xanthines	10 (18.9)	2 (11.8)	0.499

Expectorants	5 (9.4)	1 (5.9)	0.649
Antibiotics	1 (1.9)	0 (0)	0.606
mMRC, points	2 [1-3]	2 [1-3]	0.733
CAT, points	16.9±7.5	16.2±9.2	0.736
SGRQ, points			
Symptoms	55±20.5	45.8±20.1	0.112
Activities	64.8±20.9	50.3±27.8	0.060
Impact	36.6±19.8	27.8±19.1	0.114
Total	48.2±18.6	37.7±19.8	0.050
FACIT-FS, points	33.3±10	37.7±12.8	0.151
No relevant fatigue (>43), n (%)	19 (17)	5 (29.4)	0.214
Relevant fatigue (≤43), n (%)	44 (83)	12 (70.6)	
Modified-FACIT-FS	21.2±7.4	22.7±7.7	0.496
CIS-FS, points	36.9±12.8	32.7±13.9	0.258
Normal fatigue (≤26), n (%)	9 (17)	6 (35.3)	
Mild fatigue, (27-35), n (%)	12 (22.6)	5 (29.4)	0.153
Severe fatigue (≥36), n (%)	32 (60.4)	6 (35.3)	

Notes: Values are presented as mean±standard deviation or median [interquartile range], unless otherwise stated. [1]in the past-year; * p<0.05

Legend: PR – pulmonary rehabilitation; BMI – body mass index; AECOPD – acute exacerbation of chronic obstructive pulmonary disease; FEV_1 – forced expiratory volume in one second; FVC – forced vital capacity; GOLD - Global Initiative for Chronic Obstructive Lung Disease; CCI – Charlson comorbidity index; SABA – short-acting beta-agonists; SAMA – short-acting muscarinic antagonist; LABA – long-acting beta-agonists; LAMA – long-acting muscarinic antagonist; ICS – inhaled corticosteroid; LRTA – leukotriene receptor antagonist; mMRC – modified medical research council questionnaire; CAT – COPD assessment test; SGRQ – St George's Respiratory Questionnaire; FACIT-FS - Functional assessment of chronic illness therapy fatigue subscale; CIS-FS - Checklist of individual strength fatigue subscale.

Table 2: Patient-reported outcome measures before and after the community-based pulmonary rehabilitation programme (n=53).

PROM (points)	Baseline	Post-PR	Δ	95% CI	p-value	ES
CAT	16.9±7.5	13.0±6.9	-3.9±6.7	-5.8 to -2.0	<0.001*	-0.54
SGRQ						
Symptoms	55±20.5	41.1±20.5	-13.9±21.5	-19.8 to -7.9	<0.001*	-0.68
Activities	64.8±20.9	57.8±23.5	-7.0±11.6	-10.2 to -3.8	<0.001*	-0.31
Impact	36.6±19.8	30.4±18.7	-6.2±12.0	-9.5 to -2.8	<0.001*	-0.32
Total	48.2±18.6	40.6±18.1	-7.6±10.4	-10.5 to -4.7	<0.001*	-0.41
FACIT-FS	33.3±10	36.9±8.8	3.7±7.1	1.7 to 5.6	<0.001*	0.38
Modified-FACIT-FS	21.2±7.4	24.0±6.9	2.7±5.5	1.2 to 4.3	0.001	0.38
CIS-20 FS (n=52)	36.9±12.8	31.1±13.4	-5.8±10.2	-8.7 to -3.0	<0.001*	-0.44

Notes: Values are presented as mean±standard deviation. *p<0.05

Legend: PROM – Patient-reported outcome measure**;** PR – pulmonary rehabilitation; Δ – mean change; ES – Effect sizes: 95%CI – 95% confidence interval; CAT – COPD assessment test; SGRQ – St George's Respiratory Questionnaire; FACIT-FS – Functional assessment of chronic illness therapy fatigue subscale; CIS-20 FS – Checklist of individual strength fatigue subscale.

Table 3: Anchor and distribution-based methods used to compute the minimal clinically important difference of fatigue patient-reported outcome measures.

		FACIT-FS	Modified-FACIT-FS	CIS-FS
SGRQ-Impact	Mean change	5.7 (3.3 to 8.1)	4.4 (2.4 to 6.4)	-
	ROC	-	-	-
	Linear regression	3.4 (2.1 to 4.7)	2.3 (1.2 to 3.3)	-
SGRQ-Total	Mean change	4.9 (2.5 to 7.2)	3.9 (2.0 to 5.9)	-
	ROC	-	-	-
	Linear regression	3.2 (1.7 to 4.6)	1.9 (0.7 to 3.1)	-
AECOPD	Mean change	6.4 (1.2 to 11.6)	4.7 (0.1 to 9.3)	9.6 (3.2 to 15.9)
0.5SD		4.3	3.7	6.4
SEM		2.6	2.2	5.0
1.96SEM		5.1	4.4	9.7
MDC		7.2	6.2	13.8
ES		0.42	0.38	-0.44
Pooled MCID		4.7	3.8	9.3
% of change		9.1	10.6	19.3
MCID ES		0.5	0.5	0.7

Notes: Values are presented as mean and 95% confidence intervals. % of change was computed within each scale range. The MCID ES are compute as the MCID value divided by the pooled SD.

Legend: FACIT-FS – Functional assessment of chronic illness therapy fatigue subscale; CIS-20 FS – Checklist of individual strength fatigue subscale; SGRQ – St George's Respiratory Questionnaire; ROC – Receiver operating characteristic curves; SD – standard deviation; SEM – standard error of measurement; MDC – minimal detectable change; ES – effect size; MCID - minimal clinically important difference.

FIGURE LEGEND:

Figure 1: Flow diagram of participants recruited and included in the study. COPD – Chronic obstructive pulmonary disease; PR – pulmonary rehabilitation; AECOPD – acute exacerbation of chronic obstructive pulmonary disease.

Figure 2: Linear regression between changes in the A) Functional Assessment of Chronic Illness Therapy Fatigue Subscale (FACIT-FS) and changes in the St George's Respiratory Questionnaire (SGRQ)-impact; B) FACIT-FS and changes in the SGRQ-total score; C) modified-FACIT-FS and changes in the SGRQ-impact; D) modified-FACIT-FS and changes in the SGRQ-total score (n=53).

Figure 3: Plots of the pooled minimal clinically important differences (MCID) for the: A) Functional Assessment of Chronic Illness Therapy Fatigue Subscale (FACIT-FS); B) modified-FACIT-FS; C - Checklist of individual strength fatigue subscale (CIS-FS). The plots represent the MCID estimates derived in this study, and where appropriated the estimates include the 95% confidence interval (n=53). AECOPD – acute exacerbation of chronic obstructive pulmonary disease; SGRQ – St. George Respiratory Questionnaire; SD – standard deviation; SEM – standard error of measurement; MDC – minimal detectable change.

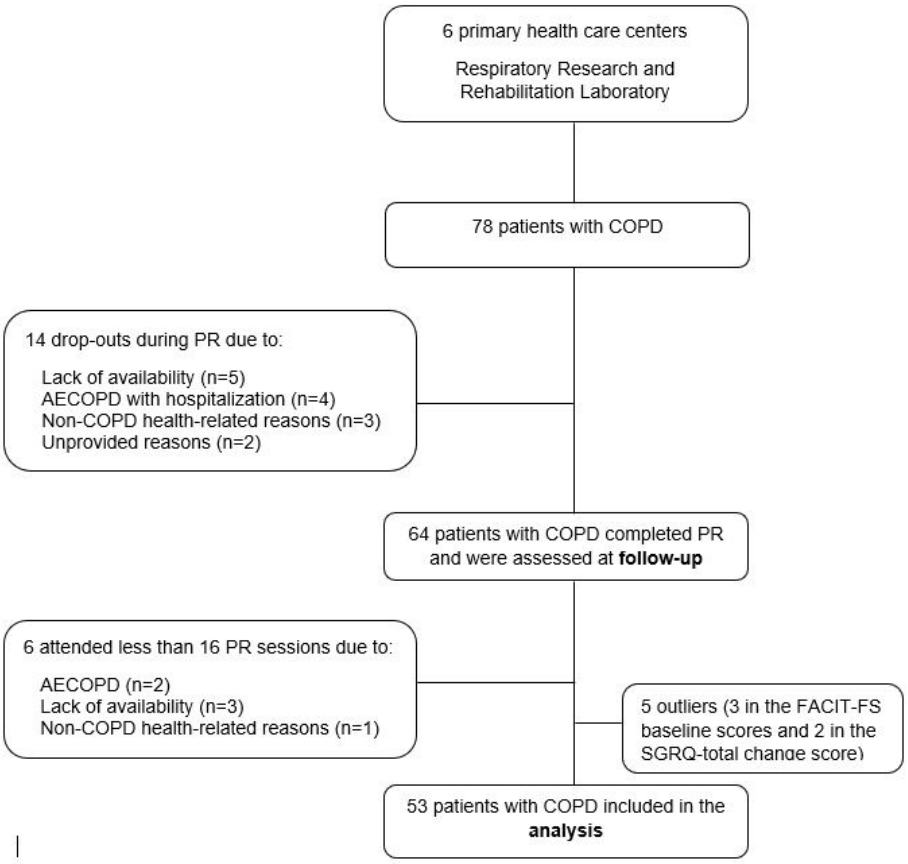


Figure 1: Flow diagram of participants recruited and included in the study. COPD – Chronic obstructive pulmonary disease; PR – pulmonary rehabilitation; AECOPD – acute exacerbation of chronic obstructive pulmonary disease.

130x114mm (144 x 144 DPI)

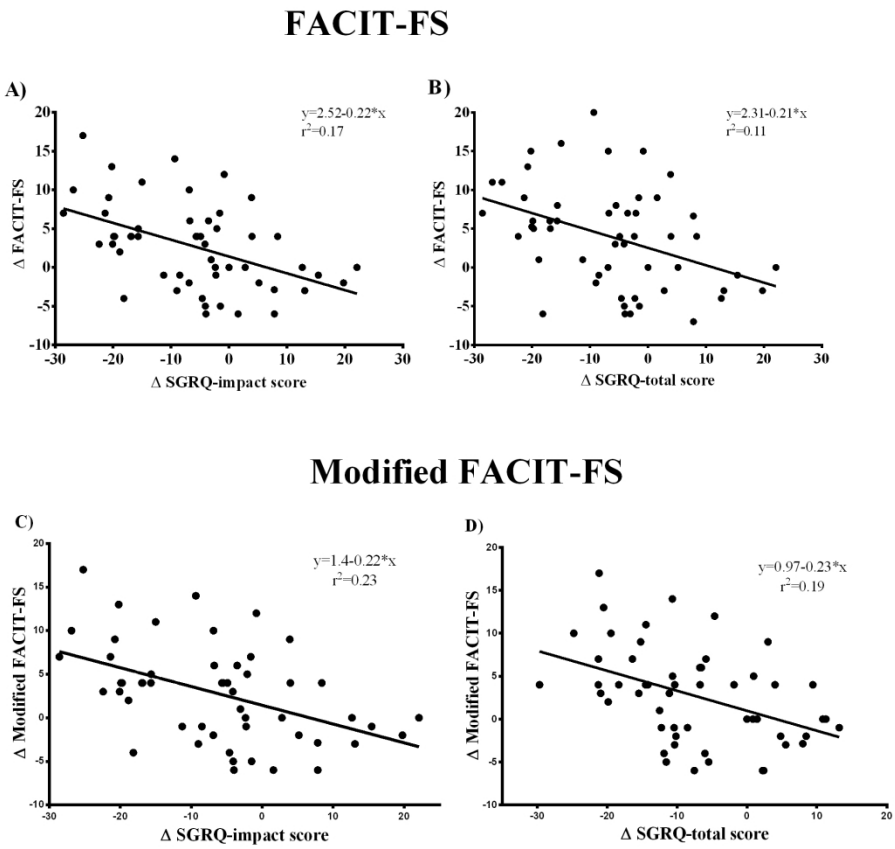


Figure 2: Linear regression between changes in the A) Functional Assessment of Chronic Illness Therapy Fatigue Subscale (FACIT-FS) and changes in the St George's Respiratory Questionnaire (SGRQ)-impact; B) FACIT-FS and changes in the SGRQ-total score; C) modified-FACIT-FS and changes in the SGRQ-impact; D) modified-FACIT-FS and changes in the SGRQ-total score (n=53).

198x177mm (300 x 300 DPI)

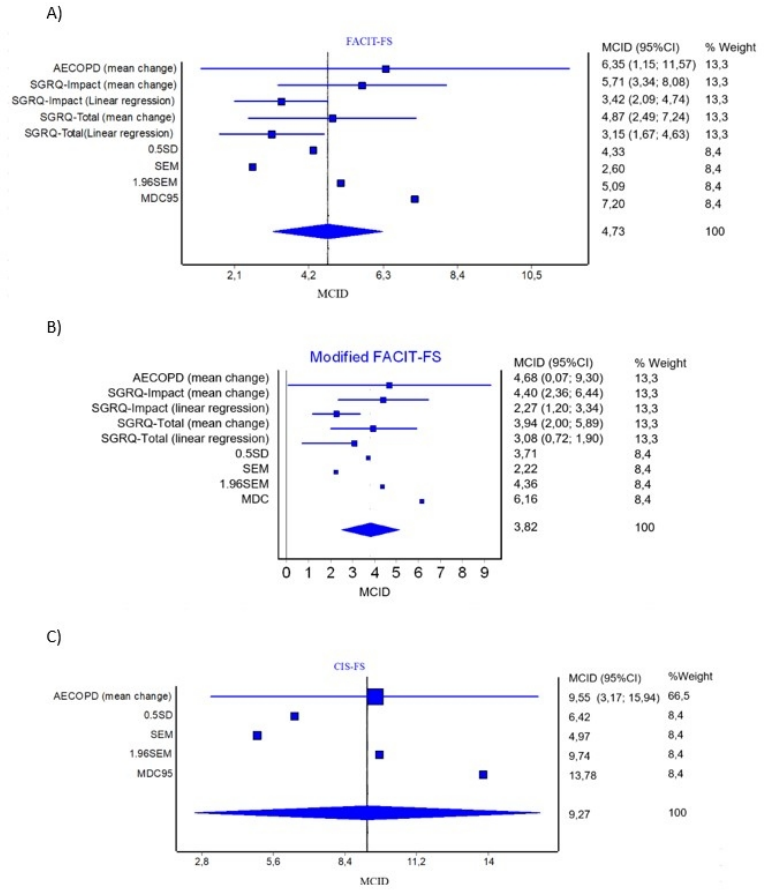


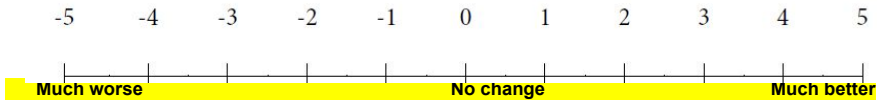
Figure 3: Plots of the pooled minimal clinically important differences (MCID) for the: A) Functional Assessment of Chronic Illness Therapy Fatigue Subscale (FACIT-FS); B) modified-FACIT-FS; C - Checklist of individual strength fatigue subscale (CIS-FS). The plots represent the MCID estimates derived in this study, and where appropriated the estimates include the 95% confidence interval (n=53). AECOPD – acute exacerbation of chronic obstructive pulmonary disease; SGRQ – St. George Respiratory Questionnaire; SD – standard deviation; SEM – standard error of measurement; MDC – minimal detectable change.

190x275mm (96 x 96 DPI)

Supplementary material

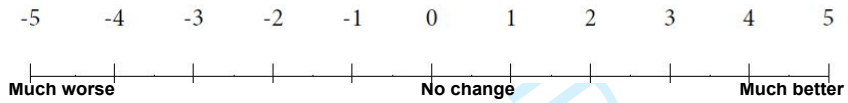
Global rating of change scale for patients

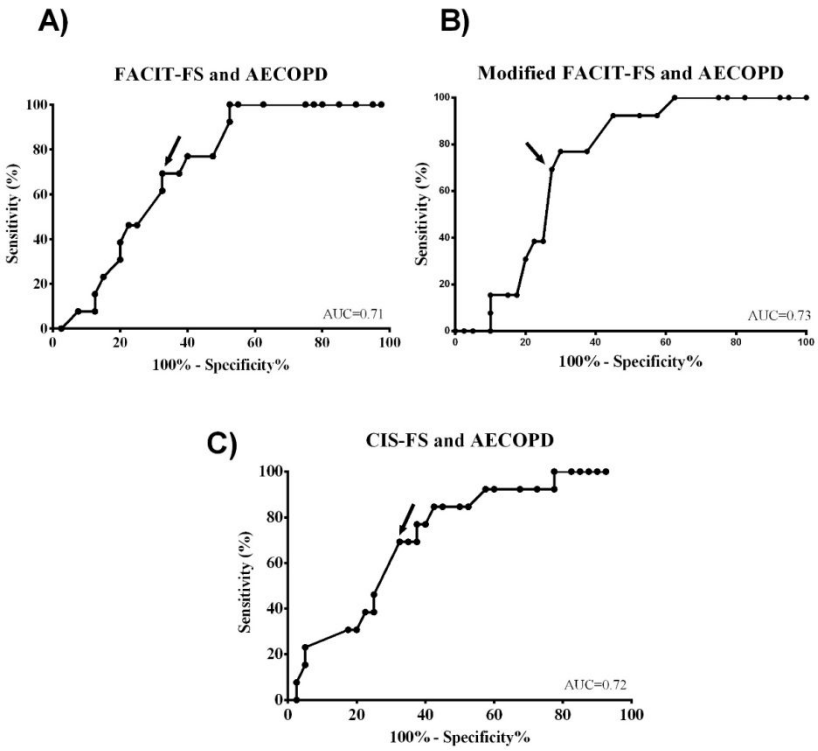
"Regarding fatigue, how would you describe your tiredness/lack of energy at this moment, in comparison to the day you started the pulmonary rehabilitation programme?"



Global rating of change scale for physiotherapists

"Regarding your patient's fatigue, how would you describe the patient's tiredness/lack of energy at this moment, in comparison to the day she/he started the pulmonary rehabilitation programme?"





e-Figure 1 - Receiver operating characteristic curves to discriminate between patients with chronic obstructive pulmonary disease who experienced an acute exacerbation (AECOPD) from those who did not using the: A) Functional Assessment of Chronic Illness Therapy Fatigue Subscale (FACIT-FS) baseline scores; B) modified FACIT-FS baseline scores and C) Checklist of individual strength fatigue subscale (CIS-FS) baseline scores. (n=53). AUC – area under the curve.

e-Table 1: Correlations between the anchors and changes in the patient-reported outcome measures.

	Δ FACIT – FS (n=53)		Δ modified FACIT – FS (n=53)		Δ CIS-20 FS (n=52)	
	r	p-value	r	p-value	r	p-value
Patient's GRC	0.025	0.858	0.059	0.678	-0.084	0.553

Physiotherapist's GRC	0.140	0.318	0.098	0.487	-0.014	0.923
Δ CAT	0.104	0.459	-0.019	0.894	-0.100	0.482
ΔSGRQ						
Symptoms	-0.055	0.697	-0.141	0.315	-0.148	0.296
Activities	-0.172	0.217	-0.288	0.037*	0.038	0.788
Impact	-0.409	0.002*	-0.474	<0.001*	0.137	0.332
Total	-0.330	0.016*	-0.439	0.001*	0.043	0.760
AECOPD	r_{pb} = -0.277#	0.044*	r_{pb} = -0.274#	0.047*	r_{pb} = 0.323#	0.018*

Notes: correlations were calculated using Pearson's (r) or point biserial correlation (r_{pb}) coefficients. # - correlations were computed using CIS-FS, FACIT-FS and modified FACIT-FS baseline scores; * p<0.05

Legend: Δ – mean change; FACIT-FS – Functional assessment of chronic illness therapy fatigue subscale; CIS-20 FS – Checklist of individual strength fatigue subscale; r – Pearson's correlation; GRC – Global rating of change scale; CAT – COPD assessment test; SGRQ – St George's Respiratory Questionnaire; AECOPD – acute exacerbations of chronic obstructive pulmonary disease.

e-Table 2: FACIT-FS and modified FACIT-FS mean scores at baseline and after community-based pulmonary rehabilitation, according to the anchor's cut-offs.

				FACIT – FS (n=53)					modified FACIT-FS (n=53)				
			n, (%)	Baseline	Post-PR	Δ	95% CI	p-value	Baseline	Post-PR	Δ	95% CI	p-value
Patient's GRC		**≥2**	46 (86.8)	33.2±10.1	37.2±8.6	4.0±6.6	2.0 to 5.9	0.805	21.2±7.4	24.1±6.9	2.8±5.5	1.2 to 4.5	0.762
		<2	7 (13.2)	33.7±9.9	37.0±9.9	3.3±7.1	-3.3 to 9.9		21.1±7.9	23.3±7.2	2.1±6.2	-3.6 to 7.9	
Physiotherapist's GRC		**≥2**	46 (86.8)	33.0±10.4	37.2±8.8	4.2±6.8	2.2 to 6.2	0.340	21.0±7.7	24.1±7.0	3.2±5.6	1.4 to 4.8	0.213
		<2	7 (13.2)	35.0±7.0	36.6±8.4	1.7±5.3	-3.3 to 6.6		23.0±5.3	23.3±6.8	0.3±3.9	-3.3 to 3.9	
Δ CAT		**≥2**	38 (71.7)	33.3±10.4	37.2±9.3	3.9±6.6	1.8 to 6.1	0.967	21.1±7.8	24.1±7.5	3.1±5.6	1.2 to 4.9	0.514
		<2	15 (28.3)	33.3±9.1	37.1±6.9	3.8±6.9	0.0 to7.7		21.7±6.7	23.6±5.4	1.9±5.4	-1.1 to 4.9	
Δ SGRQ	**Symptoms**	**≥4**	33 (62.3)	31.4±10.4	36.1±9.4	4.7±6.6	2.3 to 7.0	0.284	19.7±7.5	23.2±7.6	3.5±5.8	1.4 to 5.6	0.208
		<4	20 (37.7)	36.4±8.6	39.0±7.0	2.6±6-6	-0.5 to 5.8		23.7±6.6	25.2±5.6	1.5±4.8	-0.7 to 3.7	
	Activities	**≥4**	32 (60.4)	33.6±10.3	38.1±9.3	4.5±7.4	1.9 to 7.2	0.392	21.3±7.8	25.1±7.4	3.9±6.0	1.7 to 6.0	0.063
		<4	21 (39.6)	32.8±9.7	35.7±7.5	2.9±5.2	0.6 to 5.3		21.2±7.0	22.2±5.8	1.0±4.3	-0.9 to 3.0	
	Impact	**≥4**	30 (56.6)	31.5±10.5	37.2±9.7	5.7±6.3#	3.3 to 8.1	0.021*	20.2±8.0	24.6±7.5	4.4±5.5#	2.4 to 6.4	0.011*
		<4	23 (43.4)	35.5±8.9	37.1±7.2	1.5±6-3	-1.2 to 4.3		22.6±6.5	23.2±6.1	0.6±4.9	-1.5 to 2.7	
	Total	**≥4**	36 (67.9)	32.6±10.4	37.5±9.2	4.9±7.0#	2.5 to 7.2	0.122	20.5±7.7	24.5±7.3	3.9±5.8#	2.0 to 5.9	0.019*
		<4	17 (32.1)	34.7±9.1	36.6±7.5	1.9±5.2	-0.8 to 4.5		22.7±6.6	22.9±6.2	0.2±4.0	-1.9- to 2-2	

Notes: Values are presented as mean ± standard deviation. p-value refers to statistical differences between the mean change variables according to the anchors' cut-off. * p<0.05. # used as minimal clinically important differences.

Legend: FACIT-FS – Functional assessment of chronic illness therapy fatigue subscale; CIS-20 FS – Checklist of individual strength fatigue subscale; PR – Pulmonary rehabilitation; Δ – mean change; 95% CI – 95% confidence intervals; GRC – Global rating of change; CAT – COPD assessment test; SGRQ – St George's Respiratory Questionnaire.

Commented [PR1]: Para conseguir juntar a esta tabela as infos da modified FACIT-FS tive que a dividir…ou seja, a CIS-FS aparece numa tabela separada

Commented [AM2R2]: Não conseguimos mesmo meter nem mudando as margens? Isto d efacto não é nada o ideal…

Commented [PR3R2]: Não consigo mesmo, são 5 colunas a mais…e acho que não podemos reduzir mais o tamanho da letra..

e-Table 3: CIS-FS mean scores at baseline and after community-based pulmonary rehabilitation, according to the anchor's cut-offs.

			CIS-20 FS (n=52)					
			n, (%)	Baseline	Post-PR	Δ	95% CI	p-value
Patient's GRC		**≥2**	45 (86.5)	36.8±13.2	30.6±13.6	-6.3±10.8	-9.6 to -3.1	0.412
		<2	7 (13.5)	37.1±10.7	34.3±12.5	-2.9±4.6	-7.2 to 1.4	
Physiotherapist's GRC		**≥2**	46 (88.5)	37.3±13.3	31.2±14.0	-6.0±10.7	-9.2 to -2.9	0.704
		<2	6 (11.5)	34.1±9.5	29.8±8.3	-4.3±5.7	-10.3 to 1.6	
Δ CAT		**≥2**	37 (71.2)	36.2±12.1	30.4±14.6	-5.9±11.0	-9.6 to -2.2	0.960
		<2	15 (28.8)	38.6±14.8	32.9±10.1	-5.7±8.4	-10.4 to -1.1	
Δ SGRQ	**Symptoms**	**≥4**	33 (63.5)	39.1±12.1	33.8±14.0	-5.2±10.3	-8.9 to -1.6	0.561
		<4	19 (36.5)	33.3±13.5	26.3±11.0	-6.9±10.3	-11.9 to -2.0	
	Activities	**≥4**	32 (61.5)	35.0±13.3	29.9±14.7	-5.1±10.3	-8.8 to -1.4	0.526
		<4	20 (38.5)	39.7±11.8	33.0±11.1	-7.0±10.2	-11.8 to -2.2	
	Impact	**≥4**	29 (55.8)	37.0±12.5	29.8±15.0	-7.2±11.3	-11.5 to -7.2	0.274
		<4	23 (44.2)	36.7±13.5	32.7±11.2	-4.1±8.7	-7.8 to -0.3	
	Total	**≥4**	36 (69.2)	36.8±12.0	30.9±14.7	-5.9±11.1	-9.6 to -2.1	0.988
		<4	16 (30.8)	37.1±14.9	31.4±10.4	-5.8±8.2	-10.2 to -1.5	

Notes: Values are presented as mean ± standard deviation. p-value refers to statistical differences between the mean change variables according to the anchors' cut-off. * p<0.05. # used as minimal clinically important differences

Legend: CIS-20 FS – Checklist of individual strength fatigue subscale; PR – Pulmonary rehabilitation; Δ – mean change; 95% CI – 95% confidence intervals; GRC – Global rating of change; CAT – COPD assessment test; SGRQ – St George's Respiratory Questionnaire.

e-Table 4: Patient-reported outcome measures mean scores at baseline and after community-based pulmonary rehabilitation, according to the criterion referencing (n=53).

		AECOPD				
		No	Yes	Mean difference	95% CI	p-value
FACIT-FS	n, (%)	40 (75.5)	13 (24.5)	6.4	1.2 to 11.6	p=0.044*
	Baseline	34.8±10.3	28.5±7.1			
modified FACIT-FS	n, (%)	40 (75.5)	13 (24.5)	4.7	0.1 to 9.3	p=0.047*
	Baseline	22.4±7.8	17.7±4.6			
CIS-20 FS	n, (%)	40 (75.5)	12 (24.5)	-9.6	-15.9 to -3.2	p=0.018*
	Baseline	34.5±13.2	44.1±8.4			

Notes: Values are presented as mean ± standard deviation. * p<0.05

Legend: AECOPD – Acute exacerbation of chronic obstructive pulmonary disease; 95% CI – 95% Confidence intervals; FACIT-FS – Functional assessment of chronic illness therapy fatigue subscale; CIS-20 FS – Checklist of individual strength fatigue subscale;

Agreement from FACIT.org for licensing questionnaires from the FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY (FACIT) system of Quality of Life questionnaires

May 23, 2018

The Functional Assessment of Chronic Illness Therapy system of Quality of Life questionnaires and all related subscales, translations, and adaptations ("FACIT System") are owned and copyrighted by David Cella, Ph.D. The ownership and copyright of the FACIT System resides strictly with Dr. Cella. Dr. Cella has granted FACIT.org (Licensor) the right to license usage of the FACIT System to other parties. Licensor represents and warrants that it has the right to grant the License contemplated by this agreement. Licensor proposes to Respiratory Research and Rehabilitation Laboratory (Lab3r) the licensing agreement outlined below. If agreed to, this license will grant permission to Lab3r the right to use the FACIT to the extent outlined below. This license is applicable for vendors providing printing, dissemination or electronic data capture services to clinical services clients (e.g. hospital, physicians' office, outpatient clinic, hospice, nursing facility).

This current license extends to Lab3r's support software project offered to clinical clients only, subject to the following terms:

1) Lab3r is required to track and provide usage of the FACIT-FATIGUE questionnaire by clinicians and patients over the 2 year period of this license. At the end of this 2 year, no-fee license, Lab3r will provide this usage information to FACIT.org.

2) Due to the ongoing and evolving nature of questionnaire development, treatment modalities and cross-cultural linguistic research, Licensor reserves the right to make adaptations of revisions to wording in the FACIT, and/or related translations as necessary. If there are particular versions of the FACIT questionnaires that are requested by oncologists using Lab3r's system, it is the responsibility of Lab3r to ensure the version used in their system is the one desired by their client. Licensor will assume no liability for version control between Lab3r and their clients.

3) Lab3r may not change the wording or phrasing of any FACIT document without previous permission from licensor. If any changes are made to the wording or phrasing of any FACIT item without permission, the document cannot be considered the FACIT, and subsequent analyses and/or comparisons to other FACIT data will not be considered appropriate. Permission to use the name "FACIT" will not be granted for any unauthorized translations of the FACIT items. Any analyses or publications of unauthorized changes or translated versions may not use the FACIT name. Any unauthorized translation will be considered a violation of copyright protection and of the terms of this license.

4) Licensor grants Lab3r a worldwide non-exclusive license to use the FACIT-FATIGUE questionnaire in Portuguese in their software offered to clinical services clients only. Neither Lab3r nor their client may distribute, re-use, market or transfer the questionnaire in any form for use in any other program, nor with any other type of client outside of clinical services clients.

5) Lab3r agrees to list the copyright information on each page in which the questionnaire, items from the questionnaire, or scoring documents are listed.

6) Licensor reserves the right to withdraw this license if Lab3r engages in scientific or copyright misuse of the FACIT system of questionnaires. Included in copyright misuse will be the representation by Lab3r to any clients that Lab3r is an authorized representative of FACIT questionnaires

7) In no cases may the FACIT questionnaire be placed on the internet without password protection.

8) There are no fees associated with this license.

9) This license is good for a period of 2 years upon signature at FACIT.org.

10) Lab3r agrees to notify FACIT.org at the end of this license.

Lab3r	FACIT.org
Aldastridres de Dias Marques	
By: ALDA MARQUES	By: Jason Bredle
Title: Dr.	Title: Director
Date: 24th / May / 2018	Date: 25 May 2018

Patrícia Rebelo

From: Liesbeth.Nieboer@radboudumc.nl on behalf of Jan.Vercoulen@radboudumc.nl
Sent: 31 de janeiro de 2018 16:43
To: Patrícia Rebelo
Subject: RE: Permission to use CIS-20
Attachments: CIS8R-english.pdf; CIS20R-english.pdf; Information and conditions for use.pdf; reference paper CIS20r.pdf

Dear colleague,

Hereby my permission to use the Checklist Individual Strength.

In the attach you will find related documents.

Best regards,

Dr. Jan Vercoulen

Van: Vercoulen, Jan
Verzonden: maandag 29 januari 2018 9:11
Aan: Nieboer, Liesbeth
Onderwerp: FW: Permission to use CIS-20

Van: Patrícia Rebelo [mailto:patriciarebelo@ua.pt]
Verzonden: zondag 28 januari 2018 11:10
Aan: Vercoulen, Jan
Onderwerp: Permission to use CIS-20

Dear Sir/Madam,
My name is Patrícia Rebelo and I am writing to you on behalf of Professor Alda Marques, who is the coordinator of the Respiratory Research and Rehabilitation Laboratory (Lab3R) at School of Health Sciences, University of Aveiro Portugal.
We have currently the need to use the Checklist Individual Strength-20 (CIS-20) in one of our research projects. We therefore would like to ask your permission to use the CIS-20 Portuguese version.
I look forward to hear from you.
Kind regards,
Alda Marques

De: Marta Marques
Enviado: 18 de outubro de 2017 12:42
Para: joana.cruz@ua.pt
Assunto: RE: pedido de autorização - CIS20-P

Cara Joana Cruz,

Eu ja nao utilizo este email com regularidade daí o atraso. Por favor utilize o email marta.marques@ucl.ac.uk para futuros contactos.
Peço pf.f. para contactar a Prof. Maria Joao Gouveia que também colaborou neste projecto e peça para lhe enviar a escala e instruções. Diga que falou comigo.

A escala pode ser utilizada para fins de investigação sem ser necessária autorização, agradecemos a citação do artigo e caso obtenha dados úteis para fortalecer a validação da escala pode nos comunicar.

Obrigada,

Marta Marques

De: joana.cruz@ua.pt [joana.cruz@ua.pt]
Enviado: sexta-feira, 13 de Outubro de 2017 15:03
Para: Marta Marques
Assunto: FW: pedido de autorização - CIS20-P

Exma. Srª Professora Marta Marques,

Peço desculpa por estar a enviar novamente mail, mas queria ter a certeza de que recebeu o meu mail anterior (que reencaminho abaixo) relativamente à escala CIS20, validada no seu artigo de 2013. Estou disponível para falar por telefone, caso seja apropriado: 969196218.
Agradeço desde já a disponibilidade e peço desculpa pelo incómodo.
Os melhores cumprimentos,
Joana Cruz

De: joana.cruz@ua.pt
Enviado: 10 de outubro de 2017 17:29
Para: mmarques@ispa.pt
Assunto: pedido de autorização - CIS20-P

Exma. Srª Professora Marta Marques,

Sou um dos elementos de uma equipa de investigação da Universidade de Aveiro e encontrei o seu artigo intitulado “Psychometric Properties of the Portuguese Version of the Checklist of Individual Strength (CIS20-P)”, o qual mereceu a minha melhor atenção. Gostaríamos de utilizar e validar a escala para a população de pessoas com Doença Pulmonar Obstrutiva Crónica (DPOC), no âmbito de uma dissertação de Mestrado (com potencial publicação), pelo que gostaríamos de a questionar sobre a possibilidade de nos enviar a escala e o sistema de codificação, assim como a autorização para utilização da escala.
Estou disponível para prestar informação adicional.
Agradeço desde já a atenção dispensada.

Os melhores cumprimentos,
Joana Cruz

St George's
University of London

Medicine, Biomedical Sciences, Health and Social Care Sciences

7 March 2017

Cranmer Terrace
London SW17 0RE

Switchboard
+44 (0)20 8672 9944

www.sgul.ac.uk

To Whom It May Concern:

This is to confirm that St George's, University of London (St George's Hospital Medical School) has given permission for Lab3R, School of Health Sciences of the University of Aveiro, Portugal, to use the St George's Respiratory Questionnaire (SGRQ) in a project entitled ***"Revitalizing Pulmonary Rehabilitation (3R)"***

Professor Paul Jones, PhD FRCP
Professor of Respiratory Medicine

P.W. Jones, PhD FRCP
Professor of Respiratory Medicine
Tel. ++44 (0)20 8725 5371 **Fax. ++44 (0)20 8725 5955** **email pjones@sgul.ac.uk**

Modified Medical Research Council – does not require authorization. It is available and recommend for use by the Portuguese national health authority (*Direção-Geral de Saúde)*

COPD Assessment Test - http://www.catestonline.org – does not require authorization.

"You may, for personal use and for research purposes, read, view, print download and copy the material on this website in accordance with the license to copy for personal use conditions stipulated in the legal notices."