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PATRÍCIA FILIPA SOBRAL REBELO

Mínimas diferenças de importância clínica para medidas de fadiga, tosse e expetoração reportadas pelos doentes com DPOC

Minimal clinically important differences for fatigue, cough and sputum patient-reported outcome measures in COPD

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Dissertação apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Fisioterapia ramo Respiratória, realizada sob a orientação científica da Doutora Alda Marques, Professora Adjunta da Escola Superior de Saúde da Universidade de Aveiro e da Mestre Ana Oliveira, Professora Assistente Convidada da Escola Superior de Saúde da Universidade de Aveiro.

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O júri

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Palavras-chave

Características de medida; Sintomas; Medidas reportadas pelos doentes; Reabilitação Respiratória; DPOC.

Resumo

Enquadramento: A fadiga, a tosse e a expetoração são sintomas de elevada prevalência na doença pulmonar obstrutiva crónica (DPOC), e a sua avaliação é frequentemente realizada utilizando medidas reportadas pelos doentes (i.e., PROMs). A Reabilitação Respiratória (RR) tem demonstrado ser eficaz na gestão destes sintomas. Contudo, a interpretação da magnitude dos efeitos da RR nestes sintomas é limitada pela inexistência de pontos de corte que permitam detetar alterações clinicamente relevantes para os doentes e profissionais de saúde (i.e., mínima diferença de importância clínica – MDIC).

Objetivo: Estimar MDIC após a RR para as seguintes PROMs: c*hecklist of individual strength –fatigue subscale (CIS-20 FS), functional assessment of chronic illness therapy –fatigue (FACIT-F), Leicester cough questionnaire (LCQ)* e *cough and sputum assessment questionnaire (CASA-Q)*, na DPOC.

Métodos: Realizou-se um estudo observacional prospetivo com doentes com DPOC, que participaram num programa comunitário de RR. As PROMs foram recolhidas antes e após o programa de RR. Para calcular as MDIC foram utilizados métodos de ancora (i.e., diferenças entre médias, curvas de característica de operação do recetor e regressões lineares) e métodos de distribuição (i.e., 0.5 vezes o desvio padrão; erro *standard* da medida (ESM); 1.96 vezes o ESM; mínima diferença detetável (MDC95) e tamanhos do efeito). As âncoras usadas foram: i) g*lobal rating of change scale* dos doentes e fisioterapeutas; ii) *COPD assessment test;* iii) *st. george's respiratory questionnaire* e iv) ocorrência de exacerbações durante a RR. As MDIC finais foram calculadas agrupando os métodos de âncora e de distribuição através de um modelo de qualidade dos efeitos.

Resultados: Foram incluídos 49 doentes com DPOC (81,6% homens, 69,8±7,4 anos, FEV_1 49,4±19,2%previsto). As MDIC calculadas foram: 7,3 (4,1 a 10,6) para a CIS-20 FS, 4,2 (1,7 a 6,7) para a FACIT-F, 1,3 (0,4 a 2,2) para a LCQ, 10 para as dimensões dos sintomas/ impacto da tosse e sintomas da expetoração da CASA-Q e 7,8 para o impacto da expetoração, com intervalos entre 0 a 19,5.

Conclusão: As MDIC encontradas neste estudo, 7,3 na CIS-20 FS, 4,2 na FACIT-F, 1,3 na LCQ, 10,6 e 10,1 nas dimensões dos sintomas e impacto da tosse, e 9,7 e 7,8 nas dimensões da expetoração da CASA-Q, são potenciais estimativas que podem ser usadas pelos profissionais de saúde para interpretar os efeitos da RR nestes sintomas, e guiar futuras intervenções.

Keywords Measurement characteristics; Symptoms; Patient-reported outcome measures; Pulmonary rehabilitation; COPD.

Abstract

Background: Fatigue, cough and sputum are highly prevalent symptoms in patients with chronic obstructive pulmonary disease (COPD), which evaluation is commonly performed using patient-reported outcome measures (PROMs). Pulmonary rehabilitation (PR) has shown to be effective in managing these symptoms. However, the interpretation of the magnitude of PR effects is hindered by the lack of cut-off points to identify clinically relevant changes for patients and health professionals (i.e., minimal clinically important differences - MCIDs).

Aim: To establish MCIDs, after PR, for the following PROMs: checklist of individual strength – fatigue subscale (CIS-20 FS), functional assessment of chronic illness therapy – fatigue (FACIT-F), Leicester cough questionnaire (LCQ) and cough and sputum assessment questionnaire (CASA-Q), in patients with COPD.

Methods: An observational prospective study was conducted in patients with COPD who participated in a community-based PR programme. All PROMs were assessed pre/post PR. Anchor- (i.e., mean change, the receiver operating characteristic curves and linear regression analysis) and distribution-based methods (i.e., 0.5 times the standard deviation; standard error of measurement (SEM); 1.96 times the SEM; minimal detectable change (MDC95) and effect size) were used to compute the MCIDs. The anchors used were: i) patients and physiotherapists global rating of change scale, ii) COPD assessment test, iii) St. George's respiratory questionnaire and iv) the occurrence of exacerbations during PR. Pooled MCIDs, combing anchor- and distribution-based methods, were computed using a quality effects model.

Results: Forty-nine patients with COPD (81.6% male, 69.8±7.4 years, FEV_1 49.4±19.2%predicted) were used in the analysis. The pooled MCIDs were: 7.3 (4.1 to 10.6) for CIS-20 FS, 4.2 (1.7 to 6.7) for FACIT-F, 1.3 (0.4 to 2.2) for LCQ, 10 for CASA-Q cough symptoms/ impact and sputum symptoms domains and 7.8 for sputum impact, ranging from 0 to 19.5.

Conclusion: The MCIDs found in this study, 7.3 for CIS-20 FS, 4.2 for FACIT-F, 1.3 for LCQ, 10.6 and 10.1 for the cough symptoms and impact dimensions, and 9.7 and 7.8 for the sputum dimensions of CASA-Q, are potential estimates that can be used by health professionals to interpret PR effects in these symptoms and guide future interventions.

Abbreviations and/or acronyms

1-RM – 1 repetition maximum

6MWT – 6-minute walk test

10-RM – 10 repetition maximum

AECOPD – Acute exacerbation of Chronic Obstructive Pulmonary Disease

AUC – Area under the curve

BMI – Body mass index

CASA-Q – Cough and sputum assessment questionnaire

CASA-Q-CI – Cough and sputum assessment questionnaire - cough impact

CASA-Q-CS – Cough and sputum assessment questionnaire – cough symptoms

CASA-Q-SI – Cough and sputum assessment questionnaire – sputum impact

CASA-Q-SS – Cough and sputum assessment questionnaire – sputum symptoms

CAT – COPD assessment test

CCI – Charlson comorbidity index

CI – Confidence interval

CIS-20 FS – Checklist of individual strength – fatigue subscale

COPD – Chronic obstructive pulmonary disease

COSMIN – Consensus-based standards for the selection of health measurement instruments

ES – Effect size

ERS – European Respiratory Society

FACIT-F – Functional assessment of chronic illness therapy – fatigue

FEV_1 – Forced expiratory volume in one second

FVC – Forced vital capacity

GOLD – Global Initiative for Obstructive Lung Disease

GRC – Global rating of change scale

HRmax – Maximum heart rate

HRQoL – Health-related quality of life

ICC – Intraclass correlation coefficient

ICF – International classification of functioning, disability and health

ICS – Inhaled corticosteroid

LABA – Long-acting beta-agonists

LAMA – Long-acting muscarinic antagonist

LCQ – Leicester cough questionnaire

LRTA – Leukotriene receptor antagonist

MCID – Minimal clinically important difference

MDC – Minimal detectable change

MDC95 – Minimal detectable change with a 95% interval confidence

mMRC – Modified British medical research council questionnaire

PR – Pulmonary rehabilitation

PRO – Patient-reported outcome

PROM – Patient-reported outcome measure

R – Pearson's correlation

ROC – Receiver operating characteristic

S – Spearman's correlation

SABA – Short-acting beta-agonists

SAMA – Short-acting muscarinic antagonist

SD – Standard deviation

SEM – Standard error of measure

SN – Sensitivity

SP – Specificity

SGRQ – St. George's respiratory questionnaire

Wpeak – Work peak

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1. Introduction

Chronic obstructive pulmonary disease (COPD) affects approximately 384 million people around the world and 800.000 in Portugal (1, 2). In the past years, COPD-related morbidity and mortality has been increasing (1) and, in 2016 it was considered the third leading cause of death worldwide (3). Therefore, COPD is a growing global health concern that poses major burden on individuals, as well as, on economics and social systems (1, 4, 5).

The individual disease burden is driven by the impact of symptoms and their influence on the patient's ability to perform daily activities (6), which contribute for making COPD the 5th leading cause of disability-adjusted life years (DALYs), i.e. for the loss of years of life and years lost due to disability (1). Economic and societal costs are determined by the severity of the disease, the frequency of exacerbations and the presence of comorbidities (1, 5). In the European Union, the direct annual healthcare costs related to COPD are of €38.6 billion, along with an important productivity loss (1, 7). Nevertheless, the accurate global burden of COPD is still unknown due to its underdiagnoses (1, 5). In Portugal, efforts to overcome this underdiagnoses are in place, namely by increasing awareness of health professionals and general population for this disease, and have resulted in an increase of 241% new diagnosis of COPD from 2011 to 2016 (8).

COPD is highly symptomatic and commonly characterised by persistent dyspnoea (1). Recently, fatigue has also been recognised as an important symptom, affecting around 50 to 70% of patients with COPD (9, 10). Fatigue is a common, multi-dimensional and disabling symptom in chronic conditions, being inevitably associated to the arduous breathing in patients with COPD (11). Previous studies have been defining fatigue as a subjective phenomenon, whereas more recent authors further underline, that fatigue is a constant interaction between the perceived fatigability and the performance fatigability, the latter an objective parameter (12, 13). Although there is no consensus regarding its definition, fatigue is usually defined as an overwhelming feeling of tiredness and drain of energy, that negatively influences physical, cognitive, psychological and social functioning (14-18). Thus, fatigue is a key symptom impairing patients' health-related quality of life (HRQoL), since it limits their daily functioning, affects social and familiar relationships, and frequently leads to feelings of frustration and depression (10, 11, 18). Despite the evidence highlighting the importance of fatigue in patients with COPD, the knowledge on this symptom is scarce, making it underdiagnosed and undertreated in patients with COPD (10, 12, 18, 19).

Similarly to fatigue, cough and sputum are underappreciated symptoms in COPD (19-23), despite being present in approximately 60% of patients (24-26). Cough, in particular, is present not only in more severe stages, but also in patients with mild obstruction (24, 27). Additionally, the presence of cough and sputum has been recognised to affect significantly and negatively patients' HRQoL (6, 28, 29), and to be a powerful predictor of the frequency and severity of exacerbations and, consequently, COPD progression (22, 26, 28, 30). Thus, there is a need for more studies focusing on the assessment of these symptoms, so that effective treatments can be adjusted or developed, if needed.

The assessment of patients' symptoms has been recognised as fundamental for developing personalised interventions and, since 2011, their assessment is formally incorporated into the COPD management strategy (1). One of the most adequate and recommended ways of capturing patients' symptoms and their burden, is assessing patient-reported outcomes (PROs) (31-33). This strategy consists in using self-administered questionnaires that directly enquire patients about their symptoms and/or the results achieved with an intervention, i.e., patient-reported outcome measures (PROMs) (31-33). By providing patients' perspectives and enhancing their participation in the judgement of the benefit, or harm, of an intervention (34), PROMs are useful and important tools to guide health professionals on the effectiveness of treatments and their impact on patients' symptoms (35). Despite these well-known advantages of PROMs to assess patients' symptoms and the efficacy of pharmacological and non-pharmacological interventions, interpretation of their results remains a challenge, due to the lack of well-established minimal clinically important differences (MCID) (34).

Currently, the most comprehensive, well-established and evidence-based non-pharmacological intervention to manage patients with COPD is pulmonary rehabilitation (PR) (1, 36, 37). PR has shown to be a cost-effective intervention to reduce patients' symptoms of dyspnoea, cough, sputum and fatigue and to improve their HRQoL (1, 18, 36-40). However, to understand the magnitude of the results achieved with PR in relieving symptoms, it is essential to know if the change measured through a PROM is trivial, small but important, moderate or large (34). In other words, to better interpret the effects obtained with PR there is a need to know the MCID of PROMs (34, 41, 42). The MCID can be defined as the smallest change in a measure score that is subjectively perceived as relevant to the patient, to the health professional, or informed proxies (43, 44). Thus, establishing MCID for PROMs that assess patients' symptoms is of paramount importance, not only for health professionals to guide interventions (45, 46), but also for guideline developers and policy-makers to judge the clinical relevance and magnitude of a PR effect (34, 47), and for

researchers, as it can be used to calculate samples sizes and as an endpoint in clinical trials (42, 48, 49).

According to the authors best knowledge, the MCID for PROMs assessing fatigue, cough and sputum production after PR in patients with COPD are yet to be established, which limits patient's management during PR, hampers interpretation of their changes and ultimately leads to suboptimal tailored interventions.

This study aimed to contribute to establish the MCID of PROMs that assess symptoms of fatigue (i.e., checklist of individual strength – fatigue subscale [CIS-20 – FS] [15], functional assessment of chronic illness therapy – fatigue [FACIT-F] [50]), cough (i.e., Leicester cough questionnaire [LCQ] [51]), and sputum (i.e., cough and sputum assessment questionnaire [CASA-Q] [52]) in patients with COPD, following a PR programme.

2. Methods

This study is part of a larger study entitled "3R – revitalizing pulmonary rehabilitation; SAICT-POL/23926/2016", was funded by *Fundo Europeu de Desenvolvimento Regional* (FEDER) - *Comissão Diretiva do Programa Operacional Regional do Centro* and by *Fundação para a Ciência e Tecnologia* (FCT), by costs resulting from the FCT hirings, funded by national funds (OE), through FCT I.P., in the scope of the framework contract foreseen in the numbers 4, 5 and 6 of the article 23, of the Decree-Law 57/2016, of August 29, changed by Law 57/2017, of July 19; and partially funded by *Programa Operacional Competitividade e Internacionalização* (COMPETE), through COMPETE 2020 (POCI-01-0145-FEDER-016701) and FCT (UID/BIM/04501/2013 and POCI-01-0145-FEDER-007628- iBiMED).

2.1 Ethical considerations

Ethical approval was obtained prior to study commencement from the Ethics Committee for Health of the *Administração Regional de Saúde do Centro* (ARS-Centro, I.P.), Coimbra, Portugal, "Estudo 73/2016" (Annex I). Approval from the National Committee for Data Protection was also obtained, "n. º 7295/2016", (Annex II). Participants enrolment and data collection was preceded by a written description of the study and its purpose (Appendix I) and obtention of the written informed consent of all participants (Appendix II). Two presentations submitted as an abstract to international conferences have been developed within the scope of this dissertation (Appendix III).

2.2 Sample size

According to Terwee and colleagues, a sample size of at least 50 participants is required to determine the MCID of a PROM (53). However, as the drop-out rates during PR programmes are approximately of 20% (54), this study aimed to recruit 60 participants.

2.3 Study design

An observational prospective study was conducted.

2.4. Participants

Patients with stable COPD were recruited via clinicians at Centro Hospitalar do Baixo Vouga and primary care centers from Aveiro, Mira, Cantanhede, Oliveira do Bairro, Estarreja and Águeda, between February and September 2018.

Patients were considered eligible if meting the Global Initiative for Obstructive Lung Disease (GOLD) criteria to diagnose COPD (1), and were clinically stable over the last month (i.e., no hospital admissions, exacerbations or changes in medication for the cardiorespiratory system). Exclusion criteria included the presence of any clinical condition that precluded participants of being involved in the community-based PR programme, such as, signs of cognitive impairment (e.g. dementia) or presence of a significant cardiovascular (e.g. symptomatic ischaemic cardiac disease), neurological (e.g. neuromuscular dystrophy disease) or musculoskeletal disease (e.g. important kyphoscoliosis).

Eligible patients were identified by clinicians and contacted by the researchers, who explained the purpose of the study and asked about their willingness to participate. An appointment with the researchers was scheduled with those interested in participating in a community-based PR programme.

2.5. Data collection

Data collection was performed before and after the community-based PR programmes by 3 physiotherapists with experience in collecting the outcome measures.

Sociodemographic (age, gender, education and occupation), anthropometric (height and weight measurements to compute body mass index - BMI) and clinical data (smoking status, medication, long-term oxygen, non-invasive ventilation, number of exacerbations, hospitalisations or emergency admissions in the past year) were first obtained, using a structured questionnaire based on the International Classification of Functioning, Disability and Health – ICF (55). Comorbidities were assessed and scored according to the Charlson

comorbidity index (CCI) (56), which classifies comorbidities as mild (CCI scores of 1-2), moderate (CCI scores of 3-4) or severe (CCI scores≥5). The modified British medical research council questionnaire (mMRC) (57), COPD assessment test (CAT) (58), St. George's respiratory questionnaire (SGRQ) (59), checklist of individual strength (CIS-20) (15), functional assessment of chronic illness therapy – fatigue (FACIT-F) (50), Leicester cough questionnaire (LCQ) (51) and cough and sputum assessment questionnaire (CASA-Q) (52) were collected in the reported standardised order. Global rating of change scale (GRC) (60) was only administered following the community-based PR programme.

2.5.1. Patient reported outcome measures (PROMs)

All PROMs were applied using a supervised self-administration method, preceded by a brief explanation about the aim of each questionnaire or scale. Before applying the PROMs, formal permission for using the questionnaires was provided by each developer.

Modified British medical research council questionnaire (mMRC)

The mMRC questionnaire is a valid and reliable measure of functional dyspnoea related to respiratory impairment (57, 61, 62). It is an easy questionnaire to administer, as it is a 5-point scale, rated from 0 to 4, with higher scores indicating greater breathlessness severity (1, 63). It takes approximately one minute to complete. Since 2011, the GOLD included the mMRC as a key element for the assessment of patients with COPD, since it is significantly associated with other health measures (CAT and SGRQ) and it is a predictor of mortality risk (1, 64). A score in the mMRC ≥2 together with other clinical features is used to define the patient's GOLD stage and/or body mass, airflow obstruction, dyspnoea and exercise capacity index (BODE Index) (1, 65). Despite being an established useful marker in COPD, mMRC is predominantly a discriminative and poorly responsive tool (63, 66). A change of 1 point is suggested as being a MCID for the mMRC (63).

COPD assessment test (CAT)

The CAT is an 8-item unidimensional scale that assesses the impact of COPD and the most burdensome symptoms in patients' life (cough, sputum, chest tightness, dyspnoea, home daily activities, confidence leaving home, sleep and energy levels) in a 5-point scale (58). The scores range from 0-40, organised in 4 categories, namely <10 low impact, 10-20 medium, 21-30 high and >30 very high impact, with 5 representing the upper limit of normal in healthy non-smokers (67). The CAT takes 2-3 minutes to complete (68). In patients with COPD, CAT has shown to be reliable (Intraclass correlation coefficient - ICC=0.80-0.96; Cronbach's α=0.85-0.98) and valid (correlation with the SGRQ r=0.69-0.82) (58, 69).

Moreover, in this population, CAT has shown to be a responsive measure (69, 70), with a 2 unit change being the MCID used following PR (68).

St. George's respiratory questionnaire (SGRQ)

The SGRQ is a comprehensive well-established 50-item questionnaire, specifically designed to measure health status in patients with COPD (59). The SGRQ integrates three domains, i.e., symptoms, activities and impact, with a 3-month period recall for symptoms and a current state recall for the other 2 components (59). The 50 items vary between Likert-type scale and dichotomous form and takes approximately 10 minutes to complete (71). Scores can be provided for each domain and a total score, ranging from 0 (no impairment) to 100 (worst possible health status) can also be obtained (72). It is recommended that if a patient scores above, or equal to, 25 points in the symptom's domain of SGRQ, he or she should be referred to symptom's treatment (1). The SGRQ has been used in multiple clinical trials, with either pharmacological and non-pharmacological interventions, such as PR (73, 74). The SGRQ validity in patients with COPD, has been widely stated (72, 75). Moreover, the SGRQ has also shown excellent test-retest reliability (ICC=0.92) and good responsiveness to PR in patients with COPD (72, 74). Although there is some controversy regarding the estimate on the MCID of the SGRQ (49), we used a 4 unit change in the total score, since it is extensively used in the literature and has been developed using various methods (expert-based ratings, patient-referencing, criterion-referencing, distribution-methods) (73).

Checklist of individual strength (CIS-20)

The CIS-20 is a 20-statements self-reported measure divided into 4 dimensions of fatigue: subjective experience of fatigue (8 items), concentration (5 items), motivation (4 items) and physical activity level (3 items) (15). Each item is scored on a 7-point Likert scale ranging from "Yes, that is true" to "No, that is not true", with a period recall of two weeks (15). Scores can be calculated separately for each domain or added up, giving a total CIS-20 score, with higher scores indicating higher levels of fatigue (14). Respecting to the subscale of subjective fatigue, 3 subgroups can be categorised: normal fatigue (≤26 points), mild fatigue (27-35 points) and severe fatigue (≥36 points) (14). It takes about 5 minutes to complete the CIS-20.

This questionnaires was first designed to evaluate patients with chronic fatigue syndrome (15). More recently, it has also been applied to study fatigue in patients with COPD (9, 76).

The CIS-20 is a psychometrically sound instrument (14). It has shown high internal consistency and test-retest reliability for either the total score (Cronbach's α=0.95;

Spearman rank correlation s=0.86) and for the subscales (fatigue severity α=0.94/ s=0.85; concentration α=0.89/ s=0.79; motivation α=0.84/ s=0.79 and physical activity α=0.90/ s=0.73) (14). The CIS-20 has revealed high correlation with other fatigue measures proving its good concurrent validity (14). As no gold standard for fatigue exists, criterion validity for CIS-20 was deemed acceptable (14). The ability to detect change in subjective fatigue, using CIS-20, has been reported by several studies (9, 77-79). To our best knowledge, no MCID has been reported yet. CIS-20 has already been validated for the Portuguese population (80).

Functional assessment of chronic illness therapy – fatigue (FACIT-F)

The FACIT-F is a multi-dimensional 13-item questionnaire assessing tiredness, weakness and difficulty in handling daily activities due to fatigue, over the previous 7 days (50, 81). 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 (50, 82). The mean time to complete the FACIT-F is 5 to 10 minutes (50).

The FACIT-F, when used in COPD, has shown high internal consistency (Cronbach’s α=0.92) (83) and test-retest reliability (ICC=0.91) (84), and good concurrent and discriminating validity (83, 85). In rheumatoid arthritis, a MCID of 3 to 4 points is generally used (86). Different MCIDs have however been proposed, such as, 15.9 (on a normalised scale from 0-100), also for the rheumatoid arthritis population (87), and 5.9 in patients with systemic lupus erythematous (88). Nevertheless, no MCID has been established for patients with COPD. A Portuguese version of the FACIT-F has already been developed by the FACIT study group and can be freely accessed through their website (89).

Leicester cough questionnaire (LCQ)

The LCQ evaluates cough-related quality of life in 19 items organised in 3 domains (physical, psychological and social) (51). Each domain has a score ranging from 1 to 7 and the LCQ total score varies from 3 to 21 (51). Higher scores express a better cough-related quality of life and less impact of cough (51). The LCQ as a period recall of 2 weeks and uses a 7-point Likert Scale (51). The LCQ takes about 5 minutes to complete (51).

The LCQ was initially designed for patients with chronic cough but has also been validated for acute cough (90). Its psychometric properties have been studied in patients with COPD, demonstrating high internal consistency (Cronbach’s α=0.86) and test-retest reliability (ICC=0.92) (91), good content validity (91) and moderate concurrent validity, either established against the SGRQ or with cough frequency (51, 91-93). Responsiveness analysis indicated that the LCQ can detect changes in patients with COPD after 12 weeks

of treatment with azithromycin (91). The MCID for the LCQ has been estimated between 1.3 and 3 for chronic cough (51, 94, 95) and from 2 to 2.5 in acute cough (90, 96). Despite of all these studies regarding the LCQ's MCID, none has focused on patients with COPD. The LCQ has been already translated and validated to Portuguese, and the consent to use it was provided by the author.

Cough and sputum assessment questionnaire (CASA-Q)

The CASA-Q assesses cough and sputum symptoms, based on its reported frequency and severity, and impact on daily activities (52). It is a 20-item questionnaire containing 4 domains: cough symptoms, cough impact, sputum symptoms and sputum impact (52). Every item is scored on a 5-points Likert scale, from "never" to "always" for frequency or from "not at all" to "a lot/extremely" for intensity (52). All items are rescored and summed, achieving a score ranging from 0 to 100 for each domain, with higher scores indicating fewer symptoms and less cough and sputum impact (52). Participants complete the CASA-Q using a 7-day recall period (52, 97). The CASA-Q was originally created and validated to be used in patients with COPD and chronic (non-obstructive) bronchitis (52, 98). The CASA-Q requires about 5 minutes to complete.

The CASA-Q has shown to be a reliable tool for patients with COPD, as internal consistency coefficients surpassed the recommended threshold of 0.7 (Cronbach's $\alpha \geq 0.8$) and test-retest coefficients were greater than 0.7 (52). Validity has been studied against the SGRQ, showing a moderate correlation with the cough and sputum impact domains (52). Construct validity has been demonstrated by the negative correlation between the symptom's domains and the sputum wet weigh and by a moderate to high correlation with cough and sputum diary item (52). Regarding to responsiveness, the CASA-Q exhibited capacity to detect changes during the recovery from an acute exacerbation in patients with COPD (97). To our best knowledge, no study has established the MCID for the CASA-Q. The Portuguese validated version of the CASA-Q was provided by the author.

Global rating of change scale (GRC)

The GRC is a questionnaire used to measure the self-perceived improvement or deterioration in a patients' condition over time (60). The GRC is a simple, retrospective and numerical analogue scale that consists of asking patients to make a judgement regarding their current health status and to compare it with a previous time-point (60). This tool is frequently used as an anchor measure to determine MCID values (60, 99).

The GRC scale was used to ask participants to rate their perceived amount of change in their fatigue, cough and sputum following the community-based PR programme, compared

to the initial assessment. Following the recommendations for the design of the GRC questions, an 11-point Likert scale was used and the “explicit mention of the specific condition, construct and time anchor point” was assured (60). The numeric scale ranged from -5 on the left (much worse) to +5 on the right (much better), with 0 being labelled “no change” (Figure 1).

Figure 1: Global rating of change questions for fatigue, cough and sputum

2.6 Intervention

All participants completed a community-based PR programme, conducted at six primary health care centers and at the Respiratory Research and Rehabilitation Laboratory (Lab 3R) of the School of Health Sciences, University of Aveiro. The PR programmes lasted 12 weeks, with two exercise training sessions per week, each with an approximate duration of 60-75 minutes. The exercise training sessions were delivered by an experienced physiotherapist in accordance with the international guidelines (36), i.e., it included a warm up period, aerobic training, strength training and a period of calming down. Furthermore, an additional component of balance training was introduced (100). Heart rate, oxygen saturation, perceived dyspnoea and fatigue, measured with the modified Borg scale (101), were monitored throughout the sessions. Intensity of the aerobic and strength trainings were individually prescribed using the 6-minute walk test (6MWT) (102) and the one-repetition maximum (1-RM) or ten-repetition maximum (10-RM) methods (103) (in accordance to the

availability of the local material), respectively. During the PR programme, progression in the training intensity was tailored according to the perceived dyspnoea and fatigue (i.e., 4-6 in the modified Borg scale). A detailed description of the exercise training protocol can be found in Table 1.

Table 1: Community-based pulmonary rehabilitation– exercise training component.

Exercise Type	Modality	Intensity	Duration	
Warm-up	Global range of motion exercises; breathing control; stretching exercises	Low	5 min	
Aerobic training	Walking; cycling; step	80% of the 6MWT mean walk velocity 60 – 80% of Wpeak 60 – 80% of HRmax	20 – 30 min	 
Resistance training	Free weights and elastic bands (major muscle groups of upper and lower limbs and trunk)	60 – 70% of 1-RM or tailored in accordance to 10-RM	25 min (8 exercises, 2 sets of 10 – 12 repetitions)	 
Balance training	Upright positions; adjustments of the centre of gravity in static and dynamic postures; dual cognitive and motor task	Low	10 min	
Cool-down	Breathing control; stretching exercises; relaxation therapy	Low	5 min	

Legend: 6MWT – 6-minute walk test; Wpeak - work peak; HRmax – maximum heart rate; 1-RM – 1 repetition maximum; 10-RM – 10 repetition maximum

Six psychoeducational sessions were conducted (once every other week) by a multidisciplinary team, with a median duration of 90 minutes (104, 105). Patient's relatives and friends were invited to participate in the psychoeducational component (106). A detailed description of the psychoeducational component can be found in Table 2.

Table 2: Community-based pulmonary rehabilitation – psychoeducational component.

Sessions	Themes	Professional	Flyers
1	Information about COPD/ impact on family life Role of pulmonary rehabilitation	General practitioner, nurse and physiotherapist	
2	Management of respiratory symptoms	Physiotherapist	
3	Medication and oxygen therapy	Nurse and general practitioner	
4	Management and prevention of exacerbations Community resources	Physiotherapist, nurse and social assistant	
5	Healthy lifestyles: nutrition and sleep Management of stress and anxiety	Nurse, psychologist and nutritionist	
6	Healthy lifestyles: physical activity Action plan	Physiotherapist	

Legend: COPD – chronic obstructive pulmonary disease. Flyers available at *http://3r.web.ua.pt/* (105).

Patients were also encouraged to perform a home exercise programme composed of aerobic, strength and balance exercises. Moreover, with the support of the physiotherapist, patients completed a physical activity contract, which consisted in encouraging self-efficacy through performance feedback and individualised goals setting (107). Participants had a pedometer and a physical activity diary, so that they could record their daily steps.

2.7 Data analysis

Statistical analysis was performed using IBM SPSS Statistics, version 24 (IBM Corporation, Armonk, NY, USA) and plots created using GraphPad Prism, version 7 (GraphPad, San Diego, CA). The level of significance was set at 0.05. Analysis included only participants that adhered to at least 65% of PR sessions, following the recommendation of 6 to 8 weeks of PR (1, 108, 109).

Descriptive statistics, i.e., relative frequencies, mean±standard deviation (SD) or median [interquartile range] were used to describe the sample. Normality of the data was checked with Kolmogorov-Smirnov test. Then, PROMs were analysed at baseline (T0) and after the community-based PR programme (T1) and the significance of changes were verified using paired t-test or Wilcoxon signed-rank tests, accordingly to data normality. Data from PROMs were checked for floor or ceiling effects (less of 15% of the patients scoring at the bottom or top) (110). Outlier's analysis was performed (i.e., inspection of extreme points on the plotted graphs of the variables studied) and, when present were excluded (111). The MCID was calculated for the fatigue subscales of CIS-20 and FACIT-F, LCQ and CASA-Q.

Since a gold standard to optimally determine the MCID has not been established yet, concurrent comparisons of different methods were performed, following the current recommendations to integrate both anchor-based and distribution-based approaches (35, 46). The final MCID for each measure was pooled using MetaXL 5.3 (EpiGear International, Queensland, Australia), with the input data being the MCID generated by each anchor- and distribution-based method and, when appropriate, the respective confidence interval. A quality effects model (112) was used and anchor-based methods were weighed more than distribution methods (i.e., 2/3 against 1/3), as recommended (35, 46, 49, 113).

2.6.1 Anchor-based methods

Anchor-based methods have two established requirements: i) the anchor must be interpretable and ii) there must be a significant and moderate association (≥0.3) between the measure and the anchor (35). Correlations were assessed using Pearson's or Spearman's coefficients and then scatter plots were generated.

To calculate the MCID, 3 methods were used: i) the mean change; ii) receiver operating characteristic (ROC) curves and iii) linear regression analysis, as follows:

i) The mean change is the method most commonly used in literature and is defined as the absolute difference between the two means of the PROM score (T1 and T0), calculated for patients who achieve the MCID established for the anchor (43, 46).

ii) For the ROC curves an optimal cut-off point was determined, i.e., the point where specificity (SP) and sensitivity (SN) are both optimised (i.e., corresponding to the point closest to the top left corner). The area under the curve (AUC) and 95% confidence intervals (CIs) of the ROC curves were obtained to discriminate between improved and unimproved patients. An AUC of a ROC>0.7 was considered as adequate (53). The MCID of the anchor was used as a dichotomous variable to produce the ROC curves.

iii) Linear regression analysis was applied to estimate the MCID associated with the anchor change score, which was used as an independent variable (46).

A description of the methods used for each anchor can be found in Table 3.

Table 3: Anchor-based methods to estimate the minimal clinically important differences.

Anchor		**Categorization**	**Methods**
Patients referencing		GRC≥2	Mean change ROC curves Linear regression analysis
Physiotherapists referencing		GRC≥2	Mean change ROC curves Linear regression analysis
Criterion referencing		Exacerbation during the PR	Mean change
Questionnaire Referencing	**CAT**	Change in the CAT≥2	Mean change ROC curves Linear regression analysis
	SGRQ	Change in the SGRQ≥4	

Legend: GRC – Global rating of change scale; ROC – receiver operating characteristic; PR – pulmonary rehabilitation; CAT – COPD assessment test; SGRQ – St. George's Respiratory Questionnaire.

Patients referencing

A change of 2 points or more in an 11-point GRC scale, related to patients' perception of change in fatigue, cough or sputum, is considered a clinically meaningful change (60). Thus,

patients were categorised in two groups, those rating ≥2 and those rating <2 points in the GRC. Afterwards, the mean change score on the CIS-20, FACIT-F, CASA-Q and LCQ of the participants with a GRC≥2 was calculated, ROC curves were used to distinguish between patients scoring ≥2 points in the GRC and a regression analysis was produced using the GRC as the independent variable.

Physiotherapists referencing

The physiotherapists that followed the participants during the community-based PR programme were asked to judge about patients' change in fatigue, cough and sputum, using a GRC (Figure 2). Since a change of 2 points or more in an 11-point GRC scale is considered a clinically meaningful change (60), this value was used as the cut-off point for improvement. All physiotherapists answering the GRC were well familiarised with the PROMs being tested and it was ensured that they answered the GRC questions prior to assessing patients. To calculate the MCID, according to the physiotherapists referencing, for FACIT-F, CIS-20, CASA-Q and LCQ the 3 methods previously described were used (i.e., mean change, ROC curves and linear regression analysis, anchored against a physiotherapist GRC≥2).

Figure 2: Physiotherapists global rating of change questions for patient's fatigue, cough and sputum.

Criterion referencing

The principle underlying the criterion referencing is that the occurrence of a major health event should be correlated to a worse PROMs score (45). Therefore, and considering that exacerbations are directly related to symptoms, its occurrence during PR was used as an anchor. The difference in the baseline score between the patients who experienced an exacerbation and those who did not was considered the MCID (45, 114). Independent t-tests or Mann-Whitney tests, depending on data normality, were used.

Questionnaire referencing

Change in the CIS-20, FACIT-F, CASA-Q and LCQ scores were anchored against changes in the CAT total score and the SGRQ total score. CAT was used as an external criterion since it is a comprehensive, suitable and short measure to assess the most burdensome symptoms in patients' life (1). However, the SGRQ was also included as a referencing anchor as it is considered the most comprehensive disease-specific health status questionnaire to assess patients with COPD (1). Mean changes, ROC curves and linear regression analysis were conducted to calculate the PROMs' MCID, using the MCID established for the CAT (2 points) and the SGRQ (4 points) (68, 73).

2.6.2 Distribution-based methods

To calculate the MCID, 5 distribution methods were used: i) 0.5 times SD; ii) standard error of measurement (SEM); iii) 1.96 times SEM; iv) minimal detectable change (MDC) and v) effect size (ES). The formulas used to calculate the distribution-based methods are described in Table 4.

i) The SD constitutes the variation among a group of scores. It has been suggested that 0.5*SD was able to discriminate changes in HRQoL of chronic patients (115, 116).

ii) The SEM was calculated using the test-retest reliability coefficient. It has the advantage of being theoretically independent of the sample size and less sensitive to data distribution (42, 117). The test-retest reliability coefficients used were the Spearman rank correlation for the fatigue subscale of CIS-20 (s=0.85) (14), and the ICC for the other scales (FACIT-F ICC=0.91(84), LCQ ICC=0.92(91), CASA-Q - ICC cough symptoms =0.77, ICC cough impact =0.88, ICC sputum symptoms =0.80 and ICC sputum impact =0.82 (52)).

iii) 1.96SEM was also calculated, since there is no agreement on which SEM or 1.96SEM represents best the MCID (115).

iv) The MDC, also called the reliable change index (RCI), is defined by the consensus-based standards for the selection of health measurement instruments (COSMIN) as a change beyond the measurement error (118). We calculated the MDC using a 95% interval confidence.

v) ES is a standardised measure of change (119). ES were interpreted as small (≥0.2), medium (≥0.5) or large (≥0.8) (119). Nonparametric effect sizes were calculated when data was not normally distributed (120). ES greater than 0.2 were considered to be minimally clinically/subjectively important (119).

Table 4: Distribution-based methods to estimate the minimal clinically important difference.

Method	MCID calculation
0.5SD	$0.5*SD_{T0}$
SEM	$SD_{T0}\sqrt{(1-r)}$
1.96SEM	$1.96*(SD_{T0}\sqrt{(1-r)})$
MDC	1.96 x SEM x $\sqrt{2}$
ES	$(mean_{T1} - mean_{T0})/\sqrt{(SD_{T1}^2 + SD_{T0}^2)/2}$
ES_{NP}	$\lvert z \rvert/(\sqrt{n})$

Legend: MCID - minimal clinically important difference; SEM – standard error measurement; SD – standard deviation; r - test-retest reliability coefficient; MDC – minimal detectable change; ES – effect size; ES_{NP} – Nonparametric effect sizes; T0 – baseline; T1 – after the pulmonary rehabilitation programme; z- statistic test; n – number of total matched pairs

After combining both anchor- and distribution-based methods and pooling the final MCID for each PROM, the corresponding percentage of change was calculated. Furthermore, we used the pooled MCID value to compute the matching ES (46), using this formula:

$MCID_{ES} = MCID_{pooled}/\sqrt{(SD_{T1}^2 + SD_{T0}^2)/2}$.

3. Results

3.1 Sample characterisation

Sixty-four outpatients with COPD were referred to be included in the study. From these, nine dropped-out due to: lack of time to participate (n=4), hospitalisation due to an AECOPD (n=2), non-COPD health-related reasons (n=2) and no reason given (n=1). Fifty-five

patients completed the community-based PR programme, however only forty-nine patients were included, since six did not meet the cut-off point of 65% for PR adherence. A flow diagram of the recruited and included sample is provided in Figure 3.

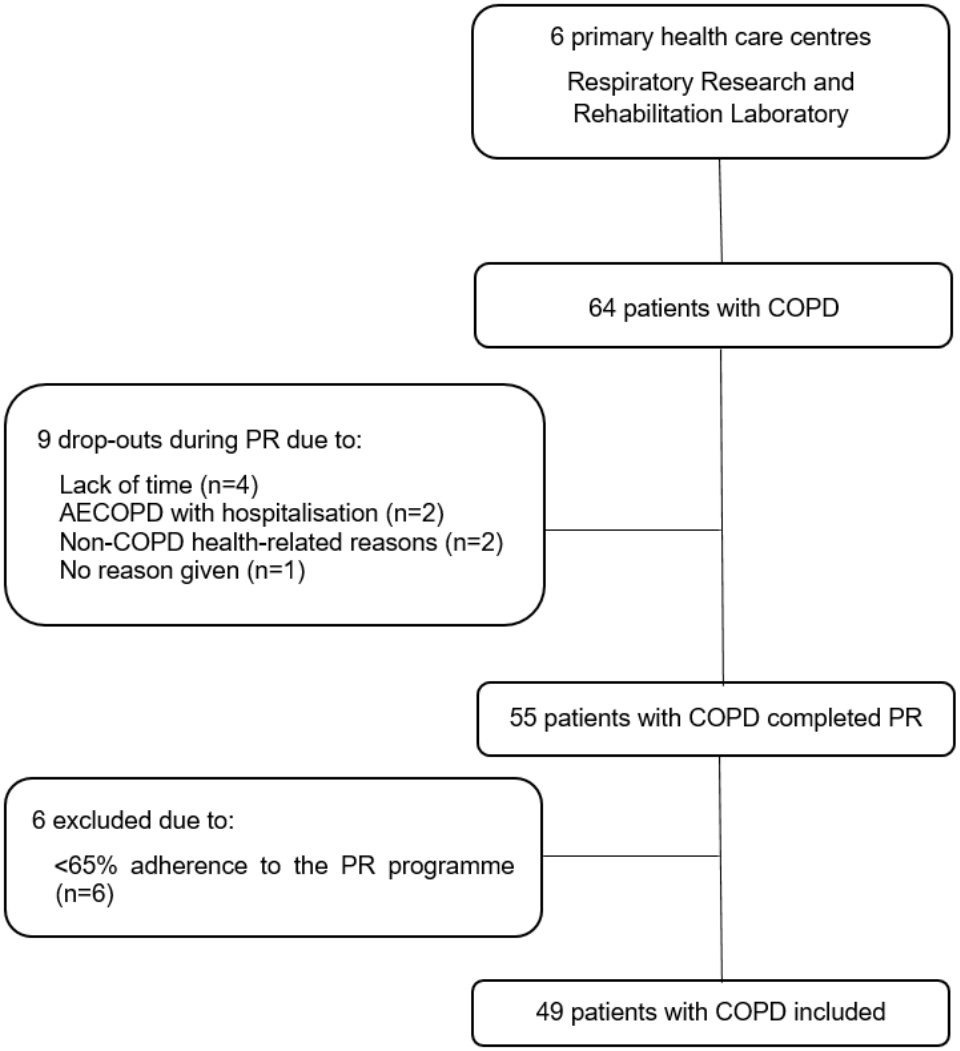

Figure 3: Flow diagram of participants included in the study.

At baseline no differences were observed between the included patients and drop-outs ($p>0.05$), except for age ($p=0.029$), the LCQ total score ($p=0.043$) and the cough symptoms from CASA-Q ($p=0.040$), with drop-outs being younger and presenting less cough symptoms (Table 5).

Included patients were on average 69.8±7.4 years old, mostly male (n=40; 81.6%), with a mean BMI of 26.4±4.9kg/m^2, completed four years of education (n=26, 53.1%), were retired (n=39, 79.6%) and former smokers (n=31, 63.3%). GOLD III was the most prevalent grade (n=22, 44.9%), with patients presenting a mean forced expiratory volume in one second (FEV_1) of 49.2±16.9% predicted. The majority of patients were at GOLD stage B (n=32,

65.3%), presenting a median number of exacerbations in the previous year of 1 [0-1] and a mean CAT score of 17.2±7.8 points. Patients mean score on the SGRQ was 45.6±20.4 points.

At baseline, all PROMs were completed by the forty-nine patients, except for the CASA-Q, which data were not possible to collect from eight participants, due to data collection commencement prior to CASA-Q author authorisation to use the scale. Additionally, one participant failed to complete the CIS-20, FACIT-F, LCQ and the GRC, since he could not attend the follow-up appointment. Patients presented mean baseline scores of 34.9±10.8 points for the CIS-20 FS and 33.6±10.3 points for the FACIT-F. Following the CIS-20 cut-off points, there was a high prevalence of severe fatigue among patients (53.1%). The LCQ mean baseline score was 16.6±3.5 points and the median for CASA-Q were 66.7 [41.7-83.3], 71.9 [56.3-93.8], 66.7 [50.0-83.3] and 79.2 [62.5-95.8] points, for cough symptoms, cough impact, sputum symptoms and sputum impact, respectively (Table 5).

Table 5: Sample characterisation (n=64).

Characteristics	**Patients included (n=49)**	**Drop-outs (n=15)**	**p-value**
Age, years	69.8±7.4	64.0±12.7	0.029*
Gender, male n (%)	40 (81.6)	9 (60.0)	0.084
Years of education, n (%)			0.469
Illiterate	1 (2.0)	0 (0)	
1-4	26 (53.1)	8 (53.3)	
5-9	12 (24.5)	4 (26.7)	
10-12	5 (10.2)	2 (13.3)	
University	5 (10.2)	1 (6.7)	
Current occupation, n (%)			0.091
Employed	5 (10.2)	0 (0)	
Housekeeper	1 (2.0)	0 (0)	
Retired	39 (79.6)	11 (73.3)	
Unemployed	3 (6.1)	4 (26.6)	
Other	1 (2.0)	0 (0)	
BMI, kg/m^2	26.4±4.9	27.5±5.2	0.463
Smoking status, n (%)			0.338
Current	8 (16.3)	5 (33.3)	
Former	31 (63.3)	7 (46.7)	
Never	10 (20.4)	3 (20.0)	
Packs/year	40.0 [26.0-70.0]	29.5 [14.0-75.4]	0.394
Exacerbations/year[1]	1.0 [0.0-1.0]	1.0 [0.0-3.0]	0.077
AECOPD hospitalisations[1], n (%)	4 (8.2)	3 (20.0)	0.146
Duration of hospitalisations (days)	9.3±4.0	10.0±9.5	0.917
COPD-related emergencies[1], n (%)	16 (32.7)	6 (40.0)	0.574
Lung function (post-bronchodilator)			
FEV_1,	1.2±0.4	1.2±0.3	0.744
FEV_1, %predicted	49.2±16.9	49.0±16.9	0.995
FVC, L	2.5±0.6	2.4±0.9	0.590
FVC, %predicted	79.0±19.0	76.3±20.8	0.640
FEV_1/FVC, %	49.9±13.5	55.5±11.9	0.158

GOLD stages, n (%)			0.996
I	6 (12.2)	2 (13.3)	
II	17 (34.7)	5 (33.3)	
III	22 (44.9)	7 (46.7)	
IV	4 (8.2)	1 (6.7)	
GOLD groups, n (%)			0.163
A	8 (16.3)	3 (20.0)	
B	32 (65.3)	6 (40.0)	
C	0 (0.0)	0 (0.0)	
D	9 (18.4)	6 (40.0)	
Long-term oxygen therapy	6 (12.2)	4 (26.7)	0.178
Non-invasive ventilation, n (%)	5 (10.2)	1 (6.7)	0.681
CCI, n (%)			0.520
Mild	5 (10.2)	3 (20.0)	
Moderate	26 (53.1)	6 (40.0)	
Severe	18 (36.7)	6 (40.0)	
Medication, n (%)			
Bronchodilators			
SABA	6 (12.2)	1 (6.7)	0.409
SAMA	3 (6.1)	0 (0.0)	0.275
LABA	7 (14.3)	3 (20.0)	0.830
LAMA	18 (36.7)	8 (53.3)	0.581
LAMA/LABA combination	14 (28.6)	3 (20.0)	0.485
ICS	10 (20.4)	1 (6.7)	0.178
ICS/LABA combination	20 (40.8)	8 (53.3)	0.427
LTRA	3 (6.1)	2 (13.3)	0.376
Xanthines	9 (18.4)	4 (26.7)	0.508
Expectorants	6 (12.2)	1 (6.7)	0.530
Antibiotics	1 (2.0)	0 (0.0)	0.540
mMRC	2 [1.0-3.0]	2 [1.0-3.0]	0.761
CAT	17.2±7.8	14.7±7.3	0.288
SGRQ (Total score)	45.6±20.4	40.9±19.9	0.406
CIS-20 FS	34.9±10.8	37.0±11.1	0.523
Normal fatigue, n (%)	11 (22.4)	1 (6.7)	0.343
Mild fatigue, n (%)	11 (26.4)	5 (33.3)	
Severe fatigue, n (%)	26 (53.1)	9 (60.0)	
FACIT-F	33.6±10.3	36.3±14.5	0.413
LCQ	16.6±3.5	18.7±3.1	0.043*
CASA-Q			
Cough symptoms	66.7 [41.7; 83.3]	91.7 [70.8; 91.7]	0.040*
Cough impact	71.9 [56.3; 93.8]	90.6 [67.7; 100.0]	0.074
Sputum symptoms	66.7 [50.0; 83.3]	75.0 [58.3; 83.3]	0.404
Sputum impact	79.2 [62.5; 95.8]	87.5 [83.3; 100.0]	0.062

Notes: Values are presented as mean±standard deviation or median [interquartile range], unless otherwise stated. [1]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; CIS-20 FS – Checklist of individual strength fatigue subscale; FACIT-F – Functional Assessment of Chronic illness therapy – Fatigue; LCQ – Leicester cough questionnaire; CASA-Q – Cough and Sputum Assessment Questionnaire

After the community-based PR programme, significant improvements were found for the CAT (mean difference of -4.7±6.6; p<0.001), the SGRQ (-6.1±14.3; p=0.005), the CIS-20 fatigue subscale (-4.2±9.1; p=0.003), the FACIT-Fatigue subscale (2.8±6.7; p=0.006), the

LCQ (0.7±2.9; p=0.001) and the CASA-Q cough impact dimension (3.1 [-3.1;9.4]; p=0.034). Baseline and post-PR scores can be found in Table 6. Thirty-seven (75.5%) patients improved beyond the MCID of 2 points established for the CAT and 31 (63.3%) above the 4 points in the SGRQ. No floor or ceiling effects were observed for the CIS-20, FACIT-F and LCQ, at T0 or T1 (i.e., >15% patients scoring at top or bottom). Scores of CASA-Q however, demonstrated a ceiling effect, at T0 and T1, in both cough and sputum impact dimensions.

Table 6: Patient-reported outcome measures before and after the community-based pulmonary rehabilitation programme.

PROM		Baseline	Post-PR	Δ	p-value
CAT (n=49)		17.2±7.8	12.5±6.5	-4.7±6.6	<0.001*
SGRQ Total (n=49)		45.6±20.4	39.9±18.4	-6.1±14.3	0.005*
CIS-20 FS (n=48)		34.9±10.8	30.8±11.5	-4.2±9.1	0.003*
FACIT-F (n=48)		33.6±10.3	36.4±8.6	2.8±6.7	0.006*
LCQ (n=48)		16.6±3.5	17.3±3.8	0.7±2.9	0.001*
CASA-Q (n=41)	**Cough symptoms**	66.7 [41.7;83.3]	70.8 [50.0;83.3]	8.3 [-8.3;8.3]	0.078
	Cough impact	71.9 [56.3;93.8]	85.9 [60.9;96.9]	3.1 [-3.1;9.4]	0.034*
	Sputum symptoms	66.7 [50.0;83.3]	66.7 [41.7;87.5]	0.0 [-8.3;16.7]	0.402
	Sputum impact	79.2 [62.5;95.8]	83.3 [64.6;100.0]	4.2 [-8.3;12.5]	0.293

Notes: Values are presented as mean±standard deviation or median [interquartile range], unless otherwise stated. *p<0.05
Legend: PROM – Patient-reported outcome measures**;** PR – pulmonary rehabilitation; Δ – mean/median change; CAT – COPD assessment test; SGRQ – St George's Respiratory Questionnaire; CIS-20 FS – Checklist of individual strength fatigue subscale; FACIT-F – Functional Assessment of Chronic illness therapy – Fatigue; CASA-Q – Cough and Sputum Assessment Questionnaire

After the community-based PR programmes, 82.5%, 56.2% and 60.4% of the participants perceived improvements (GRC) in their fatigue (3.0 [2.0-4.0]), cough (2.0, [0.0-3.0]) and sputum (2.0, [0.0-4.0]), respectively. Physiotherapists reported improvements in fatigue for 89.8% (3.0, [2.0-4.0]), in cough for 51% (2.0, [0.0-3.0]), and in sputum for 55.1% (2.0, [0.0-2.0]) of their patients.

3.2 Minimal clinically important differences

Minimal clinically important differences are individually presented for each PROM using anchor- and distribution-based methods, whenever possible. After checking for outliers, 6 participants were excluded from the analysis of the FACIT-F and 3 from the analysis of the LCQ. No differences were found between the baseline characteristics of the included patients and the outliers (p>0.05). No outliers were found in the CIS-20 FS and in the CASA-Q analysis.

Resume tables for the correlation values between changes in the PROM and changes in the anchors (Table 7), MCID achieved with criterion referencing method (Table 8) and with the mean change method (Table 9) and overall MCID from the pooled statistics (Table 10) are presented at the bottom of this section.

3.2.1 Checklist of individual strength 20 - fatigue subscale

Anchor-based methods

Changes in the CIS-20 FS were not correlated with changes in the scores of the CAT (r=-0.007; p=0.961), of the SGRQ (r=-0.05; p=0.971), nor with the patients' (s=0.102; p=0.488) and physiotherapists (s=0.012; p =0.937) GRC (Table 7). Therefore, these measures could not be used as reliable anchors, and ROC analysis and linear regressions were not computed.

Regarding to criterion referencing, 15 patients (31.3%) had an AECOPD during the community-based PR programme. No significant differences were found in the CIS-20 FS mean baseline scores between patients who experienced an AECOPD in the previous year and those who did not (33.8±12.7 vs. 35.5±10.0 points; p=0.628) (Table 8). Thus, AECOPD were not used as an anchor.

Distribution-based methods

Distribution methods results for the CIS-20 FS were: 5.4 (0.5*SD), 4.2 (SEM), 8.2 (1.96SEM), 11.6 (MDC). A small effect size (0.37) was found.

Pooled MCID

Pooled MCID for the CIS-20 FS was 7.3, ranging from 4.1 to 10.6. Results are presented in Figure 4.

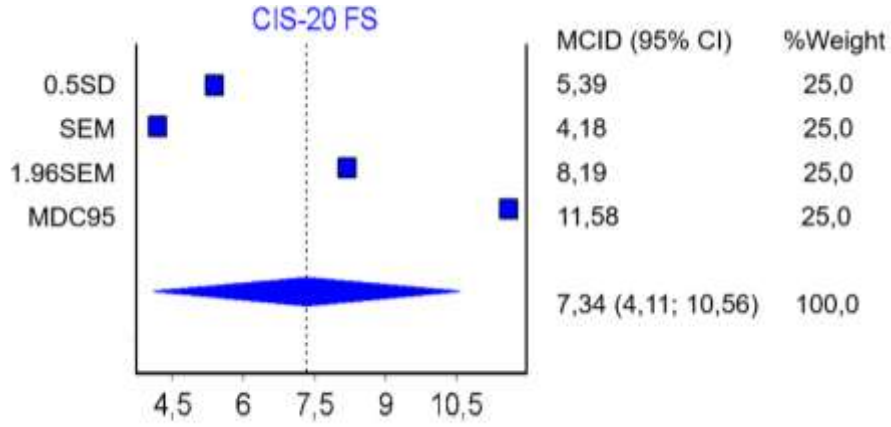

Figure 4: Plot of the pooled MCID for the CIS-20 FS. Squares represent the MCID estimates derived in this study (n=48)

3.2.2. Functional assessment of chronic illness therapy – fatigue subscale

Anchor-based methods

Changes in the FACIT-F correlated moderately, negatively and significantly with changes in the SGRQ (r=-0.307; p=0.048) (Table 7). No correlations were found between changes in the FACIT-F and changes in CAT (r=-0.043; p=0.786), patients' (s=-0.043; p=0.585) and physiotherapists GRC (s=-0.084; p=0.116). Thus, only the SGRQ was used as anchor to compute the MCID. Correlations are described in detail in Table 7.

In total, 27 patients (64.3%) improved beyond the MCID established for the SGRQ (mean difference of 4.1±7.2 points) and 15 (35.7%) did not reach that threshold (mean difference of 1.8±5.6 points) (Table 9). Thus, MCID established for the FACIT-F using the mean change according to the SGRQ was 4.1 (95% CI 1.3 to 6.9).

It was not possible to use ROC statistics to compute the MCID, since the AUC generated for the FACIT-F (AUC=0.59; 95% CI 0.42 to 0.76; p=0.345) was not statistically significant. Using linear regression, the estimated MCID for the FACIT-F was 2.6 (95% CI 0.9 to 4.3) (Figure 5).

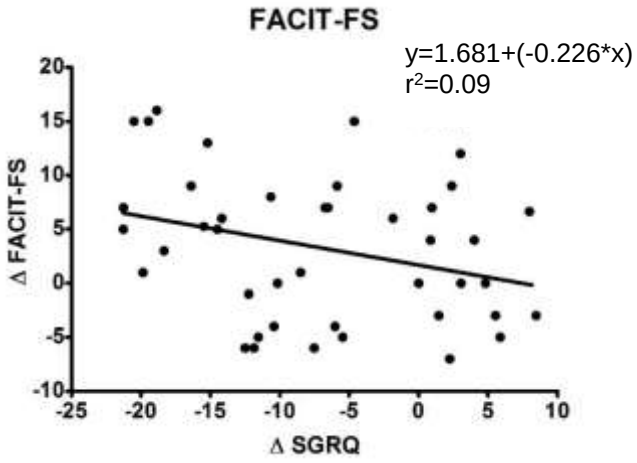

Figure 5: Linear regression between changes in the FACIT-F and changes in the SGRQ (n=42).

Regarding to criterion referencing, 12 patients (28.6%) had an AECOPD during the community-based PR programme. No significant differences were found in the FACIT-F mean baseline scores between patients who experienced an AECOPD and those who did not (31.3±11.1 vs. 34.1±10.2 points; p=0.449) (Table 8). Thus, AECOPD were not used as an anchor.

Distribution-based methods

Distribution methods results for the FACIT-F were: 5.2 (0.5*SD), 3.1 (SEM), 6.1 (1.96SEM) and 8.7 (MDC). A small effect size (0.34) was found.

Pooled MCID

Pooled MCID for the FACIT-F was 4.2 (95% CI 1.7 to 6.7). Results are presented in Figure 6.

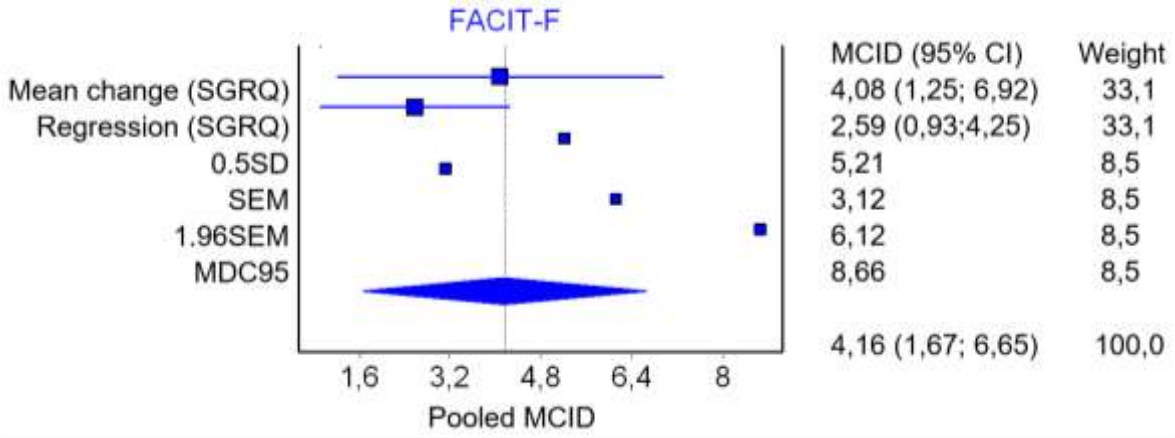

Figure 6: Plot of the pooled MCID for the FACIT-F. The plot represents the MCID estimates derived in this study, and where appropriated the estimates include the 95% confidence interval (n=42).

3.2.3 Leicester cough questionnaire

Anchor-based methods

Changes in the LCQ correlated moderately, positively and significantly with changes in the patients' GRC for cough symptoms (r=0.340; p=0.024). No correlations were found between the changes in the LCQ and the physiotherapists GRC (s=0.043; p=0.781), nor with changes in CAT (r=-0.200; p=0.187) and in the SGRQ (r=-0.289; p=0.054) (Table 7). Thus, only the patients' GRC was used as anchor to compute the MCID.

In total, 26 patients (57.8%) perceived an improvement ≥2 in the GRC for cough (LCQ mean difference of 1.4±1.9), whereas 19 (42.2%) did not reach that threshold (LCQ mean difference of -0.3±2.5) (Table 9). Thus, the MCID established for the LCQ using the mean change according to the patients GRC was 1.4 (95% CI 0.7 to 2.2).

It was not possible to use ROC statistics to compute the MCID, since the AUC generated for the LCQ (AUC=0.66; 95% CI 0.50 to 0.82; p=0.068) was not statistically significant. Using linear regression, the estimated MCID for the LCQ was 0.7 (95% CI -0.9 to 2.4) (Figure 7).

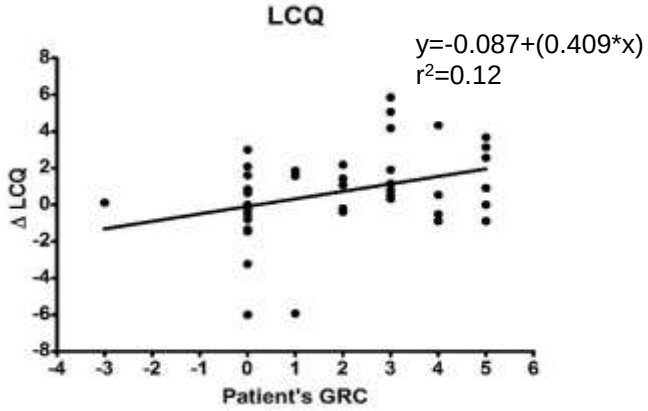

Figure 7: Linear regression between the LCQ change and the patient's global rating of change for cough (n=45).

Regarding to criterion referencing, 15 patients (33.3%) had an AECOPD during the community-based PR programme. No significant differences were found in the LCQ mean baseline scores between patients who experienced an AECOPD and those who did not (16.7±3.6 vs. 16.9±3.3; p=0.897) (Table 8). Thus, AECOPD were not used as an anchor.

Distribution-based methods

Distribution methods results for the LCQ were: 1.7 (0.5*SD), 1.0 (SEM), 1.9 (1.96SEM) and 2.6 (MDC). The effect size observed was small (0.21).

Pooled MCID

Pooled MCID for the LCQ was 1.3 (95% CI 0.4 to 2.2). Results are presented in Figure 8.

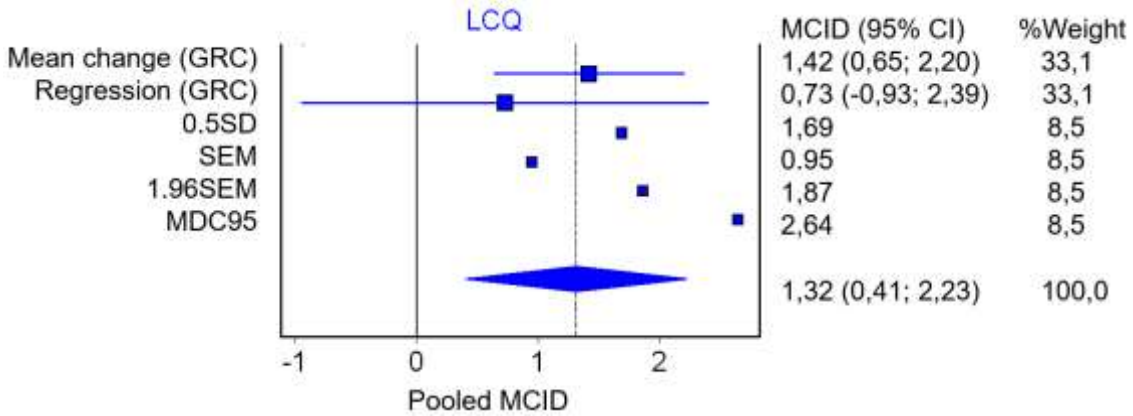

Figure 8: Plot of the pooled MCID for the FACIT-F. The plots represent the MCID estimates derived in this study, and where appropriated the estimates include the 95% confidence interval (n=45).

3.2.4 Cough and sputum assessment questionnaire

Anchor-based methods

Changes in the CASA-Q cough symptoms domain correlated moderately, negatively and significantly with changes in the SGQR (s=-0.322; p=0.040) and in the CAT (r=-0.378; p=0.015). Moderate, positive and significant correlations were also found with the patient's GRC for cough (s=0.317; p=0.043). No correlations were found between changes in the CASA-Q cough symptoms domain and the physiotherapist's GRC (s=0.212; p=0.183) (Table 7). Thus, SGRQ, CAT and the patients' GRC were used as anchors to compute the MCID.

Changes in the CASA-Q cough impact domain correlated moderately, positively and significantly with the patients' GRC for cough (s=0.464; p=0.002). No correlations were found between changes in the CASA-Q cough impact domain and the physiotherapists GRC (s=-0.002; p=0.991), changes in CAT (s=-0.238; p=0.134) and in the SGRQ (r=-0.286; p=0.070) (Table 7). Thus, only the patients' GRC was used as anchor to compute the MCID.

Changes in the CASA-Q sputum domains, both symptoms and impact, correlated moderately, negatively and significantly with changes in the SGRQ (s=-0.398; p=0.010 and r=-0.407; p=0.008, respectively). No correlations were found between the CASA-Q sputum domains, symptoms and impact, with changes in CAT (s=-0.118; p=0.463 and s=-0.041; p=0.798) patients' (s=0.214; p=0.180 and s=0.223; p=0.161) and physiotherapists' GRC (s=0.167; p=0.295 and s=0.049 and p=0.760). Thus, only the SGRQ was used as anchor to compute the MCID. Correlations are described in detail in Table 7.

In total, 25 patients (61.0%) improved beyond the MCID established for the SGRQ, 31 (75.6%) beyond the MCID established for the CAT, 21 (51.2%) and 25 (61.0%) above the threshold of 2 points in the patient's GRC for cough and sputum symptoms, respectively (Table 9).

For the CASA-Q cough symptoms domain the mean improvements found, according to the MCID established for the anchors, were: i) 9.3±17.1 points for the SGRQ; ii) 9.1±14.3 points for the CAT; and iii) 9.9±16.2 points for the patients' GRC for cough. Regarding to the CASA-Q cough impact domain the mean change in the patient's group with a GRC ≥2 was 11.8±17.6 points. Concerning to CASA-Q sputum symptoms and impact domains the mean improvements were 7.7±22.2 and 6.0±16.2 points, respectively, for patients who reached the 4 points change in the SGRQ. The mean improvements established according to the anchors are described in detail in Table 9.

Thus, the MCID derived from the mean change methods were: i) 9.3 (95% CI 2.3 to 16.4), 9.1 (95% CI 3.9 to 14.4) and 9.9 (95% CI 2.6 to 17.3) for cough symptoms, with SGRQ, CAT and patients' GRC, respectively; ii) 11.8 (95% CI 3.7 to 19.8) for cough impact; iii) 7.7 (95% CI -1.5 to 16.8) for sputum symptoms, and iv) 6.0 (95% CI -0.7 to 12.7) for sputum impact.

Using ROC statistics, the AUCs generated for CASA-Q cough symptoms domain showed adequate discrimination between those improving above and below the MCID for the SGRQ (AUC=0.70; 95% CI 0.54 to 0.86; p=0.031) and for the CAT (AUC=0.80; 95% CI 0.62 to 0.97; p=0.005) (Figure 9). The AUCs obtained for the CASA-Q cough impact (patient's GRC: AUC=0.74; 95% CI 0.59 to 0.90; p=0.008) and sputum symptoms (SGRQ: AUC=0.72; 95% CI 0.56 to 0.88; p=0.019) were also able to distinguish between patients who improved from those who did not (Figure 9).

The AUC's discrimination ability was not acceptable for CASA-Q sputum impact using the SGRQ (AUC=0.62; 95% CI 0.45 to 0.80; p=0.186) and for the CASA-Q cough symptoms using the patient's GRC for cough (AUC=0.69; 95% CI 0.52 to 0.85; p=0.039) as anchors.

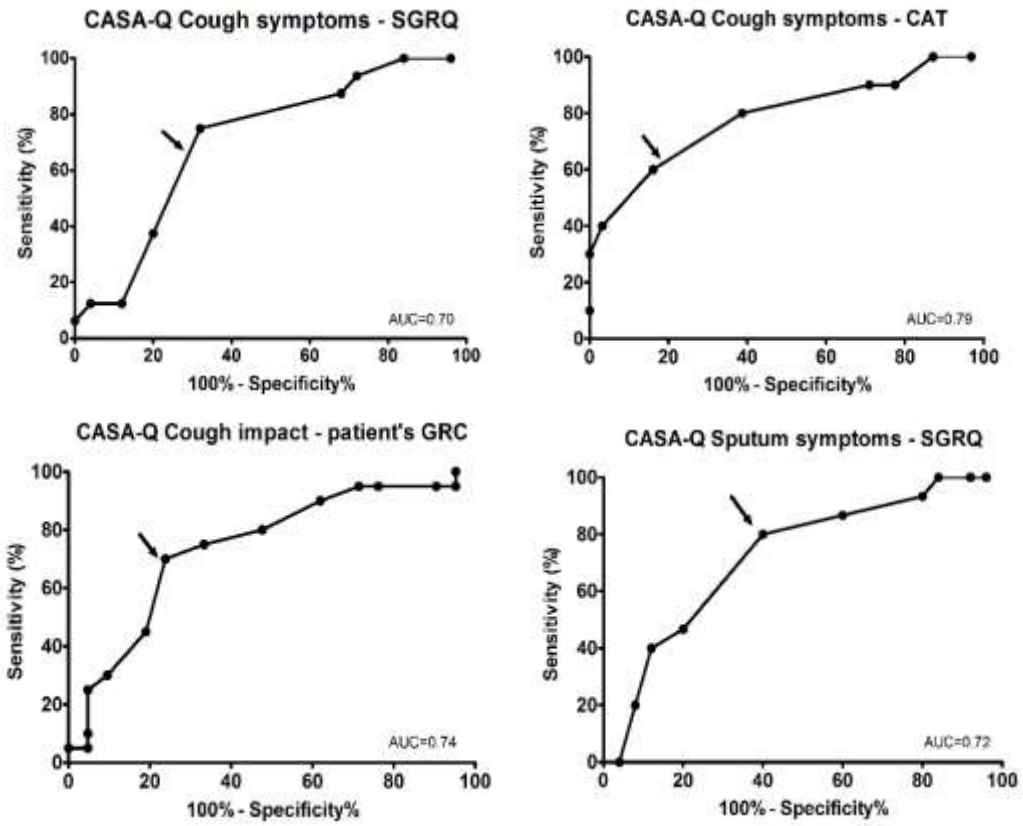

Figure 9: Receiver operating characteristic curves to discriminate between patients above and below the MCID established for the anchors for the CASA-Q domains (n=41).

According to the ROC analysis, the MCID found were 4.2 for both cough (SN=68%; SP=75% and SN=61%; SP=80%) and sputum (SN=80%; SP=60%) symptoms and 4.7 for the cough impact domain (SN=67%; SP=75%).

Using linear regression, the estimated MCID for the cough symptoms domain was 1.6 (95% CI -3.4 to 6.6) and for sputum impact domain was 2.2 (95% CI -1.5 to 6.0) (Figure 10).

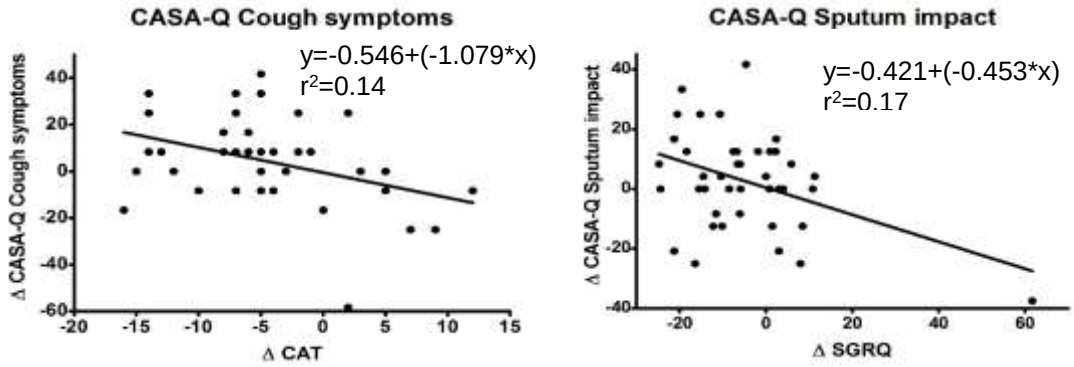

Figure 10: Linear regression between the CASA-Q cough symptoms change and the CAT change, and between the CASA-Q sputum impact change and the SGRQ change.

Regarding to criterion referencing, 12 patients (29.3%) had an AECOPD during the community-based PR programme. The median scores of the four domains of CASA-Q did not differ significantly between patients who experienced an AECOPD and those who did not (cough symptoms: 58.3 [41.7;83.3] vs. 66.7 [50.0;83.3] points, p=0.778; cough impact: 64.1 [46.9;100.0] vs. 75.0 [59.4;93.8] points, p=0.601; sputum symptoms: 50.0 [41.7;66.7] vs. 75.0 [50.0;83.3] points, p=0.127 and sputum impact: 70.8 [56.3;89.6] vs. 83.3 [66.7;95.8] points, p=0.453). Thus, AECOPD were not used as an anchor.

Distribution-based methods

Distribution methods results for the CASA-Q were: i) 11.5 (0.5*SD), 11.0 (SEM), 21.6 (1.96SEM) and 30.5 (MDC) for cough symptoms; ii) 11.2 (0.5*SD), 7.8 (SEM), 15.2 (1.96SEM) and 21.5 (MDC) for cough impact; iii) 11.4 (0.5*SD), 10.2 (SEM), 20.0 (1.96SEM) and 28.2 (MDC) for sputum symptoms; and iv) 10.3 (0.5*SD), 8.7 (SEM), 17.1 (1.96SEM) and 24.2 (MDC) for sputum impact. The effect sizes observed were small for cough impact (0.23) and very small for cough symptoms (0.19), sputum symptoms (0.09) and sputum impact (0.12).

Pooled MCID

Pooled MCID for the CASA-Q subscales were 10.6 (95% CI 4.0 to 17.2) for cough symptoms; 10.1 (95% CI 3.2 to 17.1) for cough impact; 9.5 (95% CI 0.0 to 19.5) for sputum symptoms and 7.8 (95% CI 0.5 to 15.2) for sputum impact. Results are presented in Figure 11.

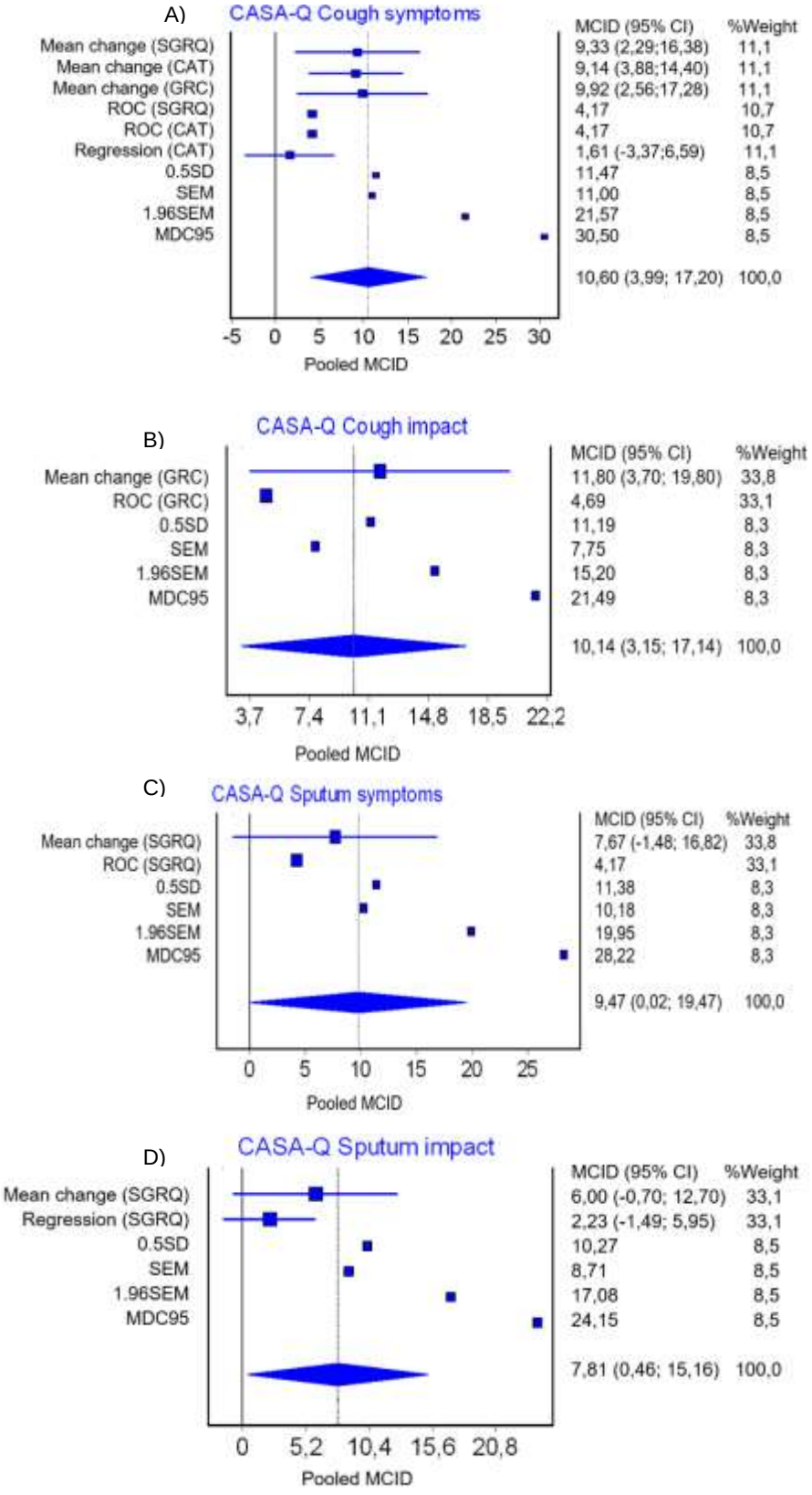

Figure 11: Plot of the pooled MCID for the A) CASA-Q cough symptoms; B) CASA-Q cough impact; C) CASA-Q sputum symptoms and D) CASA-Q sputum impact. The plots represent the MCID estimates derived in this study, and where appropriated the estimates include the 95% confidence interval.

Table 7: Correlations between the anchors and changes in the patient-reported outcome measures.

		Patient's GRC		Physiotherapist's GRC		Δ CAT		ΔSGRQ	
		s	p-value	s	p-value	r/s	p-value	r/s	p-value
Δ CIS-20 FS (n=48)		0.102	0.488	0.012	0.937	r=-0.007	0.961	r=-0.005	0.971
Δ FACIT – FS (n=42)		-0.043	0.585	0.084	0.116	r=-0.043	0.786	r=-0.307	0.048*
Δ LCQ (n=45)		r=0.340	0.024*	0.043	0.781	r=-0.200	0.187	r=-0.289	0.054
Δ CASA-Q (n=41)	**CS**	0.317	0.043*	0.212	0.183	r=-0.378	0.015*	s=-0.322	0.040*
	CI	0.464	0.002*	-0.002	0.991	s=-0.238	0.134	s=-0.286	0.070
	SS	0.214	0.180	0.167	0.295	s=-0.118	0.463	s=-0.398	0.010*
	SI	0.223	0.161	0.049	0.760	s=-0.041	0.798	r=-0.407	0.008*

Notes: correlations were calculated using Pearson's (r) or Spearman's (s) coefficients. Pearson's coefficients, when significant, were presented, as they were used to compute the linear regression. * p<0.05
Legend: s – Spearman's correlation; r – Pearson's correlation; GRC – Global rating of change scale; CAT – COPD assessment test; Δ – mean change; SGRQ – St George's Respiratory Questionnaire; CIS-20 FS – Checklist of individual strength fatigue subscale; FACIT-F – Functional Assessment of Chronic illness therapy – Fatigue; LCQ – Leicester cough questionnaire; CASA-Q – Cough and Sputum Assessment Questionnaire; CS – Cough symptoms; CI – Cough impact; SS – Sputum symptoms; SI – Sputum impact.

Table 8: Patient-reported outcome measures mean scores at baseline and after community-based pulmonary rehabilitation, according to the criterion referencing.

		AECOPD		
		No	Yes	p-value
CIS-20 FS (n=48)	**n, (%)**	33 (68.8)	15 (31.3)	
	Baseline	35.5±10.0	33.8±12.7	p=0.628
	Post-PR	30.0±11.6	32.5±11.4	p=0.496
	Δ	-5.5±9.4	-1.3±8.2	p=0.149
FACIT-F (n=42)	**n, (%)**	30 (71.4)	12 (28.6)	
	Baseline	34.1±10.2	31.3±11.1	p=0.449
	Post-PR	37.7±9.1	33.9±8.7	p=0.224
	Δ	3.6±6.4	2.5±7.6	p=0.645
LCQ (n=45)	**n, (%)**	30 (66.7)	15 (33.3)	
	Baseline	16.9±3.3	16.7±3.6	p=0.897
	Post-PR	17.7±3.6	17.4±3.2	p=0.784
	Δ	0.8±2.1	0.6±2.7	p=0.829
CASA-Q (n=41)	**n, (%)**	29 (70.7)	12 (29.3)	
Cough symptoms	**Baseline**	66.7 [50.0;83.3]	58.3 [41.7;83.3]	p=0.788
	Post-PR	75.0 [50.0;91.7]	55.7 [50.0;75.0]	p=0.342
	Δ	8.3 [0.0;16.7]	4.2 [-8.3;8.3]	p=0.703
Cough impact	**Baseline**	75.0 [59.4;93.8]	64.1 [46.9;100.0]	p=0.601
	Post-PR	90.6 [62.5;100.0]	79.7 [54.7;93.8]	p=0.357
	Δ	3.1 [-3.1;9.4]	1.6 [-9.4;14.1]	p=0.703
Sputum symptoms	**Baseline**	75.0 [50.0;83.3]	50.0 [41.7;66.7]	p=0.127
	Post-PR	75.0 [50.0;100.0]	58.3 [45.8;79.2]	p=0.300
	Δ	0.0 [-8.3;16.7]	0.0 [-8.3;16.7]	p=0.877
Sputum impact	**Baseline**	83.3 [66.7;95.8]	70.8 [56.3;89.6]	p=0.453
	Post-PR	91.7 [66.7;100.0]	79.2 [56.3;97.9]	p=0.287
	Δ	4.2 [0.0;12.5]	0.0 [-10.4;12.5]	p=0.724

Notes: Values are presented as mean ± standard deviation or median [interquartile range], unless otherwise stated. * p<0.05
Legend: AECOPD – Acute exacerbation of chronic obstructive pulmonary disease; PR – Pulmonary rehabilitation; Δ – mean change; CIS-20 FS – Checklist of individual strength fatigue subscale; FACIT-F – Functional Assessment of Chronic illness therapy – Fatigue; LCQ – Leicester cough questionnaire; CASA-Q - Cough and Sputum Assessment Questionnaire.

Table 9: Patient-reported outcome measures mean scores at baseline and after community-based pulmonary rehabilitation, according to the anchor's cut-offs.

		Patient's GRC		Physiotherapist's GRC		Δ CAT		Δ SGRQ	
		≥2	<2	≥2	<2	≥2	<2	≥4	<4
CIS-FS (n=48)	**n, (%)**	40 (83.3)	8 (16.7)	44 (91.7)	4 (8.3)	36 (75.0)	12 (25.0)	31 (64.6)	17 (35.4)
	Baseline	34.3±11.5	38.4±5.5	34.8±11.0	36.5±8.9	34.6±11.0	35.9±10.6	34.2±11.1	36.4±10.3
	Post-PR	30.0±12.1	34.5±7.6	30.4±11.9	34.8±4.6	30.0±12.1	33.1±9.4	30.1±12.9	32.0±8.6
	Δ	-4.2±9.9	-3.9±3.7	-4.4±9.4	-1.8±4.3	-4.6±10.0	-2.8±5.8	-4.1±10.5	-4.4±6.1
FACIT-F (n=42)	**n, (%)**	35 (83.3)	7 (16.7)	37 (88.1)	5 (11.9)	31 (73.8)	11 (26.2)	27 (64.2)	15 (35.7)
	Baseline	33.2±10.7	33.7±9.9	36.9±9.2	32.6±7.0	32.5±10.6	35.4±10.1	32.3±10.6	35.1±10.1
	Post-PR	36.5±9.0	37.0±9.9	33.4±10.9	33.9±8.1	36.4±9.5	37.1±8.0	36.4±9.6	36.9±8.3
	Δ	3.3±6.7	3.3±7.1	3.5±6.8	1.3±6.0	3.8±6.9	1.8±6.1	4.1±7.2	1.8±5.6
LCQ (n=45)	**n, (%)**	26 (57.8)	19 (42.2)	25 (55.6)	20 (44.4)	35 (77.8)	10 (22.2)	30 (66.7)	15 (33.3)
	Baseline	15.9±3.4	18.1±3.0	17.0±3.4	16.7±3.4	16.8±3.1	17.1±4.4	16.3±3.3	17.9±3.4
	Post-PR	17.4±3.3	17.8±3.6	17.9±3.1	17.1±3.8	17.8±3.1	16.7±4.5	17.5±3.3	17.7±3.6
	Δ	1.4±1.9	-0.3±2.5	1.0±2.2	0.4±2.5	1.0±2.1	-0.4±2.8	1.2±2.2	-0.2±2.2
CASA-Q (n=41)	**n, (%)**	21 (51.2) [#] 25 (61.0) [§]	20 (48.8) [#] 16 (39.0) [§]	18 (43.9)[#] 21 (51.2)[§]	23 (56.1)[#] 20 (48.8)[§]	31 (75.6)	10 (24.4)	25 (61.0)	16 (39.0)
Cough symptoms	**Baseline**	59.1±22.2	68.8±23.2	62.0±24.0	65.2±22.6	60.2±23.3	75.0±18.4	56.7±20.8	75.0±22.2
	Post-PR	69.0±20.8	67.1±26.3	70.8±18.8	65.9±26.6	69.4±22.3	64.2±27.2	66.0±23.7	71.4±23.2
	Δ	9.9±16.2	-1.7±19.4	8.8±15.3	0.7±20.4	9.1±14.3	-10.8±22.6	9.3±17.1	-3.6±18.5
Cough impact	**Baseline**	66.5±19.3	79.2±24.0	74.3±21.3	71.5±23.6	70.9±22.4	78.4±22.4	66.9±21.7	81.8±20.9
	Post-PR	78.3±19.8	79.1±24.8	81.4±20.2	76.5±23.7	79.4±21.7	76.3±24.3	77.3±23.1	80.9±21.1
	Δ	11.8±17.6	-0.2±14.7	7.1±18.8	5.0±16.2	8.6±16.3	-2.2±18.1	10.4±19.1	-1.0±11.1
Sputum symptoms	**Baseline**	60.0±22.7	72.9±21.2	62.3±21.8	67.9±23.9	64.0±22.7	68.3±23.8	59.7±23.3	73.4±19.8
	Post-PR	66.0±26.7	70.3±24.5	69.8±22.4	65.4±29.0	69.4±25.4	62.5±27.0	67.3±25.6	68.2±26.2
	Δ	6.0±21.2	-2.6±18.7	7.5±18.0	-2.5±22.0	5.4±19.3	-5.8±22.6	7.7±22.2	-5.2±14.9
Sputum impact	**Baseline**	71.5±21.2	83.1±17.8	74.8±18.3	77.3±23.1	76.3±19.3	75.0±25.2	71.0±22.1	83.9±15.3
	Post-PR	76.7±24.7	82.0±23.7	80.2±20.8	77.3±27.7	80.2±23.1	74.2±28.0	77.0±24.4	81.5±24.2
	Δ	5.2±16.5	-1.0±15.6	5.4±15.8	0.0±16.7	3.9±16.4	-0.8±15.9	6.0±16.2.	-2.3±15.4

Notes: Values are presented as mean ± standard deviation or median [interquartile range], unless otherwise stated. # cough-related; [§] sputum-related
Legend: GRC – Global rating of change; CAT – COPD assessment test; SGRQ – St George's Respiratory Questionnaire; PR – Pulmonary rehabilitation; Δ – mean change; CIS-20 FS – Checklist of individual strength fatigue subscale; FACIT-F – Functional Assessment of Chronic illness therapy – Fatigue; LCQ – Leicester cough questionnaire; CASA-Q - Cough and Sputum Assessment Questionnaire

Table 10: Anchor and distribution-based methods used to compute the minimal clinically important difference of patient-reported outcome measures.

	CIS-20 FS	FACIT-F	LCQ	CASA-Q			
				Cough symptoms	Cough impact	Sputum symptoms	Sputum impact
Mean change							
SGRQ	-	4.1 (1.3 to 6.9)	-	9.3 (2.3 to 16.4)	-	7.7 (-1.5 to 16.8)	6.0 (-0.7 to 12.7)
CAT	-	-	-	9.1 (3.9 to 14.4)	-	-	-
Patient's GRC	-	-	1.4 (0.7 to 2.2)	9.9 (2.6 to 17.3)	11.8 (3.7 to 19.8)	-	-
ROC							
SGRQ	-	-	-	4.2	-	4.2	-
CAT	-	-	-	4.2	-	-	-
Patient's GRC	-	-	-	-	4.7	-	-
Linear regression							
SGRQ	-	2.6 (0.9 to 4.3)	-	1.6 (-3.4 to 6.6)	-	-	2.2 (-1.5 to 6.0)
CAT	-	-	-	-	-	-	-
Patient's GRC	-	-	0.7 (-0.9 to 2.4)	-	-	-	-
Distribution methods							
0.5*SD	5.4	5.2	1.7	11.5	11.2	11.4	10.3
SEM	4.2	3.1	1.0	11.0	7.8	10.2	8.7
1.96SEM	8.2	6.1	1.9	21.6	15.2	20.0	17.1
MDC	11.6	8.7	2.6	30.5	21.5	28.2	24.2
ES	0.37	0.34	0.21	0.23	0.19	0.09	0.12
Pooled MCID	7.3 (4.1 to 10.6)	4.2 (1.7 to 6.7)	1.3 (0.4 to 2.2)	10.6 (4.0 to 17.2)	10.1 (3.2 to 17.1)	9.5 (0.0 to 19.5)	7.8 (0.5 to 15.2)
% of change	15.2	8.0	6.8	10.6	10.1	9.7	7.8
MCID ES	0.66	0.43	0.50	0.45	0.45	0.40	0.35

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: CIS-20 FS – Checklist of individual strength fatigue subscale; FACIT-F – Functional Assessment of Chronic illness therapy – Fatigue; LCQ – Leicester cough questionnaire; CASA-Q – Cough ad Sputum Assessment Questionnaire; GRC – Global rating of change; CAT – COPD assessment test; SGRQ – St George's Respiratory Questionnaire; ROC – Receiver operating characteristic curves; SD – standard deviation; SEM – standard error measurement; MDC – minimal detectable change; ES – effect size; MCID - minimal clinically important difference.

4. Discussion

According to our best knowledge, this is the first study to estimate MCIDs for a series of fatigue, cough and sputum scales. Pooled MCIDs of 7.3 (range of 4.1 to 10.6) points for the CIS-20 FS, 4.2 (range of 1.7 to 6.7) points for the FACIT-F and 1.3 (range of 0.4 to 2.2) points for the LCQ, were found following a PR programme in patients with COPD. The pooled MCIDs for each CASA-Q domain were also established, i.e., 10.6 (range of 4.0 to 17.2) points for cough symptoms, 10.1 (3.2 to 17.1) points for cough impact, 9.5 (0.0 to 19.5) points for sputum symptoms and 7.8 (0.5 to 15.2) points for sputum impact dimensions.

Fatigue, cough and sputum negatively affected the HRQoL of participants included in our study. Fatigue was present in approximately 80% of the sample (53% with severe and 26% with mild fatigue), surpassing the 50 to 70% reported in previous literature (9, 10). The high prevalence and the degree of the fatigue severity observed, should call 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 reduce it. The impact of cough and sputum in the HRQoL of our participants (16.6 points for LCQ and 66.7 to 79.2 points for CASA-Q), was somewhat comparable to other studies (15.9 points for LCQ and 66.7 to 87.5 points for CASA-Q) enrolling patients with COPD (98, 121). However, when compared to studies considering patients with chronic cough only (91, 122, 123), our sample scored considerably higher (meaning that cough had less impact) in both the LCQ and the CASA-Q. In the present study, the presence of chronic cough was not an inclusion criterion, which may explain these differences and justify the observed ceilings effects in CASA-Q.

Following the most up-to-date recommendations for establishing MCID (35, 46, 49, 113), an effort was made to combine anchor- and distribution methods to compute the MCID. However, this recommendation was not always possible to follow, e.g. for CIS-20 FS, due to the lack of correlations with the anchors chosen. It is known that fatigue is a complex, multifaceted and dynamic phenomenon (12), and PROMs focus specifically in the perceived fatigability but neglect the performance component (12). Thus, both CIS-20 FS and FACIT-F may have failed to capture the overall impact of fatigue, which justifies the paucity and poor correlations, with the chosen anchors (i.e., GRC, CAT and SGRQ). Therefore, the MCID of CIS-20 FS was computed using exclusively distribution-

based methods. Although the study of Peters and colleagues (9) reports a MCID of 10 points for CIS-20 FS, no information, or reference, regarding that estimation is given, furthermore, we were not able to find any study describing how that value was achieved. Other estimations of MCIDs for this scale are not available, even in other populations, however, the standard deviation observed in our sample was comparable to previously reported data (9, 80), and the MDC (11.6 points) was very similar to the one established for patients with multiple sclerosis (11.8 points) (124).

The MCID for the FACIT-F, computed using both distribution and anchor methods, was found to be similar to the one previously determined for rheumatoid arthritis (i.e., 3-4 points) (86), but smaller than the MCID estimated for the systemic lupus erythematosus (i.e., 5.9 points) (88). The last study (88), explored differences between individuals, and used a cross-sectional approach that consisted in gathering patients in a group, or couples, and asking them to rate whether they feel better, the same or worse in comparison to others (42, 115). In contrast, our study focused on longitudinal within-patient differences, a more appropriated method to assess changes over time and response to a given intervention (42, 47). Since each MCID was computed using a different approach, it is plausible that the resulting values could be discordant. Furthermore, MCIDs are recognised to be disease-specific (48), hence, although comparisons across populations are not desirable, it is important to use similar and robust methodologies for its establishment, so these values can be used with confidence in clinical practice.

The pooled MCID found for the LCQ matched previous estimates for patients with chronic cough (i.e., 1.3 points) (94). Nevertheless, higher MCIDs (i.e., from 2 to 3 points) have been suggested (90, 95, 96). One study established the MCID using a GRC with a period recall of 6 months (95), increasing the recall risk of bias (46, 114), and in the other two studies participants were patients with acute cough (90, 96). Both aspects could have affected the established MCID for this PROM. In fact, baseline scores significantly affect the MCIDs, with higher levels of severity usually leading to greater improvements (46, 48, 115). It seems therefore reasonable, that acute cough has yielded larger MCIDs than chronic cough. Another aspect worth mentioning, is that these studies involved pharmacological interventions, whilst our study reports on PR. Since PR demands more from patients, expectations of benefits and improvements are often high, producing

larger effect sizes when compared to medication only, and thus, generating larger MCIDs (125).

The pooled MCIDs for each CASA domain were similar between each other. The CASA-Q was the PROM presenting the highest correlations with the proposed anchors, emerging as a good tool to discriminate between patients above and below the anchor's MCIDs. Nevertheless, the CASA-Q was also the scale where a ceiling effect was notorious, and thus its MCIDs should be interpreted with caution. Although assessing PR effectiveness was not a goal of this study, the ceiling effect found might be the reason behind the almost negligible effect sizes observed in the CASA-Q. Scores close to the end of the scale limit the amount of potential change, affect responsiveness of the scale and consequently the establishment of the MCIDs (46). It is also important to mention that the 95% confidence intervals computed for the CASA-Q were large, probably due to the non-normally distribution of the data. This fact may have also impacted the development of the ROC curves, as non-normal distributed data tend to yield smaller and potentially erratic estimates (126).

Similar to previous research (35, 68, 127), the results from distribution and anchor-based methods did not consistently matched, with the MDC systematically resulting in larger estimates. From all methods used (seven in total), similar MCIDs were obtained with three of them, i.e., the mean change (anchor-based method), the 0.5SD and the SEM (distribution-based methods). This agreement supports the clinically meaningfulness advocated in the literature for these two distribution methods (116, 117). Concerning the 1.96SEM and the MDC, both are calculated by multiplying the SEM value with different factors, thus they tended to overestimate the MCIDs (48, 68, 117). On the other hand, most of the correlations between the PROMs and the anchors used where near to the cut-off point used to define a moderate association (i.e., 0.3). It is important to notice that, the MCIDs computed through linear regressions are as underestimated as the weakness of the correlation (128). It is therefore recommended, that anchor-based methods, which provide clinical meaning, are combined with distribution-based methods, that add statistical significance, and one method, should not replace the other (35, 48).

It was not possible to use neither physiotherapists GRC nor the occurrence of AECOPD (criterion method). The poor agreement on symptoms perception between patients with COPD and health professionals has been previously reported (129). As for criterion method, although symptoms tended to be slightly more severe at baseline and

improvements were also somewhat smaller in the group that had an AECOPD during PR, the differences observed between groups were not significant.

4.1 Strengths and limitations

This study presents some strengths and limitations that should be acknowledged. An important strength is that the MCIDs were computed through a combination of different methodologies, including a wide range of either anchor and distribution-based approaches. In addition, the pooled method selected allowed to attribute a higher weight to anchor than distribution-based methods, following the international recommendations for establishing MCIDs (35, 46). The community-based PR programmes implemented were standardised in terms of structure, intensity, frequency, duration and progression, as recommended (36). Thus, the heterogeneity of intervention was minimised, assuring that the MCIDs proposed are valid and suitable for PR. Apart from CIS-20 FS, all the MCIDs values fell within the recommended range of 6 to 10% change in the scale range, which corresponded to a desirable effect size of 0.2 to 0.5 (35, 46, 119), emphasising the validity of our estimates. The MCIDs established for fatigue, cough and sputum PROMs can be promptly used in clinical practice to guide the interpretation of changes, in response to PR, and to optimise the intervention. Moreover, they can be useful for policy-makers, guideline developers or researchers to establish the clinical importance of PR effects, compute sample sizes or represent an endpoint in a clinical trial.

Important limitations of this study are as follow. Firstly, to yield the MCID from anchor-based approaches all patients that improved above the anchor cut-off point were considered, regardless of the amount of change. Theoretically, this method could have resulted in overestimated values. This could have been avoided if the MCIDs were computed using only the patients that reported minimal improvements in the anchors, resulting in an analysis with a smaller sample size. However, it is unlikely that our MCIDs have been overestimated, as the pooled value corresponded to small effect sizes (0.2-0.5) (35, 46, 119). Secondly, the ceiling effects observed in the CASA-Q and the use of exclusively distribution methods to compute the MCID for the CIS-20 FS might have biased the present results. Nevertheless, to our best knowledge, this is the first study to provide MCIDs estimations to either CIS-20 FS and CASA-Q, and they can be used as a booster for future research in this field. It is also important to notice that we were not able to achieve the ideal sample size of at least 50 participants (53) required to compute

the MCIDs. Finally, our sample was composed of mainly man (82%), in contrast to recent data, describing a tendency to a prevalence almost equal between genders (1), thus, our MCIDs estimations should be applied with caution in women.

4.2 Future work

Future studies should investigate fatigue MCIDs, by adding anchorage with outcomes related to physical activity and/or exercise performance, since these could provide interesting insights into other features of fatigue (12, 84). Finally, an evaluation process, such as a Delphi method among patients, health-care professionals and experts in COPD, could have been a useful adjunct to complete the MCIDs estimations (35, 130). This method aims to obtain a formal consensus and triangulate with the MCIDs derived from both anchor and distribution-based approaches (35, 130). More studies with larger samples, and possibly with patients of different disease severities, could be useful to validate these results.

5. Conclusions

The current study suggests that for patients with COPD, improvements of 7.3 points in CIS-20 FS, 4.2 in FACIT-F, 1.3 in LCQ, 10 in the cough symptoms, cough impact and sputum symptoms dimensions of CASA-Q and 7.8 points in the sputum impact dimension should be considered clinically relevant, following a PR programme. These estimates have the potential to be used to interpret clinical relevance, as thresholds for the intervention effectiveness and to inform future studies regarding sample calculation.

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Appendix I – Participant information sheet

Folha de informação ao participante

O Sr./Sra. está a ser convidado/a para participar no estudo de investigação clínica intitulado: "Revitalizar a Reabilitação Respiratória (3R)". Mas, antes de decidir, é importante que compreenda porque é que a investigação está a ser realizada e o que é que a mesma envolve. Por favor, leia a informação com atenção e discuta a sua participação com outros, se assim o entender. Se houver algo que não esteja claro para si ou necessitar de informação adicional, por favor pergunte aos investigadores (contactos no final deste documento). Use o tempo que precisar para decidir se deseja ou não participar.

Muito obrigado desde já por ler a informação.

Qual é o propósito do estudo?

Este estudo visa o desenvolvimento, implementação e disseminação de programas de reabilitação respiratória (RR) na comunidade da região centro de Portugal, aumentando assim o acesso dos pacientes com doenças respiratórias crónicas (DRC) a este tipo de intervenção.

As DRC afetam mais de 1 bilião de pessoas a nível mundial e são a 3ª causa de morte no nosso país, sendo a região centro uma das mais afetadas. A RR é uma intervenção para a gestão das DRC que apresenta elevada evidência científica. Contudo, apesar da oferta de RR ter sido definida como prioritária, em Portugal esta continua praticamente inexistente. Adicionalmente, os programas de RR existentes no nosso país decorrem em hospitais e são dirigidos aos pacientes mais severos, todavia as recomendações internacionais apontam para o desenvolvimento de novos modelos de implementação destes programas. Assim, este projeto procura aumentar o acesso dos pacientes com DRC à RR na região centro do país, através de programas na comunidade. Para que seja possível alcançar estes objetivos vimos solicitar a sua participação neste estudo que será realizado na Escola Superior de Saúde da Universidade de Aveiro e centros de saúde do Baixo Vouga e Baixo Mondego.

Porque é que fui escolhido?

Foi escolhido/a porque é uma pessoa com DRC em fase estável. Para o estudo, precisamos de dados de aproximadamente 80 pessoas, com uma condição clínica semelhante à sua, que aceitem participar.

Tenho de participar?

A decisão de participar, ou não, é completamente sua. Se decidir participar vai-lhe ser pedido que assine um consentimento informado mas, é totalmente livre de desistir a qualquer momento, sem que para tal tenha de dar qualquer justificação. A decisão de desistir ou de não participar, não afetará a qualidade dos serviços de saúde ou qualquer outro, que lhe são prestados agora ou no futuro.

O que me acontecerá caso decida participar?

Se decidir participar, após assinar e entregar aos investigadores o consentimento informado, será feita uma avaliação do seu estado de saúde geral. Primeiro, serão gravados os sons dos seus pulmões durante aproximadamente 20 segundos (3 repetições), com um microfone, como se fosse um estetoscópio, que está ligado a um computador portátil. Seguidamente, ser-lhe-á medido o peso e a altura numa balança. Depois, ser-lhe-á avaliada a força dos seus músculos da respiração e a capacidade respiratória, através de dois testes que consistem em inspirar e soprar para um equipamento. A avaliação da força dos seus músculos da coxa ou braço realizar-se-ão de seguida através de um aparelho que se encosta à região do corpo em teste sendo-lhe pedido que realize o máximo de força que conseguir. Veremos também a sua tolerância ao exercício através de um teste de caminhada de 6 minutos e um teste de sentar e levantar de uma cadeira durante um minuto. Examinaremos igualmente o seu equilíbrio, através de alguns testes que envolvem aguentar a posição de pé ou caminhar com alguns obstáculos. Mediremos também a quantidade de oxigénio no

seu sangue e a sua frequência cardíaca através de um oxímetro (aparelho pequeno que se coloca no seu indicador e nos dá a informação desses valores em segundos). Avaliaremos também o movimento do seu diafragma (músculo principal da respiração) através de um Raio X ao tórax. Realizaremos uma ecografia ao diafragma e aos músculos da coxa e braço para medir a área transversal de cada músculo. De seguida avaliaremos a sua frequência respiratória observando a sua região abdominal e mediremos a tensão arterial com um medidor de tensão arterial digital. Por último, ser-lhe-á pedido que responda a alguns questionários simples, para avaliar a existência ou não de ansiedade e depressão, o seu nível de atividade física, a sua confiança no acesso às telecomunicações, o impacto da doença no seu dia-a-dia, qualidade de vida e, um último, para avaliar o impacto da doença na família. Ser-lhe-á também pedido que use um acelerómetro por 1 semana. A investigadora do projeto contactá-lo-á após 12 semanas, 3 meses e 6 meses para agendar as reavaliações.

Ser-lhe-á proposto que integre um programa de RR durante 12 semanas (2 vezes/semana). Caso aceite participar, durante este período terá o acompanhamento de uma equipa multidisciplinar e especializada para lhe prescrever e supervisionar as sessões de exercício personalizadas e ensinar várias técnicas e estratégias para uma melhor gestão da sua doença.

As avaliações e o programa de RR poderão decorrer no seu centro de saúde ou nas instalações da Escola Superior de Saúde da Universidade de Aveiro, de acordo com a sua preferência, com duração de aproximadamente 1 hora. Nenhum dos testes ou intervenções realizadas provoca qualquer dor ou desconforto.

Quais são os efeitos secundários, desvantagens e riscos se eu resolver participar?

Não existem efeitos secundários, desvantagens ou riscos de participar no estudo.

Quais são os possíveis benefícios se eu resolver participar?

Toda a informação clínica recolhida será fornecida aos participantes para que seja do seu conhecimento e poderá mostrá-la à equipe de saúde que habitualmente o acompanha. No caso de integrar o programa de RR, beneficiará também de um acompanhamento semanal do seu estado de saúde prestado por um fisioterapeuta respiratório qualificado. Para além disso, a informação obtida neste estudo, através da sua participação, poderá ajudar a melhorar o acesso dos milhares de pacientes que sofrem de DRC a uma intervenção qualificada.

A minha participação será confidencial?

Toda a informação recolhida no decurso do estudo será mantida estritamente confidencial e mantido o anonimato. Os dados recolhidos serão salvaguardados com um código e palavra-passe, para que ninguém o/a possa identificar. Apenas os investigadores do projeto terão acesso aos seus dados.

O que acontecerá aos resultados do estudo?

Os resultados do estudo serão analisados e incorporados em Dissertações de Mestrado e Teses de Doutoramento e alguns serão publicados em Jornais Científicos. No entanto, em nenhum momento o Sr./Sra. será identificado/a. Se gostar de obter uma cópia de qualquer relatório ou publicação, por favor diga ao investigador com quem contactar.

Contactos para mais informações sobre o estudo

Alda Marques
Escola Superior de Saúde da Universidade de Aveiro,
Telefone 234 372 462 e-*mail:* amarques@ua.pt

Appendix II – Informed consent

Termo de Consentimento Livre e Esclarecido

Título do Projeto: "Revitalizar a Reabilitação Respiratória (3R)".

Nome do Investigador Principal: Prof. Doutora Alda Sofia Pires de Dias Marques

Por favor leia e assinale com uma cruz (X) os quadrados seguintes.

1. Eu confirmo que percebi a informação que me foi dada e tive a oportunidade de questionar e de me esclarecer. ☐

2. Eu percebo que a minha participação é voluntária e que sou livre de desistir, em qualquer altura, sem dar nenhuma explicação, sem que isso afete qualquer serviço de saúde ou qualquer outro que me é prestado. ☐

3. Eu compreendo que os dados recolhidos durante a investigação são confidenciais e que só os investigadores do projeto da Universidade de Aveiro têm acesso a eles. Portanto, dou autorização para que os mesmos tenham acesso a esses dados. ☐

4. Eu compreendo que os dados recolhidos durante o estudo podem ser utilizados para publicação em Revistas Científicas e usados noutras investigações, sem que haja qualquer quebra de confidencialidade. Portanto, dou autorização para a utilização dos dados para esses fins. ☐

5. Eu concordo então em participar no estudo. ☐

_____	_____	_____
Nome da pessoa	Data	Assinatura
_____	_____	_____
Nome do Investigador(a)	Data	Assinatura

Appendix III – Scientific outputs developed under the scope of this dissertation

Abstracts in international conferences:

Rebelo P., Oliveira A., Marques A. Defining the minimal clinically important difference for fatigue and cough measures in chronic obstructive pulmonary disease. European Respiratory International Congress, Spain, Madrid, 28Th September – 2nd October 2019 (submitted)

Oral communications:

Rebelo P., Oliveira A., Marques A. Minimal clinically important difference for fatigue and cough patient-reported outcome measures in chronic obstructive pulmonary disease. World Confederation of Physical Therapy Congress, Geneva, Switzerland, 10-13rd May 2019

Annex I – Ethics approval

GOVERNO DE PORTUGAL
MINISTÉRIO DA SAÚDE

ARSC ADMINISTRAÇÃO REGIONAL DE SAÚDE DO CENTRO, I.P.

COMISSÃO DE ÉTICA PARA A SAÚDE

PARECER FINAL: Esta Comissão de Ética é favorável à concretização do estudo. Deve ser corrigida a folha de informação aos participantes, incluindo informação clara sobre os custos, enviando a mesma a esta Comissão.	**DESPACHO:** Homologado em termos e condições emitidas no parecer favorável. 20/4/2017 Conselho Directivo da A.R.S. do Centro, I.P. Dr. José Manuel Azenha Tereso Presidente, Dr. Luis Manuel Militão Mendes Cabral Vogal, Dr. Mário Ruivo Vogal,

ASSUNTO: **Estudo** 73/2016 – (Re)vitalizar a Reabilitação Respiratória
Autora: Alda Marques

A Investigadora propõe-se realizar estudo de desenho experimental, tendo como objectivo principal "Desenvolver, implementar e disseminar programas de reabilitação respiratória (RR) na comunidade em Portugal". Estima-se a inclusão de 73 pessoas com DPOC e respectivas famílias que serão divididos em dois grupos, experimental e controlo, sendo o grupo experimental submetido a um programa de RR na comunidade durante 12 semanas.
Propõem que o programa de RR decorrerá em quatro centros de saúde de 2 ACES (Baixo Vouga e Baixo Mondego), propondo que estes sejam contatados após autorização da ARS, prevendo deslocação a cada um deles para convite a médicos e enfermeiros para integrarem a equipa. São definidos os critérios de inclusão e exclusão.
Serão avaliadas variáveis físicas (função pulmonar; raio X; ecografia; sons respiratórios computorizados, força dos músculos inspiratórios, quadricípite e bicípite e tolerância ao exercício).
Serão ainda avaliados, por questionário, algumas variáveis no doente e família (qualidade de vida relacionada com a saúde, dispneia, exacerbações, utilização de cuidados de saúde, actividade física, estado emocional, coesão e adaptabilidade familiar).
São apresentados documentos para recolha dos dados, informação e consentimento.
Será utilizada chave para codificação para identificação indirecta do titular dos dados, sendo esta do conhecimento único dos investigadores, fisicamente separada dos dados e que será destruída terminado o processo de análise
O recrutamento, informação e obtenção do consentimento será realizado pelos médicos e enfermeiros da instituição.
Os participantes serão monitorizados ao nível da FC e SpO2 durante os testes de tolerância ao exercício, parando-se a atividade caso se observem desvios ou na presença de dor torácica. Serão prestados cuidados de apoio se necessário
A investigação não trará custos para o Centro de Saúde. Os momentos de recolha de dados acontecerão conjugados com vindas dos doentes ao centro de saúde. Os custos de deslocação (a existirem) para o doente, relacionados com a participação no programa de reabilitação respiratória, será assegurado pelo próprio. Este facto deve constar na folha de informação aos participantes.

Coimbra, 19 de abril de 2017

O relator,

José Carlos Amado Martins

O Presidente da CES

Prof. Dr. Fontes Ribeiro

Annex II – National Committee for Data Protection approval

N/Ref. 02.02
Proc. n.° 10968 / 2016
Of. n° 21399
Data: 2016-08-02

Assunto: Notificação de tratamento de dados de investigação clínica

Com referência ao assunto em epígrafe, ficam V. Exas. notificados de todo o conteúdo da decisão desta CNPD n° 7295/ 2016 proferido em 02-08-2016, cuja cópia se anexa.

Com os melhores cumprimentos.

A Secretária da CNPD

(Isabel Cristina Cruz)

Autorização n.º 7295/ 2016

Universidade de Aveiro , NIPC 501461108, notificou à Comissão Nacional de Protecção de Dados (CNPD) um tratamento de dados pessoais com a finalidade de realizar um Estudo Clínico com Intervenção, denominado Revitalizar a Reabilitação Respiratória (3R) .

Existe justificação específica, validada pela Comissão de Ética Competente (CEC), para o tratamento do dado pessoal raça/etnia.

O participante é identificado por um código especificamente criado para este estudo, constituído de modo a não permitir a imediata identificação do titular dos dados; designadamente, não são utilizados códigos que coincidam com os números de identificação, iniciais do nome, data de nascimento, número de telefone, ou resultem de uma composição simples desse tipo de dados. A chave da codificação só é conhecida do(s) investigador(es).

É recolhido o consentimento expresso do participante ou do seu representante legal.

A informação é recolhida diretamente do titular e indiretamente do processo clínico.

As eventuais transmissões de informação são efetuadas por referência ao código do participante, sendo, nessa medida, anónimas para o destinatário.

A CNPD já se pronunciou na Deliberação n.º 1704/2015 sobre o enquadramento legal, os fundamentos de legitimidade, os princípios aplicáveis para o correto cumprimento da Lei n.º 67/98, de 26 de outubro, alterada pela Lei n.º 103/2015, de 24 de agosto, doravante LPD, bem como sobre as condições e limites aplicáveis ao tratamento de dados efetuados para a finalidade de investigação clínica.

No caso em apreço, o tratamento objeto da notificação enquadra-se no âmbito daquela deliberação e o responsável declara expressamente que cumpre os limites e condições aplicáveis por força da LPD e da Lei n.º 21/2014, de 16 de abril, alterada pela Lei n.º 73/2015, de 27 de junho – Lei da Investigação Clínica –, explicitados na Deliberação n.º 1704/2015.

O fundamento de legitimidade é o consentimento do titular.

A informação tratada é recolhida de forma lícita, para finalidade determinada, explícita e legitima e não é excessiva – cf. alíneas a), b) e c) do n.º 1 do artigo 5.º da LPD.

Assim, nos termos das disposições conjugadas do n.º 2 do artigo 7.º, da alínea a) do n.º 1 do artigo 28.º e do artigo 30.º da LPD, bem como do n.º 3 do artigo 1.º e do n.º 9 do artigo 16.º ambos da Lei de Investigação Clínica, com as condições e limites explicitados na Deliberação da CNPD n.º 1704/2015, que aqui se dão por reproduzidos, autoriza-se o presente tratamento de dados pessoais nos seguintes termos:

Responsável – Universidade de Aveiro

Finalidade – Estudo Clínico com Intervenção, denominado Revitalizar a Reabilitação Respiratória (3R)

Categoria de dados pessoais tratados – Código do participante; idade/data de nascimento; género; raça/etnia; dados antropométricos; sinais vitais; dados da história clínica; dados dados de exame físico; dados de meios complementares de diagnóstico; medicação prévia concomitante; dados de cuidadores/acompanhantes (apenas os relacionados com as necessidades do participante); dados de qualidade de vida/efeitos psicológicos

Exercício do direito de acesso – Através dos investigadores, presencialmente

Comunicações, interconexões e fluxos transfronteiriços de dados pessoais identificáveis no destinatário – Não existem

Prazo máximo de conservação dos dados – A chave que produziu o código que permite a identificação indireta do titular dos dados deve ser eliminada 5 anos após o fim do estudo.

Da LPD e da Lei de Investigação Clínica, nos termos e condições fixados na presente Autorização e desenvolvidos na Deliberação da CNPD n.º 1704/2015, resultam obrigações que o responsável tem de cumprir. Destas deve dar conhecimento a todos os que intervenham no tratamento de dados pessoais.

Lisboa, 02-08-2016

A Presidente

Filipa Calvão