Core outcome set for pulmonary rehabilitation of patients with COPD

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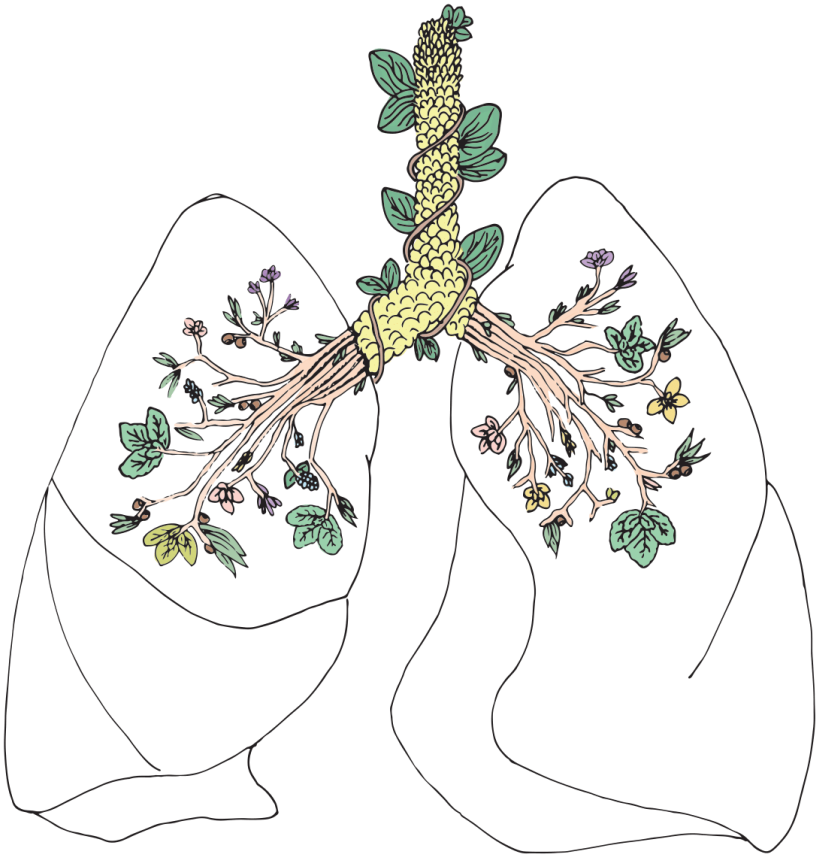

Chapter 1
General introduction

Chronic obstructive pulmonary disease (COPD)

Chronic obstructive pulmonary disease (COPD) is a complex and heterogenous respiratory disease, characterised by chronic respiratory symptoms due to airway and/or alveoli abnormalities that cause persistent and often progressive airflow obstruction[1].

COPD has an estimated global age standardized prevalence of 8.7%[2], and is currently the third major cause of mortality, with around three million deaths per year which are expected to increase due to the rising prevalence of smoking and higher population longevity in developed countries[3-5]. Although COPD has been perceived as a predominantly male disease, the prevalence of this disease is now similar between women and men, particularly in developed countries[6].

This disease causes enormous burden for people and economies. It has an estimated rate of 9261.1/100.000 disability-adjusted life years (DALYs)[2], and represents up to 56% of the costs of respiratory disease in the European Union, which are estimated to be 6% of the total healthcare budget[7].

The diagnosis of COPD is based on the presence of symptoms (e.g., dyspnoea, chronic cough, sputum), history of recurrent lower respiratory tract infections and/or exposure to risk factors (e.g., genetic/congenital, tobacco smoke, occupation, indoor/outdoor pollution), and is confirmed by a postbronchodilator spirometry if the ratio forced expiratory volume in the first second (FEV_1)/ forced vital capacity (FVC) is less than 0.70[1].

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD can be classified into four grades depending on the severity of airflow limitation - GOLD 1 (mild): $FEV_1 \geq 80\%$ predicted, GOLD 2 (moderate): $50\% \leq FEV_1 < 80\%$ predicted, GOLD 3 (severe): $30\% \leq FEV_1 < 50\%$ predicted, or GOLD 4 (very severe): $FEV_1 < 30\%$ predicted[5].

A more comprehensive classification considering the symptoms and exacerbation risk through the ABE (former ABCD) assessment tool has also been

proposed[1,5]. This tool uses the history of moderate or severe exacerbations and the modified Medical Research Council dyspnoea scale (mMRC)[8] or the COPD assessment test (CAT)[9] to divide patients into three categories[1]. The ABE tool results, therefore, in patients classified as GOLD A: 0-1 moderate exacerbation not leading to hospitalisation and mMRC score 0-1 or CAT <10 points, GOLD B: 0-1 moderate exacerbation not leading to hospitalisation and mMRC score ≥ 2 or CAT ≥ 10 points, GOLD E: ≥1 exacerbation leading to hospitalisation or ≥2 moderate exacerbations[1]. This classification is, however, insufficient to explain the heterogeneity and complexity of COPD, with different patient profiles being included in all GOLD grades and groups[10]. Recently, the Lancet Commission proposed a new COPD classification that considers the variation in causes of COPD linked with the endotypes. According to this classification five types of COPD exist: type 1 – genetically determined COPD; type 2 – COPD related to early-life events; type 3 – infection-related COPD; type 4 – COPD related to vaping or smoking; type 5 – environmental exposure-related COPD[11].

COPD has often systemic manifestations, with pulmonary (e.g., dyspnoea, cough, lung function limitations), but also extra-pulmonary traits that can be physical (e.g., low exercise tolerance, low functional status, sarcopenia, reduced muscle strength, fatigue), psychological (e.g., high levels of anxiety and depression), behavioural (e.g., sedentary behaviour, low physical activity levels), or social (e.g., social isolation)[12,13]. These impairments, limitations and restrictions together with the progression of the disease, lead to an increased dependence of the person with COPD on a caregiver (e.g., family member) in daily living, even during simple tasks such as showering or getting dressed[12,14].

This high burden of the disease for patients and families, requires strategies to address these traits and prevent a further decline of the disease.

Management of COPD

Due to the complexity of this disease, a treatable traits' approach, i.e., a comprehensive assessment to identify treatable traits followed by the activation of the most suitable interventions to address each trait, has been recommended[15-17]. Such interventions can include preventive measures to avoid the progression of the disease and hospitalisations, pharmacological and non-pharmacological treatments.

Preventive measures

Smoking cessation is one of the main priorities to prevent COPD or its decline[5]. It is an important approach, considering its influence on the progression of the disease and the high prevalence of active smokers with COPD (about 40%)[5,18]. Pharmacological treatment such as the prescription of varenicline, besides providing patient education and encouragement, is advised to aid smoking cessation[19].

Another important prevention measure is vaccination. The influenza vaccine has shown to reduce serious illness and death in people with COPD, as well as to diminish the number of acute exacerbations[20-22]. The pneumococcal vaccine has also been recommended due to its potential in reducing the incidence of community-acquired pneumonia[5]. Besides these standard vaccines, the United States Centres for Disease has also recommended Tdap vaccination for people with COPD who are 50 years old or older[23], and more recently due to the COVID-19 pandemic, the SARS-Cov-2 vaccination scheme[24].

Pharmacological treatment

One of the most important treatments for patients with COPD is pharmacological therapy. Common drugs delivered through inhalers are $beta_2$-agonists, either short (SABA) or long-acting (LABA) and/or short (SAMA) or long-acting (LAMA) anticholinergics[1,25]. Combinations of these are also commonly prescribed and other medication usually consist of inhaled corticosteroids, methylxanthines, phosphodiesterase-4 inhibitors and mucolytic agents[1].

Non-pharmacological treatment

Long-term oxygen therapy and non-invasive mechanical ventilations are additional therapies often prescribed for specific patients, namely during acute exacerbations, severe chronic resting hypoxemia or when there is an overlap of COPD with obstructive sleep apnoea (OSA)[26,27].

Surgical interventions (e.g., lung volume reduction surgery) might be needed for some patients, such as those with high hyperinflation due to extensive emphysema[1,28,29].

Similarly, palliative and end-of-life care should be considered for some patients, particularly those with persistent distressing dyspnoea, impaired exercise capacity, fatigue, anxiety and depression besides optimisation of other therapies[30,31].

Other strategies such as self-management programmes and pulmonary rehabilitation (PR) are more frequently proposed to people with COPD, as more patients benefit from them. Self-management programmes have been shown to be valuable has they are associated with an increase in health-related quality of life (HRQoL) and a lower probability of hospital admissions[32]. PR is a crucial intervention that should be more accessible due to its effectiveness in reducing the symptomatology and deconditioning and as it is one of the most cost-effective interventions[33]. Therefore, this intervention will now be discussed in more detail.

Pulmonary rehabilitation

PR defined as "*a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies, which include, but are not limited to, exercise training, education, and behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence of health-enhancing behaviours*", has become a cornerstone of the management of COPD[34].

Most PR programmes have a duration of eight to 12 weeks and occur two to three times a week, with a group of patients that receive at least exercise training and education delivered by a multidisciplinary team[35]. In terms of exercise prescription, resistance training usually consists of one to three sets of eight to twelve exercises at 70% of the weight in the 1 maximum repetition test (1RM); and endurance training usually consists of walking or cycling for 20-60 minutes at more than 60% of the maximal work rate[34]. Common topics of the education component include pulmonary anatomy and physiology, pathophysiology of chronic respiratory disease, communication with healthcare provider, interpretation of medical testing, breathing strategies, secretion clearance techniques, role and rationale for medications, use of respiratory devices, benefits of exercise and physical activity, energy conservation techniques, diet, avoidance of airway irritants, recognition and treatment of exacerbations, leisure activities and coping with chronic lung disease[34].

PR has consistently shown to be an effective intervention for people with COPD, as it improves dyspnoea, exercise tolerance and HRQoL[36-38]. However, only a minority of patients who meet the inclusion criteria, have access to PR[33]. Barriers to access and uptake PR such as poor awareness and knowledge of PR by healthcare professionals, location of programs, transport and cost of attendance, have been reported[33,39].

To overcome the inaccessibility of this highly effective intervention, new models of PR are emerging, such as home-based PR or telerehabilitation. Home-based and telerehabilitation have been shown to be equivalent to centre-based PR in terms of improving the exercise capacity, dyspnoea and HRQoL of people with COPD[37,40] and might therefore be offered more regularly in the future.

Although PR has undeniable benefits for people with COPD, there is a large proportion of patients that do not respond to the intervention, and most trials are not adequately addressing the patients' treatable traits[41-44]. The type of response (responder vs non-responder) varies with the outcomes and measures chosen for the

assessment of the effects of PR which could ultimately result in a patient being both a good and a poor responder[41].

Thus, it is essential to meticulously select the outcomes and measures used to assess the effects of PR. Outcome selection is dependent on various factors, such as patients' comorbidities, resources available and health professionals or researchers' views, which results in miscellaneous outcomes reported in the literature[35,45]. This lack of homogeneity is of most importance, as it can hamper comparisons of studies and the conduction of meta-analysis[46].

Additionally, there is a need to ensure that all PR programmes guarantee minimum quality for patients, and to benchmark PR. Some initiatives in the United States of America, United Kingdom and Switzerland have been established to improve the quality of programmes through accreditation schemes[47]. However, to date there is no worldwide recommendation regarding how programmes should demonstrate their effectiveness (e.g., in which outcomes) to meet high quality standards. To overcome this problem, a consensus in reporting outcomes of PR in patients with COPD has been advocated by international societies (European Respiratory Society and American Thoracic Society) and worldwide renowned researchers[47-51].

Core Outcome Set

A core outcome set (COS) is "*an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care*"[52,53] and is often "*suitable for use in other types of research and clinical audit*"[54]. A COS comprises a group of outcomes that should always be measured, however, it does not restrict researchers or healthcare professionals to explore other outcomes[46].

COS have the potential to improve evidence synthesis and minimize research waste by reducing the heterogeneity of measures and outcome reporting bias in trials

(reporting only convenient/positive outcomes), and to increase the statistical power in systematic reviews, as less studies are excluded from meta-analysis[46].

Furthermore, by integrating views of different stakeholders, COS result in trials with meaningful endpoints for service users[46,52].

Other initiatives such as the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) and the International Consortium for Health Outcomes Measurement (ICHOM) have successfully developed numerous COS[55]. In fact, the Core Outcome Measures in Effectiveness Trials (COMET) initiative has recognised a crescendo interest in developing COS with 61 COS developed in 2019[56]. This increase in COS development has also been accompanied by COS uptake in systematic reviews[57]. Nonetheless it is still necessary to increase COS uptake among trialists and systematic reviewers[53,57].

The development of a COS follows a robust methodology according to the COMET initiative recommendations - i) identify existing knowledge, ii) fill the gaps in knowledge if needed, iii) elicit views of different stakeholders about important outcomes, iv) hold a meeting to finalise the recommended COS and v) report the work using the guidelines[52,58]. This pathway refers to the definition of "what to measure", i.e., the core outcomes, but additional steps are encouraged to define "how to measure", i.e., core measures, once the first part is established[52,59].

Therefore, this thesis is presented in chapters, following the path recommended by the COMET initiative to define the core outcomes of PR for people with COPD.

Aim and outline of the thesis

This thesis aimed to define the core outcomes of PR for people with COPD and to expand the existing knowledge on treatable traits of people with COPD and response to PR.

The work developed throughout this thesis is presented in eight chapters. Following the COS methodology proposed by the COMET initiative[52], **Chapter 2** was developed to identify the existing knowledge, **Chapters 3 to 5** were developed to fill the gaps in the exiting knowledge of treatable traits and response to PR, **Chapter 6 and 7** were developed to elicit views of different stakeholders on the important outcomes, with **Chapter 7** also including a consensus meeting to finalise recommendations.

Chapters of the thesis are now briefly explained. **Chapter 1** consists of a general introduction with an overview of COPD, PR and COS, as well as a description of the aims and research questions of the thesis. This chapter is followed by **Chapter 2**, where a systematic review was conducted to gather all outcomes and measures reported in PR trials since the year 2000. This review was conducted to confirm the need of a COS for PR in people with COPD, as based on the literature, high heterogeneity of outcomes was expected.

Chapters 3 to **5** filled the gaps in the literature by exploring PR-relevant treatable traits with the aim of better enhancing our understanding of responses to PR and factors influencing them.

Chapter 3 investigated the possibility of defining the presence/absence of a functional impairment in people with COPD, through a simple office-based functional test (the one-minute sit-to-stand test [1-minute STS]). Although this trait was already possible to assess with field-based walking tests (e.g., six-minute walk test [6MWT]), these tests can be too time consuming for routine clinical practice, and therefore other tests such as the 1-minute STS could have the potential to be quick first screening tools.

Chapter 4, expanded on the topic of **Chapter 3**, by investigating the existence of responders and non-responders to PR in terms of functional status, and exploring if different and commonly used measures to assess functional status (6MWT and 1-min STS) classified the response similarly. These research questions

were thought to be useful to ascertain the best measure to assess functional exercise capacity in the future, if this outcome was to be included in the COS.

Given the multiple traits exhibited by people with COPD and their differential response to PR, **Chapter 5** focused on exploring whether the presence of treatable traits had an influence on being a responder or non-responder to PR. We hypothesized that determining this relationship could help to understand the potential of a treatable trait strategy withing PR (by selecting only the necessary PR components to target the treatable traits exhibited) and consequently establishing if there was a need to conduct treatable trait-based PR trials.

In **Chapter 6**, different stakeholders were invited to participate in an interview in order to investigate their perspectives on outcomes - which ones were more important and which ones should not be included in the COS – and measures of PR. Peoples' perspectives on outcomes and measures were thought to be important to understand in depth, as they could be useful for the design of the COS and strategies for its uptake, as well as to obtain advice for selecting measurement instruments in the future.

Chapter 7 presents the final consensus on the core outcomes of PR. This research consisted of a modified Delphi study, with 2 rounds of outcome scoring from a combined list of outcomes of **Chapter 2 and Chapter 7**, and a final consensus meeting where uncertain outcomes from the Delphi study were consensually included or excluded from the COS. This study was designed to provide a final COS that could be useful for benchmarking and conducting audits in PR and improve systematic reviews.

Lastly, **Chapter 8** provides a summary and general discussion of this thesis where the strengths and limitations of the findings are discussed considering the current knowledge.

An overview of the studies developed to answer each research question can be found in **Figure 1**.

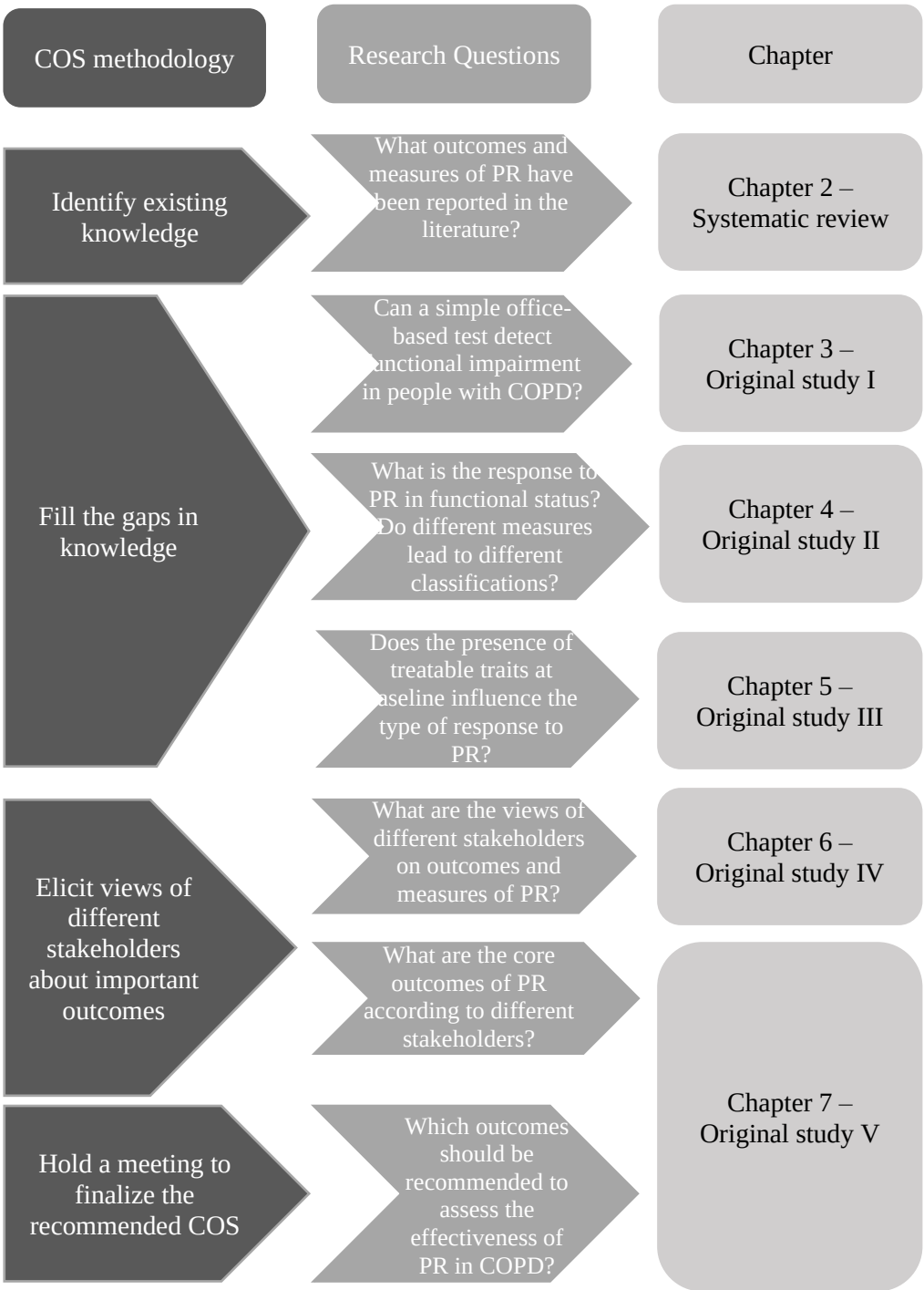

Figure 1. Flow chart representing the rationale and path of this thesis.

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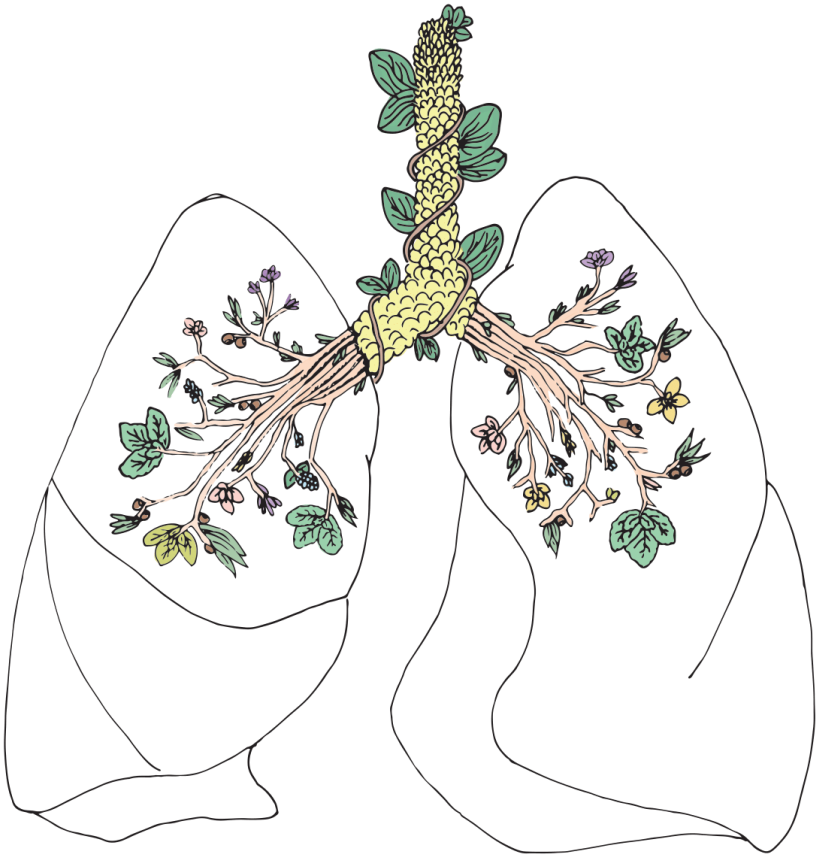

Chapter 2
Pulmonary rehabilitation outcomes in individuals with chronic obstructive pulmonary disease: a systematic review

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ABSTRACT

Background: The magnitude of response to pulmonary rehabilitation (PR) is influenced by the selection of outcomes and measures. This systematic review aimed to review all outcomes and measures used in clinical trials of PR for individuals with chronic obstructive pulmonary disease (COPD).

Methods: The review involved a search of Scopus, Web of Knowledge, Cochrane Library, EBSCO, Science Direct and PubMed databases for studies of stable individuals with COPD undergoing PR. Data were extracted into a standardized table. Frequency of reporting for each domain, outcome and measure was synthesized by using Microsoft Excel.

Results: We included 267 studies (43153 individuals with COPD). A broad range of domains (n=22), outcomes (n=163) and measures (n=217) were reported. Several measures were used for the same outcome. The most reported outcomes were exercise capacity (n=218) assessed with the 6-min walk test (n=140), health-related quality of life (n=204) assessed with the Saint George's respiratory questionnaire (n=99), and symptoms (n=158) assessed with the modified Medical Research Council dyspnea scale (n=56). The least reported outcomes were comorbidities, adverse events and knowledge.

Conclusions: This systematic review reinforces the need for a core outcome set for PR in individuals with COPD because of high heterogeneity in reported outcomes and measures. Future studies should assess the importance of each outcome for PR involving different stakeholders.

PROSPERO ID: CRD42017079935

Introduction

Pulmonary rehabilitation (PR) is a fundamental intervention for managing chronic obstructive pulmonary disease (COPD)[1] in individuals who remain symptomatic despite optimal medical therapy[1]. Indeed, it is more cost-effective than any pharmacological treatment[2]. Generally, it improves activity-related symptoms (e.g., dyspnoea and fatigue), exercise capacity and quality of life[3]. However, some individuals respond poorly to PR, and this is at least in part affected by the outcomes and measures used[4].

The selection of outcomes and measures depends on various factors, including the patient's or assessor's preference, the patient's comorbidities, and available resources (e.g., staff, infrastructures, equipment, budget)[5,6], which can lead to high heterogeneity of outcomes and measures reported in the literature. This heterogeneity limits bench-marking within and between PR centres[2], the production of effective evidence synthesis[7] and guidelines development. Nevertheless, the exact extent of this heterogeneity is unknown because no study has comprehensively and systematically reviewed all outcomes and measures used in peer-reviewed PR trials.

The current systematic review aimed to investigate all previously reported outcomes and measures used to assess the effectiveness/efficacy of PR in individuals with COPD. It constitutes the first step toward the development of a core outcome set (COS), or a minimum set of outcomes that should be consistently measured and reported[7], for PR of people with COPD.

Methods

This systematic review will be part of a COS for PR of individuals with COPD. The COS is registered in the Core Outcome Measures in Effectiveness Trial (COMET) initiative, available at http://www.comet-initiative.org/Studies/Details/1151. This systematic review is registered on the international prospective register of systematic reviews (PROSPERO;

CRD42017079935)
(https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017079935) and was reported according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines[8].

Search strategy

PROSPERO, Cochrane Library and PubMed databases were first searched to ensure that no similar systematic review was published or registered. Then the databases Scopus, Web of Knowledge, Cochrane Library, EBSCO, Science Direct and PubMed were comprehensively searched in September 2019 following the Population, Intervention, Comparators, Outcomes, Time, Setting (PICOTS) framework[9]. Monthly search alerts for new articles in each database were set up until November 2020 to guarantee the update of the systematic review until its submission for peer review. We included studies of individuals with stable COPD; with PR as an intervention, with at least exercise training and education; written in English, Portuguese, Spanish or French; and published from January 1, 2000 onward. The cut-off of the year 2000 was a pragmatic choice because it was believed that the last 20 years of literature would be representative of what has been assessed and how in this field. We excluded studies of participants who reported acute exacerbations of COPD (AECOPD) in the month before initiating PR; investigated clinimetric properties of measures with no pre-post data comparisons; and study protocols, qualitative studies, news, theses/dissertations, articles in conference proceedings, abstracts, letters to the editor, commentaries, reviews, books and chapters or unpublished work. We also excluded systematic reviews; however, they were hand-searched for potential articles to be included. The full search strategy can be found in **Appendix A**.

After retrieving all references from the search, duplicates were removed. The title, abstract and keywords for all references were screened by one author (SS-M), and another independent author (GR) screened a random sample of 10%. The full

texts of potential articles were then assessed by one author (SS-M). In cases of uncertainty, the decision to include/exclude was debated between the additional members of the team to reach consensus.

Data extraction

Two researchers (SS-M, GR) extracted the following data from the included studies into a pre-developed standardized table: author name, year and country; study design; characteristics of participants (sample size, sex, age, forced expiratory volume in 1 sec (FEV_1), severity of disease according to the GOLD criteria (1-4 and A-D), number of individuals with AECOPD before the intervention, body mass index (BMI), smoking status and pack-years, ethnicity, comorbidities, medication, individuals on long-term oxygen therapy and using non-invasive ventilation); characteristics of the PR programme (setting, duration of programme, duration of sessions; type, intensity and frequency of exercise; type and frequency of education; type, frequency and duration of unsupervised exercise; type of technology used when applicable; and health care professionals involved); baseline assessments; positive, negative and unchanged outcome domains; and outcomes with the outcome measures used.

Domains, outcomes and measures were identified from the methods, results and discussion sections of the included articles. For the purpose of this systematic review, a domain was defined as a high-level category that grouped outcomes with similar health meanings (e.g., the domain exercise capacity grouped outcomes such as walking distance and endurance time); an outcome consisted of any effect of PR that had been measured or described as a result of the intervention (e.g., walking distance); and a measure was the instrument used for assessing a specific outcome (e.g., 6-min walk test [6MWT]). Additionally, a positive outcome was defined as an outcome with a positive meaning and statistically significant result (e.g., a significant improvement in muscle strength), a negative outcome was defined as an outcome with

negative meaning and statistically significant result (e.g., a significant increase in pain), and an unchanged outcome was defined as an outcome that did not reach statistical significance.

Data analysis

IBM SPSS 25 was used to calculate inter-rater agreement of included studies by using Cohen's kappa, interpreted as <0, poor agreement; 0.00–0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61-0.80, substantial agreement and 0.81–1.00, almost perfect agreement[10]. Data from the full data set of included studies were pooled and synthesized by using Microsoft Excel to analyse the frequency of reported domains, outcomes and measures. Interactive tables with drop-down menus were used to aid visualization of each measure used for each outcome and domain.

Results

Study selection

From the initial 1870 records retrieved, a total of 267 reports of studies were included in the analysis; 5 were retrieved from search alerts. The PRISMA flowchart is presented in **Figure 1**.

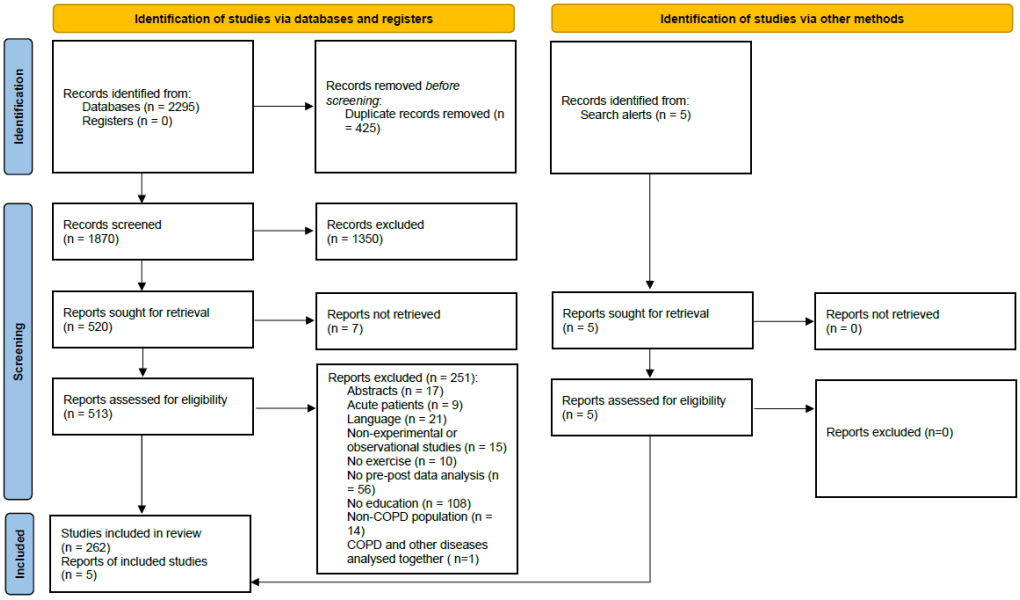

Figure 1. PRISMA 2020 flowchart of included studies.

The agreement for 10% of the abstracts (187 records) reviewed by the 2 independent researchers was almost perfect, with Cohen's kappa 0.866 (95% confidence interval [CI] 0.76–0.97).

Characteristics of included studies

Study design, population, and structure of pulmonary rehabilitation

Of the 267 included studies, 99 were observational studies[4,11-108], 87 were randomized controlled trials[109-195], 66 were quasi-experimental studies[105,196-260], 9 had experimental designs[51,261-268], 5 were pilot studies[269-273] and 1 was a mixed-methods study[274].

A total of 43153 individuals with COPD were included in the studies. Participants were mostly males (64%, reported in 247 studies), with a mean baseline age of 51 to 84 years (reported in 248 studies), mean baseline FEV_1 % predicted of 18 to 97 (reported in 218 studies) and mean baseline BMI of 15.9 to 35 kg/m^2 (reported in 177 studies) (see **Appendix B)**. In total, 72 studies reported individuals

on long-term oxygen therapy (25% of included individuals). Only 60 studies reported individuals' baseline comorbidities and 31 their regular medication (see **Appendix C** available at https://ars-els-cdn-com.mu.idm.oclc.org/content/image/1-s2.0-S1877065721000828-mmc4.xlsx).

Most PR programmes were implemented in an outpatient setting (n=146 studies, 55%), with a multidisciplinary team reported in less than half of the studies (n=116, 43%) (see **Appendix B** and **C**). The most frequently reported professionals were physiotherapists (n=128 studies), followed by nurses (n=92) and medical doctors (n=91) (see Appendix C). Most PR programmes lasted between 8 and 12 weeks (n=124 studies, 46%) and occurred mainly 2 to 3 times per week (n=150, 56%) (see Appendix B). Exercise sessions consisted mainly of combined aerobic and resistance training (n=200 studies, 75%) (see **Appendix B**). Additionally, 83 (31%) studies reported supplementary unsupervised exercise sessions.

The education component of PR was mainly delivered face-to-face (n=225, 84%) and occurred most frequently twice a week (n=52, 20%) or once a week (n=27, 10%) (see **Appendix B**).

In total, 115 (43%) studies reported add-ons to the intervention, mostly nutritional support (n=43), breathing exercises (n=33) and psychological support (n=32) (see **Appendix C**). The main characteristics of the included studies can be visualised in **Figure 2** and are presented in **Appendix B**, with the full dataset presented in **Appendix C**.

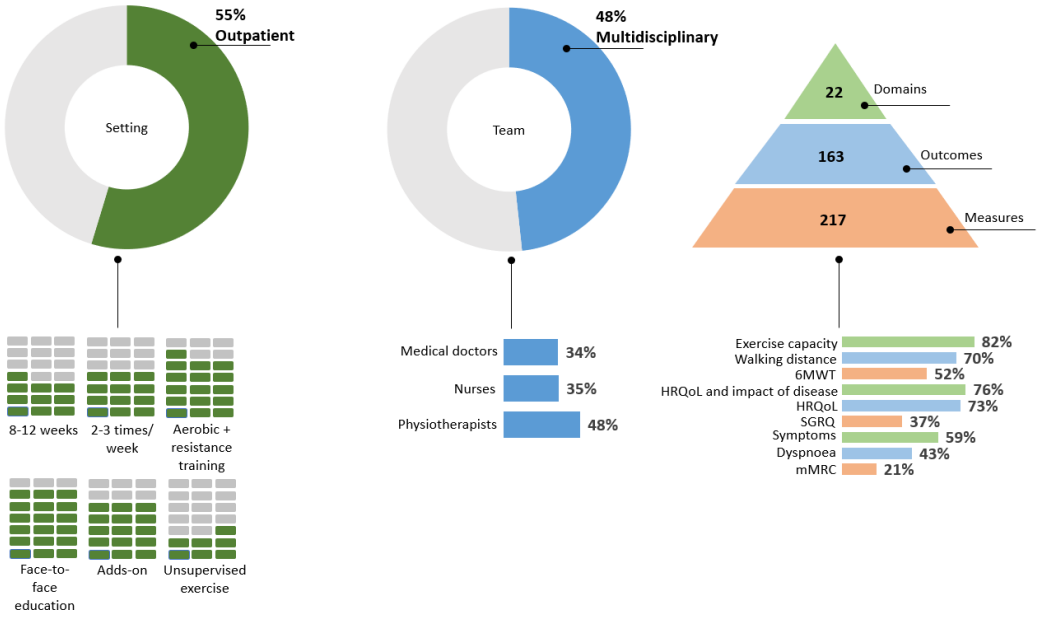

Figure 2. Main characteristics of pulmonary rehabilitation programmes and top 3 domains, outcomes and measures of the included studies (n = 267).

Domains, outcomes and measures of pulmonary rehabilitation

A total of 22 domains including 163 outcomes and 217 measures were reported. The 22 domains found were exercise capacity; health-related quality of life (HRQoL) and impact of the disease; symptoms; lung function; muscle structure and function; functional status; body composition; mental health and behaviour; vital signs; blood gases; physical activity; AECOPD and healthcare utilization; multiple domains; biochemical markers; nutritional status; well-being and social status; medication; mortality; sleep; knowledge; adverse events; and comorbidities. The top 3 most reported domains were exercise capacity, HRQoL and impact of the disease, and symptoms (). The least reported domains were comorbidities, adverse events and knowledge. Several measures were used to assess each outcome within the same domain. The **Table 1** reports the top 3 most reported outcomes and measures used for each domain. A full list of outcomes and measures is in **Appendix C**.

A total of 27 measures were used to assess 33 outcomes in exercise capacity, 26 to assess 3 outcomes in HRQoL and impact of the disease, 37 to assess 9 outcomes in symptoms, 4 to assess 16 outcomes in lung function, 20 to assess 11 outcomes in muscle structure and function, 35 to assess 7 outcomes in functional status, 3 to assess 8 outcomes in body composition, 23 to assess 12 outcomes in mental health and behaviour, 10 to assess 3 outcomes in vital signs, 2 to assess 5 outcomes in blood gases, 8 to assess 11 outcomes in physical activity, 11 to assess 2 outcomes in AECOPD and healthcare utilization, 1 to assess 1 outcome in multiple domains, 2 to assess 27 outcomes in biochemical markers, 7 to assess 2 outcomes in nutritional status, 4 to assess 2 outcomes in well-being and social status, 7 to assess 2 outcomes in medication, 2 to assess 1 outcome in mortality, 2 to assess 3 outcomes in sleep, 3 to assess 2 outcomes in knowledge, 2 to assess 1 outcome in adverse events and 1 to assess 1 outcome in comorbidities.

The following presents the most common measures used to assess each domain (see **Table 1** and **Appendix C**).

Table 1. Top 3 most frequently reported outcomes and measures for each domain across the included studies (n=267).

Outcome domain (number of studies)	**Outcome (number of studies)**	**Outcome measure (number of studies)**	**Studies**
Exercise capacity (n=218)	Walking distance (n=188)	6-min walk test (n=140)	4,13-17,19,21,23,24,27,33-40,42,45-48,53,54,58-60,62,64,65,67-71,73,81,82,86,89,93,94,96,101,103,104,106,109,111-113,115-117,119,123-125,127,130-134,136,138,140,142,144,146,147,150,152-155,161,162,166-169,172-175,177,182-185,193,195-198,200,202-204,208,211-214,216-219,222,223,225,229,231,233-235,238,240,242,243,245,248,251-253,255-257,259-262,264,265,267,272,273
		Incremental shuttle walk test (n=43)	15,23,25,26,28,40-44,52,63,78,80,84,87,88,99,100,114,129,135,143,148,149,151,159,170,174,176,190,205,215,220,221,226,228,237,239,244,247,266,270
		Endurance shuttle walk test (n=15)	25,28,40,122,128,129,148,149,151,156,188,190,191,204,270

	Endurance time (n=74)	Cardiopulmonary exercise testing (n=44)	15,25,32,33,46,66,72,85,90-92,94,102,111,113,115,116,120,127,135,137-139,145,146,152,154,155,157,187,195,199-201,206,208,210,212,217,221,232,250,253,263
		Endurance shuttle walk test (n=26)	25,28,40,43,84,122,128,129,135,141,148,149,151,156,158,174,176,188,190,191,204,205,209,244,258,270
		Constant load ergometry test (n=9)	4,15,18,24,66,150,152,224,225
	Workload (n=42)	Cardiopulmonary exercise testing (n=40)	15,25,32,33,46,66,85,90-94,102,111,115,116,127,135,137,146,154,155,157,169,185,195,199-201,203,206,208,210,214,217,232,249,250,253,263
		Constant load ergometry test (n=2)	24,225
		Interval cycling test (n=1)	66
Health-related quality of life and impact of the disease (n=204)	Health-related quality of life (n=195)	Saint George's respiratory questionnaire (n=99)	4,13-15,18,24,38,40,42,43,46,47,56-59,62,69,73,74,82-84,87,88,90-94,100-103,111,114-117,127,130,133-135,138,140,142,147,150,153-156,163,170,174,181,183-185,191-193,195-

		197,199-203,205,207,209,211,215,219,221,223,227,228,231,236,239,243-245,247,249,250,253,258,261,262,267,268,270,273,274
	Chronic respiratory disease questionnaire (n=81)	16,17,21,23,26,28,35-37,40,43,45,52,54,63,72,78,80,81,87,88,97,99,100,113,114,120-122,125,128,130-132,138,141,143,145,146,148,149,152,158-160,164-167,170-173,175-177,179,182,186-190,194,198,204,209,212,214,217,221,226,237,238,247,259,271,272,275
	Medical Outcomes Study 36-item Short Form (n=30)	22,27,38,60,65,68,81,83,86,103,113,119,120,130,140,152,153,158,159,166,171,207,210,225,226,248,253,255,256
Impact of the disease (n=27)	COPD assessment test (n=25)	23,24,28,34,40,48,56,57,59,73,79,87,88,95,96,112,147,195,222,247,256,262,264,266
	Visual analog scale (n=2)	249,250
Health status (n=2)	Visual analog scale (n=1)	32
	Feeling thermometer (n=1)	146

Symptoms (n=158)	Dyspnoea (n=115)	Modified Medical Research Council dyspnoea questionnaire (n=56)	4,13,19,22,23,33,35,38,40,42-44,46,48,59,62,73,87,96,103,112,116,127,130,132,136,140,144,150,156,174,175,177,179,195,197,203,205,207,211,215,227,228,231,244,247,248,253,256,259,262,264,267,269,272,273
		Modified Borg dyspnoea scale (n=46)	38,42,43,48,63,65,66,68,72,81,90-92,102,115,117,120,133,135,139,142,145,152,157,165,174,184,192,193,199-201,204,205,209,214,217,224,225,232,245,253,259,265,269,276
		Baseline/Transitional dyspnoea index (n=15)	15,46,68,70,71,115,147,152,187,222,225,248,253,261,264
	Anxiety (n=67)	Hospital Anxiety and Depression scale (n=56)	4,14,18,20,21,23,24,28-30,38,40,43,49,51,52,59,62,68,73,77,78,80,82,84,95,101,103,127,128,130,132,136,142,146,150,159,163-165,174,175,188,196,202,204,205,209,223,234,236,237,244,253,262,266
		Spielberg state-trait anxiety inventory (n=5)	96,105,207,235,264

		21-item depression, anxiety and stress scale (n=2)	51,228
	Depression (n=66)	Hospital Anxiety and Depression scale (n=55)	4,14,18,20,21,23,24,28-30,38,40,43,49,51,52,59,62,68,73,77,78,80,82,84,95,101,103,127,128,132,136,141,142,146,150,159,163-165,174,175,188,196,202,204,205,209,223,234,237,244,253,262,266
		Patient health questionnaire-9 (n=4)	58,255,256,262
		Beck depression inventory (n=3)	12,96,123
Lung function (n=70)	Forced expiratory volume in 1 sec (n=65)	Spirometry (n=47)	15,19,22,33,42,48,59,64,65,67,69,81,86,90-92,102,106,127,130-133,135,147,164,166,182-184,194,199,204,207,210,214,215,224,225,243,251,253,259,261,264,267,276
		Plethysmography (n=15)	38,64,69,86,102,103,147,167,197,202,203,235,250,257,276
	Forced vital capacity (n=28)	Spirometry (n=23)	15,42,65,81,90-92,102,106,127,132,133,164,166,173,184,194,199,210,251,253,264,267
		Plethysmography (n=1)	102

	Forced expiratory volume in 1 sec/forced vital capacity (n=24)	Spirometry (n=18)	15,59,64,69,81,90-92,106,127,132,133,194,199,210,215,253,261,264
		Plethysmography (n=4)	38,64,103,202
Muscle structure and function (n=54)	Peripheral muscle strength (n=37)	Hand-held dynamometry (n=19)	15,32,47,67,97,102,135,140,151,153,155,168,202,208,215,223,248,253,269
		Number of arm lifts (n=8)	21,36,54,66,72,127,172,187
		Isokinetic (n=4)	135,150,154,263
	Inspiratory muscle strength (n=27)	Maximum inspiratory mouth pressure (n=26)	13,15,32,42,64,69,81,90-92,127,132,133,135,140,147,154,155,164,172,177,193,199,202,253,272
		Length of time to withstand 70% maximal inspiratory pressure (n=1)	172
		Plethysmography (n=1)	47
	Expiratory muscle strength (n=19)	Maximum expiratory mouth pressure (n=18)	13,15,64,69,81,90-92,127,132,133,140,164,177,193,199,202,257
		Plethysmography (n=1)	47
Functional status (n=45)	Functional performance (n=22)	4-m gait speed (n=7)	26,87,88,97,100,108,113
		5 times sit-to-stand test (n=6)	88,100,108,167,168,239
		Timed up and go (n=5)	29,30,109,211,234

	Activities of daily living (n=19)	London chest activity of daily living scale (n=7)	47,132,164,188,209,246,269
		Canadian occupational performance measure (n=3)	4,148,150
		Barthel index (n=1)	112
	Balance (n=3)	Berg balance scale (n=2)	17,76
		Balance evaluation systems test (n=1)	76
		Force platform (n=1)	168
Body composition (n=32)	Body mass index (n=22)	Body mass index formula (n=22)	19,33,42,59,62,67,81,84,96,108,136,150,151,154,155,169,174,177,189,205,264,267
	Fat free mass index (n=10)	Bioimpedance (n=10)	59,67,84,132,150,154,155,169,174,205
	Weight (n=9)	Scale (n=9)	31,32,69,92,131,135,140,151,263
Mental health and behaviour (n=24)	Self-efficacy (n=10)	Pulmonary rehabilitation adapted index of self-efficacy (n=4)	141,175,180,189
		COPD self-efficacy scale (n=3)	47,184,213
		Coping self-efficacy scale (n=1)	178
	Coping styles (n=4)	Utrecht coping list (n=2)	61,62
		Coping Inventory for Stressful Situations (n=1)	98
		Brief religious coping scale (n=1)	262

	Behaviour (n=2)	Pulmonary Rehabilitation Behaviour Questionnaire (n=1)	260
		Smoking, nutrition, alcohol, physical activity (SNAPPS) score (n=1)	118
Vital signs (n=24)	Heart rate (n=22)	Cardiopulmonary exercise testing – not specified (n=14)	66,85,90,92,94,102,111,137,139,145,152,199,206,208
		Constant load ergometry test – not specified (n=4)	18,66,152,224
		Sphygmomanometer (n=1)	26
	Respiratory rate (n=8)	Cardiopulmonary exercise testing – not specified (n=8)	94,102,137,139,145,152,208,232
		Constant load ergometry test – not specified (n=1)	152
	Blood pressure (n=6)	Sphygmomanometer (n=3)	26,145,163
		Cardiopulmonary exercise testing – not specified (n=3)	90,140,199
Blood gases (n=22)	Peripheral oxygen saturation (n=14)	Oximetry (n=14)	38,59,64,65,90,92,103,131,142,184,199,204,209,214
	Partial pressure of carbon dioxide (n=13)	Gasimetry (n=13)	15,33,38,64,86,90,103,139,145,164,193,199,261

	Partial pressure of oxygen (n=11)	Gasimetry (n=11)	15,33,38,64,86,103,139,145,164,193,261
Physical activity (n=21)	Number of steps (n=9)	Accelerometer (n=4)	42,175,215,222
		Pedometer (n=3)	35,129,156
	General physical activity (n=7)	Voorips questionnaire (n=2)	185,249
		Physical activity scale for the elderly (n=2)	16,112
		Modified Baecke physical activity questionnaire (n=1)	156
	Energy expenditure (n=6)	Accelerometer (n=5)	42,175,179,215,222
		Diary (n=1)	160
Acute exacerbations and healthcare utilization (n=17)	Healthcare utilization (n=14)	Number of hospitalizations (n=10)	46,51,55,107,136,138,198,230,241,254
		Length of stay during hospitalizations (n=10)	11,55,74,107,117,185,198,230,241,254
		Emergency visits (n=8)	11,51,55,74,107,136,241,254
	Acute exacerbations (n=6)	Number of acute exacerbations (n=6)	27,46,55,58,138,229
Multiple domains (n=13)	Multidimensional score (n=13)	Body mass index, airflow obstruction, dyspnoea and exercise index (n=13)	13,19,33,46,116,124,136,167,171,177,231,259,267
Biochemical markers (n=7)	Albumin (n=3)	Blood analysis (n=3)	31,32,169
	Serum proteins (n=2)	Blood analysis (n=2)	32,169
	Norepinephrine (n=2)	Blood analysis (n=2)	139,140
Nutritional status (n=4)	Nutrients intake (n=4)	Dietary intake (n=4)	31,32,140,151

		Protein intake (n=2)	32,151
		Carbohydrate intake (n=2)	32,151
	Energy expenditure (n=1)	Calorimetry system (n=1)	31
Well-being and social status (n=4)	Well-being (n=3)	Medical psychological questionnaire for chronic lung patients (n=1)	32
		Quality of well-being scale (n=1)	83
		Psychological General Well-being index (n=1)	192
	Loneliness (n=1)	De Jong Gierveld Loneliness Scale (n=1)	255
Medication (n=3)	Medication (n=2)	Use of short-acting bronchodilator (n=1)	11
		Medication for COPD (n=1)	107
		Use of antibiotics (n=1)	11
	Oxygen utilization (n=1)	Flow (n=1)	133
Mortality (n=3)	Mortality (n=3)	Number of deaths (n=2)	136,138
		Number of deaths in follow-up (n=1)	241
Sleep (n=3)	Sleep quality (n=2)	Pittsburgh sleep quality index (n=2)	91,266
	Sleep efficiency (n=1)	Accelerometer (n=1)	42
	Sleep duration (n=1)	Accelerometer (n=1)	42
Knowledge (n=2)	Patients' knowledge (n=2)	Bristol COPD knowledge questionnaire (n=1)	95
		Patient activation measure (n=1)	73

	Information needs (n=1)	Lung information needs questionnaire (n=1)	73
Adverse events (n=1)	Adverse events (n=1)	Number of adverse events (n=1)	138
		Cardiovascular events (n=1)	138
Comorbidities (n=1)	Arterial stiffness (n=1)	Tonometry (n=1)	216

COPD, chronic obstructive pulmonary disease

Exercise capacity was the most reported domain (n=218 studies), with the 6MWT the most frequently used measure (n=140).

HRQoL and impact of the disease was also largely reported (n=204), mostly by use of the Saint George's respiratory questionnaire (SGRQ) (n=99).

Symptoms was the third most reported domain (n=158), the most frequently used measure being the modified Medical Research Council dyspnoea scale (mMRC) to assess dyspnoea (n=56).

Lung function was reported in 70 studies, measured mostly by spirometry (n=47).

Muscle structure and function (n=54) was mostly measured with a hand-held dynamometer (n=19) for peripheral muscle strength and maximum inspiratory mouth pressure (n=26) for respiratory muscle strength.

Functional status was reported in 45 studies, using several measures, such as 4-m gait speed (n=7) or the London chest activity of daily living scale (n=7).

Body composition (n=32) was mostly measured by the BMI (n=22).

Mental health and behaviour were reported in 24 studies, with diverse measurements, the most frequently used measure being the pulmonary rehabilitation adapted index of self-efficacy (n=4).

Vital signs (n=24), specifically heart rate, were also reported and were mostly measured during cardiopulmonary exercise testing (n=14).

Blood gases were reported in 22 studies, which mostly used oximetry for peripheral oxygen saturation (n=14).

Physical activity (n=21) was assessed with several measures such as accelerometery (n=4) and the physical activity scale for the elderly (n=2).

Seventeen studies also reported AECOPD and healthcare utilization and mostly measured the number of hospitalizations (n=10) or the hospital length of stay (n=10).

Multidimensional outcomes were reported in 13 studies, using the BMI, airflow obstruction, dyspnoea and exercise (BODE) index.

Several biochemical markers were also reported (n=7), mostly with blood analysis (n=6).

Nutritional status was reported in 4 studies, mostly by measuring dietary intake (n=4).

Well-being and social status were reported in 4 studies, which used different measures such as the medical psychological questionnaire for chronic lung patients (n=1), the quality of well-being scale (n=1), the psychological general well-being index (n=1), and the De Jong Gierveld loneliness scale for social status (n=1).

Medication was reported in 3 studies, measuring the use of medication for COPD (n=1), use of short-acting bronchodilators (n=1), use of antibiotics (n=1) or oxygen flow (n=1).

Mortality was reported in 3 studies, mostly measuring the number of deaths after PR (n=2).

Sleep was only reported in 3 studies[42,91,266], mostly with the Pittsburgh sleep quality index (n=2).

Patients' knowledge, measured with the Bristol COPD knowledge questionnaire (n=1), or the patient activation measure (n=1) was reported in 2 studies.

Adverse events were reported in 1 study, measuring the number of adverse events and cardiovascular events.

Lastly, comorbidities were reported by only 1 study, measuring arterial stiffness by tonometry.

Among all outcomes found, 115 using 170 measures were positive, 8 using 11 measures were negative and 121 using 125 measures were unchanged.

The most reported positive outcomes were exercise capacity (n=214) measured with the 6MWT (n=138), HRQoL (n=181) with the SGRQ (n=84) and symptoms (n=96) with the mMRC (n=41). The most reported negative outcomes were

subdomains of HRQoL (n=4) measured with the Medical Outcomes Study 36- or 12-item Short Form (n=2), number of acute exacerbations 1 year after PR (n=2), and lung function with FEV_1 or forced vital capacity (n=2). The most reported outcomes that did not change with PR were exercise capacity measured with cardiopulmonary exercise testing (n=174), symptoms (n=57) measured with the Hospital Anxiety and Depression Scale (n=22) or the modified Borg scale (mBorg) (n=18), and lung function (n=56).

The full list of positive, negative and unchanged outcomes with respective measures is in **Appendix C**.

Discussion

This systematic review identified domains, outcomes and measures that were used to assess the effectiveness/efficacy of PR in individuals with COPD in the last 20 years. We found an extensive list of domains, outcomes and measures (22, 163 and 217, respectively) and widespread measures used to assess the same outcome/domain. The existence of such dispersed measurements is of most importance because it can hinder comparisons across studies and the conduct of meta-analysis[7], which reinforces the need for a COS in this field.

Exercise capacity with the 6MWT, HRQoL with the SGRQ, symptoms with the mMRC, lung function with spirometry and muscle structure, and function with a hand-held dynamometer were the 5 most reported domains and measures of PR. However, careful interpretation of this result is recommended because domains and measures being frequently reported does not necessarily imply their adequacy for PR. PR benefits exercise capacity, HRQoL, symptoms and muscle structure and function of individuals[3,277-279], but it does not aim to improve lung function[1]. In fact, lung function has been found not to infer responsiveness of PR and is not expected to change with this intervention when pharmacological treatment has been optimized before the PR programme[280,281]. Similar to lung function, arterial blood gases,

medication and comorbidities are likely important domains to characterise individuals' baseline clinical status but not relevant outcomes of PR.

Clinicians and researchers are encouraged to continue to use exercise capacity, HRQoL, and muscle structure and function domains with the respective identified measures (i.e., 6MWT, SGRQ and hand-held dynamometry) because of the good psychometric properties demonstrated[223,282-284]. The Chronic Respiratory Disease Questionnaire has also been widely reported (n=70 studies vs SGRQ, n=84) and has similar psychometric properties to the SGRQ[283,285], so choosing between these measures to assess HRQoL seems appropriate for now. The COPD Assessment Test was less reported (n=25 studies), but its use is expected to increase because it was only developed in 2009 and has good psychometric properties with the advantage of being easy and quick to apply[59,286].

However, the symptoms domain might need further reflection. The mMRC is commonly used to stratify individuals[287], but the baseline/transitional dyspnoea index has shown better psychometric properties[288]. Moreover, researchers and clinicians keep measuring the usual suspects within the symptoms' domain (e.g., dyspnoea, anxiety and depression), whereas other underexplored symptoms, which greatly affect individuals' daily living, such as fatigue and pain, might be relevant outcomes to consider[5,67,289,290].

Furthermore, the selection of specific outcomes and measures (e.g., respiratory muscle strength and maximum respiratory mouth pressures), might be of interest only when there is a recognized deficit at baseline that is followed by an additional targeted intervention (e.g., inspiratory muscle training)[291]. The same is true for symptoms of anxiety and depression, which only show improvements when baseline scores indicate the presence of high levels of these symptoms[77].

Some of the less reported domains, such as functional status and knowledge, have been cited as important by individuals with COPD, informal caregivers and health professionals[5], which suggests that further investigation related to the

effectiveness of PR in these domains might be necessary. In these less reported domains, we found use of a variety of measures (e.g., 32 measures identified for functional status), which hinders the comparison of results across studies and a summary of the evidence. Thus, the establishment and/or comparison of the psychometric properties of these measures is necessary to recommend one that should be used.

The heterogeneity of outcomes and measures found highlights the need for a COS because defining "what to measure" and "how to measure" in a set, validated by different stakeholders, will improve consistency in trials, lessen the risk of outcome reporting bias, and provide recommendations for clinical practice.

Although this study was the first step toward a COS for PR in individuals with COPD, it is already valuable for both researchers and clinicians because they can choose to use the most frequently reported outcomes and measures to compare novel interventions against the current evidence. Future patient and public involvement is now necessary to ascertain the most relevant outcomes. Providers tend to measure what they control and to use outcomes easy to measure, so patient-relevant outcomes are often not taken into account[292]. Indeed, to move toward value-based healthcare, outcomes that have high value for individuals with COPD and that are rigorously measured should be in the main agenda of healthcare delivery[292]. Hence, engaging individuals with COPD in the decision-making process of selecting outcomes and measures is fundamental to assure high-quality care in all settings including those with low resources.

Finally, when choosing what to measure in PR, clinicians and researchers should take into account not only what is most frequently measured but also each person's treatable traits (i.e., traits that are treatable and recognized based on phenotypes)[293,294]. After identifying the patient's treatable traits (e.g., cachexia) based on the several domains, PR can be adapted to include targeted interventions (e.g., exercise training combined with nutritional modulation) and appropriate outcomes

(e.g., body composition) and measures (e.g., bioelectrical impedance) selected to (re)assess the affected domain.

This study has some limitations. The search was restricted to studies from 2000 onward and indexed databases, which might have resulted in missing outcomes. Nonetheless, because we included a large number of studies reporting on similar outcomes/measures, we believe we minimized this limitation. Additionally, outcomes were defined as positive, negative or unchanged based on only the p-values of the included studies. A more meaningful approach using the minimal clinical important difference could have been used. However, because not all measures have their minimal important differences calculated, this approach would hinder the allocation of numerous outcomes to the positive, negative or unchanged categories, which might be a useful classification for future studies aiming to explore the effectiveness of PR.

Conclusions

This study reinforces the need for a COS for PR in individuals with COPD because of high heterogeneity in reported outcomes and measures in studies. Future studies should assess the importance of each outcome for PR involving different stakeholders.

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Supplementary material

Appendix A. Search strategy

Questions

I. What outcomes have been reported as effects of pulmonary rehabilitation in patients with COPD?
II. What outcome measures have been reported to assess outcomes of pulmonary rehabilitation in patients with COPD?

Search strategy
PICOTS (Population, Intervention, Comparison, Outcome, Time frame, Setting) framework:

P= COPD, chronic obstructive pulmonary disease, COAD, Chronic Airflow Obstruction, Chronic Obstructive Airway Disease, Chronic Obstructive Lung Disease, emphysema, chronic bronchitis.

I= pulmonary rehabilitation, respiratory rehabilitation, respiratory physiotherapy, respiratory physical therapy, exercise, exercise training

C= Not applicable

O= symptoms, exercise tolerance, physical fitness, functional capacity, muscle strength, flexibility, balance, physical activity, body composition, number of exacerbations, ADL, knowledge, functioning, health literacy, emergency admissions, hospital length of stay, medication, smoking habits, health-related quality of life, mental health, social dysfunction, self-efficacy, survival

T= Studies from 2000 onwards

S= Ambulatory patients, inpatients, outpatients, community patients, primary care, hospital, home, domiciliary

Databases
Scopus, Web of Knowledge, Cochrane, EBSCO, Science Direct, PubMed

Typical Search

("COPD" OR "chronic obstructive pulmonary disease" OR "COAD" OR "chronic airflow obstruction" OR "chronic obstructive airway disease" OR "chronic obstructive lung disease" OR "emphysema" OR "chronic bronchitis") *AND* ("pulmonary rehabilitation" OR "respiratory rehabilitation" OR "respiratory physiotherapy" OR "respiratory physical therapy" OR "exercise" OR "exercise training") *AND* ("ambulatory" OR "inpatients" OR "outpatients" OR "community" OR "primary care" OR "hospital" OR "home" OR "domiciliary").

Inclusion criteria

- Studies involving patients with stable (i.e., optimal respiratory medications with no exacerbation or hospital admission within the previous month) at start and end of a pulmonary rehabilitation programme; COPD in any grade of severity according to GOLD criteria (I-IV and A-D);
- Involving a structured pulmonary rehabilitation program with the minimum components: education and exercise training;
- Experimental designs and observational studies;
- Studies written in English, Portuguese, Spanish or French;

Exclusion criteria

- Qualitative studies
- Studies exploring clinimetric properties without pre-post data
- News, research protocols, theses, dissertations, abstracts, letters to the editor and unpublished work.

Appendix B. Main characteristics of included studies of pulmonary rehabilitation (PR) (n=267).

Studies	Patient characteristics	Setting of PR	Duration of PR (weeks)	Type of exercise	Frequency of exercise sessions	Type of education	Frequency of education sessions	Additional interventions	Type of unsupervised exercise	Frequency of unsupervised exercise
Akinci & Olgun (2011), Turkey[261]	N=32 Sex NR 71.8 (7.8) years old FEV1pp=36.1 (10.8) BMI (kg/m2) NR	Home-based	12	Aerobic	7 times per week	Face-to-face and booklet	2-3 times per week	NR	aerobic and resistance and breathing exercises and bronchial hygiene	Everyday
Al Moamary (2010), Saudi Arabia[11]	N=50 54% males 66 (11.9) years old FEV1pp=49.4 (20.2) BMI (kg/m2) 28 (7.6)	Outpatient	8-12	Aerobic	2-3 times per week	Face-to-face	NR	NR	NR	NR
Alexander & Benton (2008), USA[109]	N=20 40% males 68 (1.9) years old FEV1pp 35.9 (3.7)	Outpatient	8	Aerobic and resistance	2 times per week	NR	NR	NR	NR	NR

	BMI (kg/m2) 26.6 (1.8)									
Alexander et al. (2008), USA[110]	N=20 70% males 69 (9) years old FEV1pp=58.7 (18) BMI (kg/m2) 26.6 (5.3)	Outpatient	8-10	Aerobic and resistance	2 times per week	NR	NR	NR	NR	NR
Alsaaireh & Aloush (2017), USA[12]	N=105 Sex NR 73 (9) years old FEV1pp NR BMI (kg/m2) 22 (7)	Outpatient	NR	Aerobic and resistance	1 time per week	NR	NR	NR	NR	NR
Ambrosino et al. (2015), Italy[13]	N=364 76% males 70.1 (7.9) years old FEV1pp=47.5 (18) BMI (kg/m2) 26.5 (5.4)	Inpatient	8-10	Aerobic and resistance	NR	NR	NR	NR	NR	NR
Andrews et al.	N=363 49% males	Community	6, 7 and 8	Aerobic and	2 times per week	Face-to-face	NR	NR	NR	NR

(2015), UK[14]	71 (9.7) years old FEV1pp NR BMI (kg/m2) NR			resistance						
Arizono et al. (2017), Japan[15]	N=27 96% males 69.3 (6.7) years old FEV1pp=43 (15.6) BMI (kg/m2) NR	Outpatient	10	Aerobic and resistance	2 times per week	NR	NR	IMT	NR	NR
Baumann et al. (2012), Germany [111]	N=37 62% males 63 (11 years old FEV1pp=47 (13) BMI (kg/m2) 24 (5)	Outpatient	26	Aerobic and resistance	1 time per week	Face-to-face	Not specified (14h)	NR	Aerobic and resistance and breathing exercises and bronchial hygiene	Yes
Beauchamp et al. (2013), Canada[16]	N=29 34% males 66.8 (7.8 years old FEV1pp=45.1 (18.8)	Community	48	Aerobic and resistance	2 times per week	NR	NR	NR	NR	NR

	BMI (kg/m2) 27.1 (8.9)									
Beauchamp et al. (2010), Canada[17]	N=29 59% males 69.8 (10.3 years old FEV1pp=46.3 (22.3) BMI (kg/m2) 29.2 (7.8)	Inpatient	6	Aerobic and resistance	4-5 times per week	Face-to-face	2 times per week	NR	NR	NR
Beaumont et al. (2018), France[269]	N=6 50% males Age NR FEV1pp NR BMI (kg/m2) NR	Inpatient	4	Aerobic and resistance	5 times per week	Face-to-face	NR	IMT and relaxation tecnhiques	aerobic	2 times per week
Bellocq et al. (2019), France[18]	N=29 31% males Age NR FEV1pp NR BMI (kg/m2) NR	Outpatient	10	Aerobic and resistance	2-3 times per week	Face-to-face	NR	Breathing exercises and bronchial hygiene	Physical activity (not specified)	NR
Córdoba and Wilches-	N=24 58% males	Outpatient	8	Aerobic and resistanc	2-5 times per week	Face-to-face	1 time per week	Psychological and	NR	NR

Luna (2018), Colombia[19]	71.7 (10.4) years old FEV1pp=47 (15.9) BMI (kg/m2) 22 (3.6)			e and balance				occupational therapy		
Bentsen et al. (2012), Norway[20]	N=66 50% males 66.2 (8.2) years old FEV1pp=46 (15) BMI (kg/m2) NR	Outpatient	6	Aerobic and resistance	2-3 times per week	Face-to-face	3 times per week	NR	Physical activity (not specified)	NS
Bernocchi et al. (2017), Italy[112]	N=56 88% males 71 (9) years old FEV1pp=66.6 (18.6) BMI (kg/m2) 28.5 (5.8)	Home-based	16	Aerobic and resistance	3 times per week	Phone call	1 time per week	NR	aerobic	3-7 times per week
Berry et al. (2010), USA[113]	N=89 54% males 66 (10) years old FEV1pp=53 (18.5)	Outpatient	12	Aerobic and resistance	3 times per week	Face-to-face	2 times per month	NR	NR	NR

	BMI (kg/m2) NR									
Bestall et al. (2003), UK[114]	N=29 Sex NR 68.2 (8.4) years old FEV1pp=37 (11) BMI (kg/m2) NR	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	NR	NR	NR
Bhandari et al. (2013), USA[21]	N=366 53% males 69 (9) years old FEV1pp=46 (17) BMI (kg/m2) NR	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face	NR	NR	NR	NR
Bianchi et al. (2002), Italy[115]	N=33 100% males 64.5 (NR) years old FEV1pp=47.7 (18.7) BMI (kg/m2) 22.8 (13.9)	Outpatient	6	Aerobic and resistance	3 times per week	Face-to-face	NR	NR	NR	NR
Bjornshave et al. (213),	N=148 46% males	Inpatient and Outpatient	8	Aerobic and	2 times per week	Face-to-face	NR	NR	NR	NR

Denmark [22]	68 (NR) years old FEV1pp=37 (NR) BMI (kg/m2) 24 (NR)			resistance						
Bonnevie (2018), France[116]	N=51 86% males 59.2 (9.6) years old FEV1pp=35 (NR) BMI (kg/m2) 23.5 (NR)	Outpatient and Home-based	8	Aerobic and resistance	3-5 times per week	Face-to-face	NR	NMES	NMES	5 times per week
Boutou et al. (2014), UK[1]	N=787 57% males 68.9 (10.2) years old FEV1pp=51.9 (20.7) BMI (kg/m2) 27.1 (6.4)	Outpatient	8-12	Aerobic and resistance	2 times per week	NR	NR	NR	Aerobic and resistance	1-3 times a week
Boxall et al. (2005), Australia [117]	N=23 48% males 77.6 (7.6) years old FEV1pp=40.5 (15.9)	Home-based	12	Aerobic and resistance	NR	Face-to-face	1 every 2 weeks	NR	Aerobic and resistance	NR

	BMI (kg/m2) NR									
Braeken et al. (2017), The Netherlands[24]	N=518 55% males 64.3 (8.8) years old FEV1pp=48.9 (20) BMI (kg/m2) 26.2 (5.7)	Inpatient and Outpatient	8-16	Aerobic and resistance	3-5 times per week	NR	NR	Supervised 30 min walk	NR	NR
Bratas et al. (2010), Norway[196]	N=161 49% males 65 (9.1) years old FEV1pp NR BMI (kg/m2) NR	Inpatient	4	Aerobic and resistance	5 times per week	Face-to-face	NR	Water gymnastics and walking and cycling and relaxation techniques	NR	NR
Burkow et al. (2015), Norway[274]	N=10 50% males Age NR FEV1pp= 403 (24.48) BMI (kg/m2) NR	Home-based	9	Aerobic and resistance	2 times per week	Online lectures	1 time per week	NR	All exercise was unsupervised	All exercise was unsupervised
Calvert et al.	N=35 72% males	Outpatient	7	Aerobic and	2 times per week	Face-to-face	NR	NR	Aerobic	Everyday

(2011), UK[25]	67 (8) years old FEV1pp=47 (18) BMI (kg/m2) 28 (6)			resistance						
Cameron-Tucker et al. (2016), Australia[118]	N=35 46% males 68 (9.9) years old FEV1pp NR BMI (kg/m2) NR	Home-based	8	Aerobic and resistance	1 time per week	NR	1 time per week	NR	All exercise was unsupervised	All exercise was unsupervised
Cameron-Tucker et al. (2014), Australia[119]	N=43 53% males 64.5 (9.13) years old FEV1pp NR BMI (kg/m2) 28.4 (7.6)	Inpatient and Outpatient	6	Aerobic and resistance	1 time per week	Face-to-face	1 time per week	NR	NR	NR
Canavan et al. (2015), UK[26]	N=507 57% males Age NR FEV1pp=47 (20) BMI (kg/m2) NR	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	NR	NR	NR

Carone et al. (2007), Italy[197]	N=1130 82% males 69.3 (8.4) years old FEV1pp=43 (15.1) BMI (kg/m2) 26.9 (11.2)	Inpatient	4	Aerobic and resistance	7 times per week	Face-to-face	NR	Breathing exercises and bronchial hygiene	NR	NR
Carrieri-Kohlman et al. (2005), USA[120]	N=103 42% males 67 (0.8) years old FEV1pp=46.9 (1.6) BMI (kg/m2) NR	NR	8	Aerobic	3 times per week	Face-to-face	NR	NR	NR	NR
Casey et al. (2013), Ireland[121]	N=178 66% males 68.8 (10.2) years old FEV1pp=57.6 (14.3) BMI (kg/m2) NR	Community	8	Aerobic and resistance	2 times per week	Face-to-face	1 time per week	NR	Aerobic and resistance	1 time per week
Cecins et al. (2008),	N=250 35% males	NR	8	Aerobic and	2 times per week	Face-to-face	2 times per week	NR	NR	2-3 times per week

Australia [198]	67.5 (8.4) years old FEV1pp=41.4 (19.3) BMI (kg/m2) 25 (5.6)			resistance						
Chalise et al. (2016), USA[27]	N=112 55% males 68 (9.4) years old FEV1pp=41.3 (17.1) BMI (kg/m2) NR	Outpatient	12	Aerobic and resistance	2-3 times per week	Face-to-face	2-3 times per week	NR	NS	NR
Chaplin et al. (2015), UK[28]	N=125 59% males 71.1 (8.9) years old FEV1pp NR BMI (kg/m2) 28.5 (6.7)	Outpatient	7	Aerobic and resistance	NR	Face-to-face	NR	NR	aerobic	Everyday
Chaplin et al. (2017), UK[122]	N=51 75% males 66.4 (10.1 years old FEV1pp=58.7 (29.1)	Home-based	12	Aerobic and resistance	NR	Web-based platform	NR	NR	All exercise was unsupervised	All exercise was unsupervised

	BMI (kg/m2) 27.9 (6.4)									
Cheng et al. (2014), Taiwan[199]	N=64 86% males 70.1 (8.7) years old FEV1pp=44.9 (11.7) BMI (kg/m2) 22.9 (3.6)	Outpatient	12	Aerobic	2 times per week	Face-to-face	2 times per week	NR	NR	NR
Clini et al. (2001), Italy[200]	N=27 100% males 65 (6) years old FEV1pp=55 (14) BMI (kg/m2) 27 (2)	Outpatient	8	Aerobic and resistance	3 times per week	Face-to-face	NR	NR	NR	NR
Clini et al. (2002), Italy[201]	N=47 100% males 67 (7) years old FEV1pp=56 (6.3) BMI (kg/m2) 27 (3)	Outpatient	8-10	Aerobic and resistance	3 times per week	Face-to-face	NR	NR	NR	NR
Coquart et al.	N=117 62% males	Home-based	8	Aerobic and	5 times per week	NR	1 time per week	Balance recommendations	All exercise was unsupervised	All exercise was unsupervised

(2016), France[29]	63.3 (9.9 years old FEV1pp=40.7 (17.4) BMI (kg/m2) 26.3 (7.5)			resistance						
Coquart et al. (2017), France[30]	N=298 67% males 63.8 (11) years old FEV1pp=40.9 (17.1) BMI (kg/m2) 27 (7.6)	Home-based	8	Aerobic and resistance	5 times per week	NR	1 time per week	Balance recommend-ations	All exercise was unsupervised	All exercise was unsupervised
Coronado et al. (2003), Switzerland[202]	N=15 87% males 66.7 (8.7) years old FEV1pp=54 (16) BMI (kg/m2) 23.6 (4.7)	Inpatient	3	Aerobic and resistance	6-7 times per week	NR	NR	NR	ADL and aerobic	NR
Creutzberg et al. (2000), The Netherlands[31]	N=24 67% males 64.3 (6) years old FEV1pp=33.9 (12.7)	Inpatient	8	Aerobic and ADL training	NR	Face-to-face	NR	nutritional therapy	NR	NR

	BMI (kg/m2) NR									
Creutzberg et al. (2003), The Netherlands[32]	N=64 77% males 65 (9) years old FEV1pp=35 (14) BMI (kg/m2) 20.2 (1.7)	Inpatient	8	Aerobic and ADL training	NR	Face-to-face	NR	nutritional therapy	NR	NR
Croitoru et al. (2013), Romania[203]	N=25 72% males 60.4 (12) years old FEV1pp=44.5 (13) BMI (kg/m2) NR	Outpatient	7	Aerobic and resistance	3 times per week	Face-to-face	NR	Psychological support	NR	NR
Cui et al. (2019), China[33]	N=29 62% males 68.7 (5.4) years old FEV1pp=43.2 (4.9) BMI (kg/m2) 21.2 (1.5)	Hospital - NR	12	Aerobic	3 times per week	Face-to-face	NR	Breathing exercises and psychological support	NR	NR
Cullen et al.	N=134 72% males	Hospital - NR	8	Aerobic and	2 times per week	Face-to-face	2 times per week	NR	NR	NR

(2017), Ireland[34]	67.8 (8.6) years old FEV1pp NR BMI (kg/m2) 29 (6.8)			resistance						
Da Silva et al. (2018), Brazil[262]	N=38 53% males 67.7 (6.9) years old FEV1pp=46.1 (17.4) BMI (kg/m2) 27.1 (6.3)	Outpatient	12	Aerobic and resistance	3 times per week	Face-to-face	NR	Nutritional support and psychological support	NR	NR
Dallas et al. (2009), USA[35]	N=59 47% males 69 (8) years old FEV1pp=45 (18) BMI (kg/m2) 27 (5)	Outpatient	6-12	Aerobic and resistance	2-3 times per week	Face-to-face	2-3 times per week	NR	NS	NS
Datta and ZuWallack (2013), USA36	N=373 51% males 69 (9) years old FEV1pp=50 (20) BMI (kg/m2) 28 (7)	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	NR	NR	NR

De Godoy and Godoy (2003), Brazil[123]	N=14 86% males 62.1 (14.9) years old FEV1pp NR BMI (kg/m2) NR	Community	12	Aerobic and resistance	2 times per week	Face-to-face	1 time per month	Physiotherapy and psychotherapy	NR	NR
De Oliveira et al. (2010), Brazil[124]	N=46 83% males 71.3 (6.7) years old FEV1pp=51.5 (23.9) BMI (kg/m2) 23.5 (4.2)	Outpatient	12	Aerobic and resistance	3 times per week	Face-to-face	NR	NR	NR	NR
De Roos et al. (2018), The Netherlands[125]	N=28 36% males 69 (9.7) years old FEV1pp=68 (7.7) BMI (kg/m2) 28.2 (5.5)	Community	10	Aerobic and resistance	2 times per week	Face-to-face	1 time per week	NR	aerobic	1 time per week
Demeyer et al. (2016),	N=74 76% males 66 (7) years old	Outpatient	12	Aerobic and resistance	3 times per week	Face-to-face	NR	NR	NR	NR

Belgium[37]	FEV1pp=48 (22) BMI (kg/m2) 26 (6)									
Deniz et al. (2019), Turkey[38]	N=25 32% males 59.5 (6.8) years old FEV1pp=45.7 (16.2) BMI (kg/m2) 27.2 (5.1)	NR	2	Aerobic and resistance	2 times per week	Face-to-face	NR	Breathing exercises and bronchial hygiene	NR	NR
Di Meo et al. (2008), Italy[39]	N=74 85% males 73.95 (4.35) years old FEV1pp=44.1 (12.15) BMI (kg/m2) 25.6 (3.9)	Outpatient	4	Aerobic and resistance	5 times per week	Face-to-face	NR	IMT	NR	NR
Dodd et al. (2011), UK[40]	N=297 63% males 69.2 (9.3) years old FEV1pp=50.9 (18.9) BMI (kg/m2) 27.7 (6.5)	Community and hospital (NR)	8	Aerobic and resistance	2 times per week	Face-to-face	NR	NR	Aerobic and resistance	1 or more times per week

Donesky et al. (2014), USA[126]	N=38 39% males 66.2 (6.4) years old FEV1pp=43.7 (9.9) BMI (kg/m2) NR	NR	8	Aerobic	3 times per week	Face-to-face	1 every 2 weeks	Relaxation techniques	Aerobic	NR
Duruturk et al. (2015), Turkey[127]	N=16 73% males 61.2 (5) years old FEV1pp=58.4 (14.4) BMI (kg/m2) 26.7 (3.9)	Outpatient	6	Aerobic	3 times per week	Face-to-face	Only 1 time through the course of the programme	NR	NR	NR
Dyer et al. (2013), UK[41]	N=34 54% males 69.5 (7.5) years old FEV1pp NR BMI (kg/m2) NR	Community	7	NR	2 times per week	Face-to-face	NR	NR	NR	NR
Dyer et al. (2012), UK[128]	N=27 65% males 70 (7) years old	Hospital - NR	6-7	Aerobic and resistance	2 times per week	Face-to-face	NR	NR	Aerobic and resistance	NR

	FEV1pp=44 (11) BMI (kg/m2) 29 (7)									
Eaton et al. (2006), New Zealand[204]	N=22 55% males 71 (9) years old FEV1pp NR BMI (kg/m2) 25 (NR)	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	NR	Aerobic and resistance	NR
Effing et al. (2011), The Netherlands[129]	N=80 58% males 62.9 (8.1) years old FEV1pp=49.6 (14.2) BMI (kg/m2) 26.1 (5)	Outpatient	24	Aerobic and resistance	3 times per week	Face-to-face	Only 3 sessions through the course of the programme	NR	Aerobic and resistance	1 time per week
Egan et al. (2012), Ireland[42]	N=45 ~50% males Age NR FEV1pp=46.8 (16.6) BMI (kg/m2) 27.5 (6.2)	Outpatient	7	Aerobic and resistance	2 times per week	Face-to-face and booklet	2 times per week	IMT	NR	3 times per week
	N=33	Outpatient	8			NR	NR		NR	

Ekren et al. (2018), Turkey[43]	91% males 66 (8.6) years old FEV1pp NR BMI (kg/m2) NR			Aerobic and resistance	2 times per week			Breathing and relaxation exercises		1 time per week
Elci et al. (2008), Turkey[130]	N=39 85% males 59.7 (8.6) years old FEV1pp 47.8 (NR) BMI (kg/m2) NR	Outpatient	12	Aerobic and resistance	2 times per week	Face-to-face and booklet	NR	Nutritional support	Aerobic and resistance	5 times per week
Elliott et al. (2004), Australia[131]	N=22 64% males 66.4 (2.1) years old FEV1pp=46 (3.9) BMI (kg/m2) NR	Outpatient	12	Aerobic and resistance	2 times per week	NR	NR	NR	Aerobic and resistance	2 times per week
Ergun et al. (2011), Turkey[205]	N=28 Sex NR 63.3 (10.1) years old	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face	1 time per month	Nutritional and psychological support and	NR	NR

	FEV1pp=42.5 (17.4) BMI (kg/m2) 27.4 (5.5)							breathing exercises and relaxation techniques		
Evans et al. (2009), UK[44]	NR 55% males 69.5 (8.9) years old FEV1pp=20 (17.5) BMI (kg/m2)	Outpatient	7	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	NR	Aerobic and resistance	Everyday
Fabre et al. (2007), France[206]	N=18 Sex NR 57.2 (1) years old FEV1pp=51.4 (4.3) BMI (kg/m2) 29.6 (1.4)	NR	7	Aerobic	3 times per week	Face-to-face	3 times per week	NR	NR	NR
Felcar et al. (2018), Brazil[132]	N=36 56% males 68 (8) years old FEV1pp=46 (14) BMI (kg/m2) 26 (5)	Community	12	Aerobic and resistance	3 times per week	Face-to-face	1 every 2 weeks	NR	NR	NR

Fernández et al. (2009), Spain[133]	N=27 100% males 66 (NR) years old FEV1pp=33 (NR) BMI (kg/m2) 28.4 (6.1)	Home-based	48	Aerobic and resistance	5 times per week	Face-to-face	Only 3 sessions through the course of the programme	Breathing exercises and IMT	Aerobic and resistance	5 times per week
Ferreira et al. (2006), USA[45]	N=309 40% males 70.5 (NR) years old FEV1pp NR BMI (kg/m2) NR	Outpatient	8	Aerobic and resistance	3 times per week	Face-to-face	3 times per week	NR	NR	NR
Finnerty et al. (2001), UK[134]	N=40 69% males 70.4 (8) years old FEV1pp=41.2 (19.2) BMI (kg/m2) NR	Outpatient	6	Aerobic	1 time per week	Face-to-face	1 time per week	Nutritional support and occupational therapy	Aerobic	5 times per week
Foglio et al. (2007), Italy[46]	N=48 69% males 59.6 (8.1) years old	Inpatient	8	Aerobic and resistance	3 times per week	Face-to-face	3 times per week	Nutritional support and psychological support	NR	NR

	FEV1pp=79.8 (14.4) BMI (kg/m2) 26.9 (4.4)									
Franssen et al. (2004), The Netherlands[263]	N=50 74% males 64 (9) years old FEV1pp=39 (16) BMI (kg/m2) 26.4 (2.5)	inpatient	8	Aerobic and resistance	5 times per week	Face-to-face	NR	Psychosocial and behavioural and nutritional support	NR	NR
Fukuoka et al. (2016), Japan[207]	N=8 88% males 75.5 (6.4) years old FEV1pp NR BMI (kg/m2) 21 (4.8)	Outpatient	2	NR	NR	Video lectures	Only 5 sessions through the course of the programme	Laughter yoga	NR	NR
Fuld et al. (2005), UK[135]	N=18 56% males 61.7 (8) years old FEV1pp=45.4 (14) BMI (kg/m2) 23.2 (3.6)	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face	NR	NR	NS	NS
	N=24	inpatient	3						NR	NR

Lorenzi et al. (2004), Italy[265]	58% males 75 (4) years old FEV1pp=44 (12) BMI (kg/m2) 22 (3)			Aerobic and resistance	7 times per week	Face-to-face	6 times per week	Breathing exercises and bronchial hygiene		
Lou et al. (2015), China[136]	N=4197 48% males 61.6 (13.5) years old FEV1pp NR BMI (kg/m2) NR	Community	NR	Aerobic and resistance	1-2 times per week	Face-to-face	1 every 2 weeks	Breathing exercises and psychological support and nutritional support	NR	NR
Luk et al. (2017), Australia[51]	N=18 43% males 70.5 (7.5) years old FEV1pp NR BMI (kg/m2) 24.1 (12.3)	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	NR	NR	NR
Luk, E. et al. (2017), Australia[275]	N=315 58% males 71.7 (9.5) years old FEV1pp=45.9 (15.8)	community	8	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	NR	NR	NR

	BMI (kg/m2) NR									
Luk et al. (2015), Australia [52]	N=217 47% males 70.7 (7) years old FEV1pp=46 (16) BMI (kg/m2) 26.9 (6)	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	NR	NR	NR
Mador et al. (2005), USA[137]	N=19 Sex NR 70.9 (2) years old FEV1pp=26.9 (0.9) BMI (kg/m2) 26.9 (0.9)	Outpatient	8	Aerobic	NR	Face-to-face	1 time per week	NR	NR	NR
Mador et al. (2001), USA[208]	N=29 Sex NR Age NR FEV1pp=48 (2) BMI (kg/m2) NR	Outpatient	8	Aerobic and resistance	3 times per week	Face-to-face	1 time per week	NR	NR	NR
Maekura et al.	N=46 96% males	Inpatient	4	Aerobic and ADL training	5 times per week	Booklet	NR	Occupational therapy and	NR	NR

(2015), Japan[53]	68.7 (7.1) years old FEV1pp=30.6 (9.1) BMI (kg/m2) 19.7 (2.7)							psychosocial and nutritional support		
Majewski et al. (2010), UK[209]	N=13 62% males 70.5 (NR) years old FEV1pp NR BMI (kg/m2) 26.1 (NR)	Outpatient	6	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	NR	NR	NR
Maltais et al. (2008), Canada[138]	N=126 57% males 66 (9) years old FEV1pp=43 (13) BMI (kg/m2) 27 (5)	Outpatient	8	Aerobic and resistance	3 times per week	Face-to-face	2 times per week	NR	NR	NR
Ferrari et al. (2004), Italy[210]	N=32 Sex NR 70.4 (5.3) years old FEV1pp=55.2 (17.5)	Home-based	12	Aerobic	3 times per week	Face-to-face	NR	NR	aerobic	3 times per week (all)

	BMI (kg/m2) 28.4 (3.4)									
Marques et al. (2015), Portugal[211]	N=34 59% males 68 (11.8) years old FEV1pp=72.2 (22.3) BMI (kg/m2) 28.4 (6)	Community	12	Aerobic and resistance and balance	3 times per week	Face-to-face	1 time per week	NR	NR	NR
Marquis et al. (2015), Canada[212]	N=26 42% males 65.2 (7.1) years old FEV1pp=47.7 (12.7) BMI (kg/m2) 27 (5.8)	Home-based	8	Aerobic and resistance	3 times per week	Video lectures and booklet	1 time per week	NR	NR	NR
McCarroll et al. (2013), USA[213]	N=35 44% males 73.1 (8.4) years old FEV1pp=71 (6) BMI (kg/m2) 29.5 (6)	Outpatient	NR	NR	NR	Face-to-face	NR	NR	NR	NR
McFarland et al.	N=13 46.2% males	Home-based	8	Aerobic	3 times per week	Face-to-face and booklet	Only 6 sessions	NR	NR	NR

(2012), USA[271]	72.2 (11.2) years old FEV1pp=51 (NR BMI (kg/m2) NR						through the course of PR			
Miki et al. (2013), Japan[139]	N=10 90% males 73.1 (5.6) years old FEV1pp=33.3 (10.5) BMI (kg/m2) 18.1 (2.3)	Hospital - NR	3	Aerobic	5 times per week	Face-to-face	NR	Physiotherapy	NR	NR
Miki et al. (2012), Japan[140]	N=17 87% males 73.9 (6) years old FEV1pp=34.5 (9.1) BMI (kg/m2) 18 (2.1)	Inpatient	3	Aerobic	7 times per week	Face-to-face	NR	NR	NR	NR
Mitchell et al. (2014), UK[141]	N=89 67% males 69 (8) years old FEV1pp=56.04 (16.76)	Home-based	6	Aerobic and resistance	3 times per week	Booklet	NR	NR	Aerobic and resistance	3 times per week (all)

	BMI (kg/m2) 28.1 (5.6)									
Miyahara et al. (2000), Japan[214]	N=21 94% males 69.2 (7.3) years old FEV1pp=42.3 (14.6) BMI (kg/m2) NR	Inpatient	3	Aerobic	5 times per week	Face-to-face	Only 8 sessions through the course of the programme	Respiratory muscle exercises	NR	NR
Miyamoto et al. (2014), Japan[215]	N=11 36% males 78.8 (5.2 years old FEV1pp=77 (20) BMI (kg/m2) 24.1 (3.1)	Inpatient and Outpatient	12	Aerobic and resistance	6 times per week and 1-2 times per week	Face-to-face	NR	Breathing and relaxation exercises	Aerobic and resistance	NR
Mkacher et al. (2015), Tunisia[142]	N=30 100% males 63.5 (2.6) years old FEV1pp=39.3 (8.1) BMI (kg/m2) 26.7 (1.8)	Inpatient	24	NR	3 times per week	NR	NR	NR	NR	NR
	N=14		6				NR	NR		

Moore et al. (2009), UK[143]	60% males 70 (13) years old FEV1pp NR BMI (kg/m2) NR	Home-based		Aerobic and resistance	4 times per week	Video lectures and booklet			Aerobic and resistance	4 times per week (all)
Moore et al. (2017), Canada[216]	N=39 46% males 66.4 (6.6) years old FEV1pp=60.7 (21.9) BMI (kg/m2) 27.2 (4.7)	Outpatient	6-8	Aerobic and resistance	2-3 times per week	Face-to-face	2-3 times per week	NR	NR	NR
Paneroni et al. (2015), Italy[273]	N=18 89% males 65.7 (10.5) years old FEV1pp=46.8 (17.4) BMI (kg/m2) NR	Home-based	~7	Aerobic and resistance	7 times per week	Face-to-face and phone call/ videoconference	As needed	NR	Aerobic and resistance	6 times per week (all)
Péran et al. (2018), France[144]	N=6 50% males Age NR FEV1pp NR	Hospital - NR	4	Aerobic and resistance	5 times per week	Face-to-face	NR	NMES and relaxation	NR	NR

	BMI (kg/m2) NR									
Persson et al. (2000), Sweden[217]	N=27 35% males 67 (5.3) years old FEV1pp=38 (13.4) BMI (kg/m2) 24 (3.7)	Outpatient	8-12	Aerobic and resistance	2 times per week	Face-to-face	Only 6 sessions through the course of PR	NR	NR	NR
Pichon et al. (2016), France[218]	N=62 60% males 61.8 (9) years old FEV1pp=46.1 (16) BMI (kg/m2) 26.2 (5.7)	Inpatient	3	Aerobic and resistance	5 times per week	Face-to-face	NR	IMT and sociopsychological and nutritional advices	NR	NR
Puente-Maetsu et al. (2003), Spain[145]	N=20 100% males 63 (5) years old FEV1pp=39 (6) BMI (kg/m2) NR	Outpatient	8 +12	Aerobic	4 times per week	Face-to-face	Only 2 sessions through the course of PR	NR	Aerobic	4 times per week after initial programme
Puhan et al. (2006),	N=49 60% males	Inpatient	3	Aerobic	5 times per week	Face-to-face	3 times per week	Relaxation techniques	Physical activity (not specified)	Everyday

Switzerland[146]	69 (9.2) years old FEV1pp=34.5 (9) BMI (kg/m2) 25.4 (6.9)									
Ragaselvi et al. (2019), India[219]	N=102 93% males 60.9 (9.1) years old FEV1pp NR BMI (kg/m2) NR	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	IMT	NR	5 times per week
Ramachandran et al. (2008), USA[54]	N=114 41% males 70 (8) years old FEV1pp=46 (16) BMI (kg/m2) 28 (6.4)	Outpatient	16 sessions (NR)	Aerobic and resistance	NR	NR	NR	Nutritional support	NR	NR
Rasekaba et al. (2009), Australia[55]	N=29 41% males 72 (2) years old FEV1pp NR BMI (kg/m2) NR	Outpatient	8	Aerobic and resistance	1 time per week	Face-to-face	1 time per week	PA counselling	NR	NR

Schuler et al. (2018), Germany [58222]	N=383 65% males 57.8 (7.1) years old FEV1pp=51 (14.9) BMI (kg/m2) 26.8 (6)	Inpatient	3	Aerobic and resistance	4-5 times per week	Face-to-face	Only 7 sessions through the course of the programme	IMT and whole body vibration and physiotherapy and optional psychological, social, nutritional and occupational therapies	NR	NR
Schultz et al. (2018), Germany [147]	N=304 67% males 57.9 (6.6) years old FEV1pp=49.5 (15) BMI (kg/m2) 26.9 (6.69)	Inpatient	3	Aerobic and resistance	4-5 times per week	Face-to-face	Only 7 sessions through the course of the programme	whole body vibration and physiotherapy and optional psychological, social, nutritional and occupational therapies	NR	NR
Sewell et al. (2005), UK[148]	N=90 67% males 69.3 (8.7) years old	Outpatient	7	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	NR	aerobic	Everyday

	FEV1pp NR BMI (kg/m2) NR									
Sewell et al. (2006), UK[149]	N=50 54% males 71.96 (8.3) years old FEV1pp NR BMI (kg/m2) NR	Outpatient	7	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	NR	aerobic	Everyday
Shahin et al. (2008), France[267]	N=40 85% males 63.7 (11.9) years old FEV1pp=41.9 (2.6) BMI (kg/m2) 24.2 (6.4)	Outpatient	14	Aerobic	2 times per week	Face-to-face	1 time per week	Nutritional support	NR	NR
Sillen et al. (2014), The Netherlands[150]	N=40 48% males 64 (1.3) years old FEV1pp=33 (2) BMI (kg/m22) 4.9 (0.8)	Inpatient	8	Resistance	5 times per week	Face-to-face	NR	Occupational therapy and relaxation therapy and psychosocial counselling	NR	NR

Singh et al. (2008), UK[220]	N=372 55% males 69.4 (8.4) years old FEV1pp= 43.6 (24.0) BMI (kg/m2) 26.7 (6.3)	Outpatient	7	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	NR	aerobic	Everyday
Singh et al. (2001), UK[221]	N=97 60% males 67 (8.7) years old FEV1pp NR BMI (kg/m2) NR	Outpatient	7	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	NR	aerobic	NR
Smid et al. (2017), The Netherlands[59]	N=518 55% males 64.3 (8.8) years old FEV1pp=48.9 (20) BMI (kg/m2) 26.2 (5.7)	Inpatient and Outpatient	8	Aerobic and resistance	3-5 times per week	Face-to-face	NR	Daily supervised walks and NMES (when too dyspnoeac) and occupational therapy, nutritional and pscychosocial counsellin	NR	NR

								g (when needed		
Spielmanns et al. (2016), Germany [60]	N=1946 53% males 62 (9) years old FEV1pp=31.7 (9.3) BMI (kg/m2) 23.2 (6)	Inpatient	4	Aerobic and resistance	5-6 times per week	Face-to-face	2 times per week	Respiratory physiotherapy and psychosocial support	NR	NR
Spruit et al. (2015), The Netherlands[4]	N=3349 57% males 64 (9) years old FEV1pp=49 (19) BMI (kg/m2) 25.6 (5.3)	Inpatient and Outpatient	8	Aerobic and resistance	3-5 times per week	Face-to-face	NR	Daily supervised walks and NMES (when too dyspnoeac) and occupational therapy, nutritional and pscychosocial counselling (when needed	NR	NR
Stickland et al. (2011), Canada[268]	N=262 44% males 69.5 (9.7) years old	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	Breathing exercises and bronchial hygiene	NR	NR

	FEV1pp=48.97 (19.27) BMI (kg/m2) 29.5 (7.7)									
Stoilkova et al. (2013), The Netherlands[61]	N=303 53% males 62.3 (8.3) years old FEv1pp=47.7 (19.5) BMI (kg/m2) 25.8 (5.2)	Inpatient and Outpatient	8-14	Aerobic and resistance	7 times per week	Face-to-face	20 sessions through the course of the programme	Nutritional and psychological support	NR	NR
Stoilkova-Hartmann et al. (2015), The Netherlands[62]	N=439 55% males 65.7 (8.8) years old FEV1pp=47.8 (18.6) BMI (kg/m2) 25.7 (5.5)	Inpatient and Outpatient	8-14	Aerobic and resistance	7 times per week	Face-to-face	20 sessions through the course of the programme	Nutritional and psychological support	NR	NR
Stulbarg et al. (2002), USA[152]	N=38 65% males 66.2 (6.4) years old FEV1pp=43.7 (9.9) BMI (kg/m2) NR	NR	8	Aerobic	3 times per week	Face-to-face	Only 4 sessions through the course of PR	NR	Aerobic	4 times per week

Sundararajan et al. (2010), UK[63]	N=102 66% males 76 (4.1) years old FEV1pp=38 (NR) BMI (kg/m2) NR	Outpatient	6	Aerobic	2 times per week	Face-to-face	NR	NR	NR	1 time per week
Takigawa et al. (2007), Japan[64]	N=225 89% males Age NR FEV1pp=37.5 (6.2) BMI (kg/m2) 19.3 (3.1)	Inpatient	4-8	Aerobic and resistance	5 times per week	Face-to-face	3 times per week	Breathing and relaxation exercises	NR	NR
Theander et al. (2009), Sweden[153]	N=15 25% males 66 (6) years old FEV1pp=35.1 (7.6) BMI (kg/m2) 24.3 (3.9)	Outpatient	12	resistance	2 times per week	Face-to-face	Only 5 sessions through the course of the programme	Nutritional supplement-ation	Aerobic and resistance	Everyday
Tomioka et al. (2016), Japan[65]	N=49 74% males 73.4 (9) years old	Inpatient	3	Aerobic and resistance	7 times per week	Face-to-face	NR	IMT and ocupational therapy	NR	Everyday

	FEV1pp=33.8 (16.6) BMI (kg/m2) 20 (4)									
Steiner et al. (2003), UK[151]	N=43 63% males 68 (8) years old FEV1pp=34.4 (14.3) BMI (kg/m2) 23.5 (3.8)	Outpatient	7	Aerobic	2 times per week	Face-to-face	2 times per week	NR	Aerobic	NR
Tsujimura et al. (2019), Japan[222]	N=12 100% males 71.5 (4.3) years old FEV1pp NR BMI (kg/m2) 19.6 (3)	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	NR	Aerobic and resistance	Everyday
Vaidiya et al. (2018), France[223]	N=157 59% males 63 (9) years old FEV1pp=47 (19) BMI (kg/m2) 26 (6)	Outpatient and Home-based	4-12	Aerobic and resistance	2-5 times per week	NR	NR	Physiotherapy and nutritional and sociopsychological support	NR	NR
	N=18	Inpatient	12			NR			NR	NR

Van Helvoort et al. (2011), The Netherlands[66]	67% males 58 (2) years old FEV1pp=41 (3) BMI (kg/m2) 25.8 (1.3)			Aerobic and resistance	3 times per week		1 time per week	Physiotherapy and breathing retraining and psychosocial support and nutritional intervention if needed		
Van Herck et al. (2019), The Netherlands[67]	N=446 53% males 60.5 (8.8) years old FEV1pp=42.5 (17.7) BMI (kg/m2) 25.9 (5.5)	Inpatient	12	NR	5 times per week	Face-to-face	NR	NR	NR	NR
Van Wetering et al. (2010), The Netherlands[154]	N=160 73% males 66.7 (8.9) years old FEV1pp=60 (15.8) BMI (kg/m2) 22 (1.9)	Outpatient	16	Aerobic and resistance	2 times per week	Face-to-face	NR	Nutritional supplement-ation	NR	NR
Van Wetering et al.	N=102 71% males	Outpatient	16	Aerobic and	NR	Face-to-face and booklet	NR	Nutritional support	Aerobic and resistance	Everyday

(2010.2), The Netherlands[155]	65.9 (8.8) years old FEV1pp=58 (16) BMI (kg/m2) 26.1 (4.4)			resistance						
Varas et al. (2018), Spain[156]	N=21 86% males 69.5 (7.4) years old FEV1pp=45.8 (16.5) BMI (kg/m2) 26.3 (4.9)	Community	8	Aerobic	5 times per week	Face-to-face	NR	PA counselling	Aerobic	Everyday
Voduc et al. (2010), Canada[224]	N=24 Sex NR 65.9 (6.6) years old FEV1pp=41.5 (13.8) BMI (kg/m2) NR	Outpatient	12	Aerobic and resistance	2 times per week	Face-to-face	NR	Breathing exerises and bronchial hygiene and postural corrections	Aerobic	1-2 times per week
Vogiatzis et al. (2005), Greece[157]	N=9 Sex NR 67 (2) years old FEV1pp=39 (6)	Outpatient	10	Aerobic	3 times per week	Face-to-face	NR	Relaxation techniques and nutritional and	NR	NR

	BMI (kg/m2) 26.9 (1.3)							psychological support		
von Leupoldt et al. (2008), Germany [225]	N=210 59% males 64 (9) years old FEV1pp=53.9 (17.5) BMI (kg/m2) 26.5 (5.2)	Outpatient	3	Aerobic and resistance	5 times per week	Face-to-face	NR	Nutritional support and breathing therapy and relaxation therapy	NR	NR
von Leupoldt et al. (2011), Germany [68]	N=238 57% males 62 (9.9) years old FEV1pp=53.9 (18.1) BMI (kg/m2) 26.6 (5.5)	Outpatient	3	Aerobic and resistance	5 times per week	Face-to-face	NR	Nutritional support and breathing therapy and relaxation therapy	NR	NR
Ward et al. (2002), UK[226]	N=28 93% males 70.3 (NR) years old FEV1pp=40 (2) BMI (kg/m2) NR	Community	8	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	NR	NR	NR
Waterhouse et al.	N=111 56% males	Community	6	Aerobic and	2 times per week	Face-to-face	2 times per week	NR	NR	NR

(2010), UK[158]	68.7 (8.3) years old FEV1pp=45.1 (16.3) BMI (kg/m2) 25.4 (5.6)			resistance						
White et al. (2002), UK[159]	N=54 67% males 67 (9) years old FEV1pp=26.6 (8) BMI (kg/m2) NR	Outpatient	6	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	NR	NR	2 times per week
Wilson et al. (2015), UK[160]	N=73 56% males 67.3 (15.1) years old FEV1pp=41 (16) BMI (kg/m2) 28.8 (5.7)	Community	12	Aerobic and resistance	1 time per week	Face-to-face	1 time per week	NR	NR	NR
Wiyono et al. (2006), Indonesia[161]	N=30 93% males 64.3 (6.3) years old FEV1pp NR	Outpatient	6	Aerobic	3 times per week	Face-to-face	NR	Breathing exercises and bronchial hygiene	NR	NR

	BMI (kg/m2) 19.6 (8.5)									
Yohannes et al. (2016), UK[227]	N=257 49% males 71 (8.5) years old FEV1pp=56.9 (15.2) BMI (kg/m2) NR	Community	8	Aerobic and resistance	1 time per week	Face-to-face	1 time per week	NR	NR	NR
Yohannes et al. (2019), UK[228]	N=557 51% males 71.6 (9.4) years old FEV1pp=54.91 (14.15) BMI (kg/m2) NR	Community	8	Aerobic and resistance	1 time per week	Face-to-face	1 time per week	NR	NR	NR
Yoshimi et al. (2012), Japan[69]	N=31 100% males 67 (7) years old FEV1pp=39.3 (15.7) BMI (kg/m2) NR	Outpatient	6	Aerobic and resistance	2 times per week	Face-to-face	11 sessions through the course of the programme	Physiotherapy and IMT and nutritional support	Low-intensity aerobic and resistance training and flexibility	5 times per week
Zackrisson et al. (2011),	N=49 51% males	Community	6	Resistance	1 time per week	Face-to-face	1 time per week	Breathing and	NR	NR

Sweden[229]	67 (4) years old FEV1pp=49 (8) BMI (kg/m2) 28.6 (6)							relaxation exercises		
Zanaboni et al. (2013), Norway[230]	N=10 50% males Age NR FEV1pp NR BMI (kg/m2) NR	Home-based	2 years	Aerobic and resistance	3 times per week	web-based platform	NR	NR	Aerobic and resistance	2 times per week
Zanini et al. (2015), Italy[70]	N=439 82% males 71 (8) years old FEV1pp=55 (20) BMI (kg/m2) 28.5 (5.3)	Inpatient	3	Aerobic and resistance	5 times per week	Face-to-face	Only 5 sessions through the course of the programme	IMT	NR	NR
Zanini et al. (2015.2), Italy[162]	N=30 80% males 72 (8) years old FEV1pp=51 (16) BMI (kg/m2) 26 (5)	Inpatient	3	Aerobic and resistance	5 times per week	Face-to-face	Only 5 sessions through the course of the programme	IMT	NR	NR
	N=75	Inpatient	3				NR		NR	NR

Zanini et al. (2013), Italy[71]	85% males 71 (8) years old FEV1pp=57 (18) BMI (kg/m2) 29.7 (5.3)			Aerobic and resistance	4 times per week	Face-to-face		Nutritional and psychological support (if needed) and IMT and postural exercises		
ZuWallack et al. (2006), USA[72]	N=16 38% males 66 (8) years old FEV1pp=34 (11) BMI (kg/m2) NR	Outpatient	12	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	Individual counselling (if needed)	NS	NR
Beaumont et al. (2011), France[231]	N=50 72% males 64 (8.5) years old FEV1pp=42.4 (16.19) BMI (kg/m2) 24.2 (6.1)	Inpatient	4	Aerobic and resistance	2 times per week	Face-to-face	NR	Nutritional support	NR	NR
Groisbois et al. (2019), France[49]	N=459 64% males 64.2 (11.3)	Home-based	8	Aerobic and resistance	5 times per week	Face-to-face	1 time per week	Psychosocial and motivational support	Aerobic and resistance	4 times per week

	FEV1pp NR BMI (kg/m2) NR									
Lahham et al. (2020), Australia [179]	N=29 59% males 68 (9) years old FEV1pp=90 (8) BMI (kg/m2) 28 (4.5)	Home-based	8	Aerobic and resistance	5 times per week	Phone call	1 time per week	NR	Aerobic and resistance	5 times per week
Rebelo et al. (2020), Portugal [56]	N=70 79% males 68.4 (7.6) years old FEV1pp=48.1 (17.4) BMI (kg/m2) 25.6 (4.3)	Community	12	Aerobic and resistance	2 times per week	Face-to-face	1 every 2 weeks	NR	NR	NR
Rebelo et al. (2020.2), Portugal [57]	N=63 82% males 69.8 (7.4) years old FEV1pp=50.4 (19.4) BMI (kg/m2) 26.4 (4.9)	Community	12	Aerobic and resistance	2 times per week	Face-to-face	1 every 2 weeks	NR	NR	NR
	N=45	Inpatient	3			NR	NR		NR	NR

Gloeckl et al. (2017), Germany [168]	38% males 63 (9) years old FEV1pp=36.6 (11.7) BMI (kg/m2) 25.6 (6.3)			Aerobic and resistance	5 times per week			Supervised Squat Exercise Program		
Garrod (2000) et al, UK[3]	N=45 62% males Age NR FEV1pp=35.2 (12.8) BMI (kg/m2) NR	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face	Only 1 time through the course of the programme	NR	NS	4 times per week
Gigliotti et al. (2003), Italy[232]	N=20 90% males 64 (8.4) years old FEV1pp=42.4 (11.76) BMI (kg/m2) NR	Outpatient	6	Aerobic and resistance	NR	NR	NR	NR	NR	NR
Gloeckl et al. (2012), Germany [167]	N=40 53% males 65 (7) years old FEV1pp=38 (12)	Inpatient	3	Aerobic and resistance	5 times per week	Face-to-face	NR	Supervised Squat Exercise Program	NR	NR

	BMI (kg/m2) 27 (6)									
Gouzi et. al (2019), France[169]	N=32 50% males 61.1 (8.7) years old FEV1pp=62 (27) BMI (kg/m2) 25.3 (4.7)	Inpatient	6	Aerobic and resistance	NR	Face-to-face	NR	NR	NR	NR
Garrod (2000.2) et al, UK[165]	N=26 73% males Age NR FEV1pp=20 (9.9) BMI (kg/m2) NR	Outpatient	6	Aerobic and resistance	3 times per week	Face-to-face	Only 1 time through the course of the programme	NR	NR	NR
Godtfredsen (2019) et al., Denmark[233]	N=581 42% males Age NR FEV1pp NR BMI (kg/m2) NR	Community	6-12	Aerobic and resistance	2 times per week	Face-to-face	NR	Nutritional and psychosocial support	NR	NR
Ghanem et al.	N=39 Sex NR	Home-based	8	Aerobic and	4 times per week	Face-to-face and booklet	NR	IMT	Aerobic and resistance	4 times per week

(2009), Egypt[166]	57.0 (11.6) years old FEV1pp=29.44 (13.14) BMI (kg/m2) NR			resistance						
Garrod (2008) et al, UK[47]	N=74 61% males Age NR FEV1pp=47.9 (22.6) BMI (kg/m2) 27.1 (6.5)	Outpatient	7	Aerobic and resistance	2 times per week	Face-to-face	NR	NR	NR	5 times per week
Greulich (2015) et al., Germany[48]	N=544 59% males 57.2 (6.82) years old FEV1pp=34.19 (7.67) BMI (kg/m2) 24.3 (5.7)	Inpatient	3	Aerobic and resistance	5 times per week	Face-to-face	NR	IMT and bronchial hygiene (when needed)	NR	NR
Gurgun (2013) et al., Turkey[174]	N=65 96% males 66.2 (9) years old FEV1pp=41.9 (13.2)	Outpatient	8	Aerobic and resistance	NR	NR	NR	NR	NR	NR

	BMI (kg/m2) 20 (1.5)									
Güell (2008) et al., Spain[172]	N=57 100% males 64.6 (6.2) years old FEV1pp=38.5 (6.9) BMI (kg/m2) NR	Outpatient and Home-based	9	Aerobic and resistance	3 times per week	Face-to-face	Only 2 sessions through the course of PR	IMT	Aerobic and IMT	3-7 times per week
Grosbois (2015) et al., France[234]	N=226 68% males 62.3 (11.1) years old FEV1pp=41.5 (17.7) BMI (kg/m2) 26.8 (7.3)	Home-based	8	Aerobic	5 times per week	Face-to-face	NR	NR	Resistance and stretching and balance	3 times per week
Grosbois (2016) et al., France[50]	N=91 84% males 60.3 (9.3) years old FEV1pp=55 (19) BMI (kg/m2) 27.3 (6.3)	Outpatient	6	NR	4 times per week	Face-to-face	4 times per week	NR	NR	NR
	N=132	Inpatient	4	NR				NR	NR	NR

Haave (2008) et al., UK[105]	50% males 59 (NR) years old FEV1pp NR BMI (kg/m2) NR				5 times per week	Face-to-face	5 times per week			
Haave (2008.2) et al., UK[75]	N=249 50% males 59.1 (5.9) years old FEV1pp=51.8 (18.4) BMI (kg/m2) NR	Inpatient	4	NR	NR	Face-to-face	NR	NR	NR	NR
Haave (2007) et al., UK[235]	N=95 46% males 59.2 (5.7) years old FEV1pp=50.8 (18.9) BMI (kg/m2) NR	Inpatient	4	NR	NR	Face-to-face	NR	NR	NR	NR
Güell (2000) et al., Spain[173]	N=65 100% males 65 (7) years old FEV1pp=35 (14)	Outpatient	24	Aerobic	5 times per week	Face-to-face	NR	Breathing exercises and bronchial hygiene	Aerobic	NR

	BMI (kg/m2) NR									
Haugen (2007) et al., Norway[23 6]	N=115 64% males 60 (8) years old FEV1pp=48.5 (12.5) BMI (kg/m2) 27.1 (5.1)	Inpatient	4	NR	NR	Face-to-face	NR	NR	NR	NS
Güell (2017) et al., Spain[171]	N=143 89% males 64 (8.5) years old FEV1pp=34 (10) BMI (kg/m2) 27.5 (5)	Outpatient	8	Aerobic and resistance	3 times per week	Face-to-face	Only 4 sessions through the course of PR	NR	Aerobic and resistance and breathing exercises and bronchial hygiene	3 times per week
Harrison (2015) et al., Canada[76]	N=50 53% males 73 (6) years old FEV1pp=41 (17) BMI (kg/m2) 28 (8)	Inpatient and Outpatient	6-12	Aerobic and resistance and balance	3 times per week	NR	NR	NR	NR	NR
Harrison (2012) et	N=518 58% males	Outpatient	7	Aerobic and	2 times per week	Face-to-face	NR	NR	aerobic	Everyday

al., Canada[77]	69.2 (8.8) years old FEV1pp=39.89 (15.1) BMI (kg/m2) 26.2 (5.7)			resistance						
Houben-Wike et al. (2018), The Netherlands[79]	N=497 54% males Age NR FEV1pp NR BMI (kg/m2) NR	Inpatient and Outpatient	8-16	Aerobic and resistance	NR	Face-to-face	NR	NR	NR	NR
Hogg et al. (2012), UK[78]	N=812 56% males Age NR FEV1pp NR BMI (kg/m2) NR	Community	8	Aerobic and resistance	2 times per week	NR	NR	NR	NR	NR
Holland et al. (2017), Australia[175]	N=295 63% males 69 (10) years old FEV1pp=49 (19) BMI (kg/m2) 28 (6)	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face and booklet	NR	NR	NR	3 times per week

Jones et al. (2009), UK[80]	N=122 65% males 68 (8.2) years old FEV1pp NR BMI (kg/m2) NR	Community	NR	NR	1-2 times per week	NR	NR	NR	NR	NR
Johnston et al. (2017), Australia[238]	N=59 48% males 68.4 (9.8) years old FEV1pp=47.8 (20.2) BMI (kg/m2) 26.7 (5.9)	Outpatient	8	NR	2 times per week	Face-to-face	1 time per week	NR	NR	NR
Olarewaju et al. (2010), Nigeria[237]	N=44 56% males 66 (7.4) years old FEV1pp NR BMI (kg/m2) NR	Outpatient	6	Aerobic and resistance	2 times per week	Face-to-face	NR	NR	NR	NR
Incorvaia et al. (2014), Italy[106]	N=190 57% males 71.1 (7.1) years old	Outpatient	6	Aerobic and resistance	2 times per week	Face-to-face	NR	IMT	Resistance and IMT	Everyday

	FEV1pp=57.3 (NR) BMI (kg/m2) 28.3 (5.6)									
Jacobsen et al. (2014), Denmark [107]	N=221 52% males 70.5 (NR) years old FEV1pp=44.5 (NR) BMI (kg/m2) NR	Outpatient	7	NR	2 times per week	Face-to-face	1 time per week	Nutritional support and smoking cessation	NR	NR
Griffiths et al. (2000), UK[170]	N=99 62% males 68.2 (8.2) years old FEV1pp=39.7 (16.2) BMI (kg/m2) 25.2 (4.6)	Outpatient	6	Aerobic and resistance	3 times per week	Face-to-face	3 times per week	NR	ADL training	NR
Horton et al. (2018), UK[176]	N=287 65% males 68 (8.9) years old FEV1pp=48.34 (17.92) BMI (kg/m2) 27.5 (6)	Outpatient and Home-based	7	Aerobic and resistance	2 times per week	Face-to-face and booklet	NR	NR	Aerobic and resistance	3 times per week

Katajisto et al. (2017), Finland[241]	N=78 60% males 67 (7.9) years old FEV1pp=36 (14.3) BMI (kg/m2) 25 (6.2)	Outpatient	8	Aerobic and resistance	NR	Face-to-face	Only 1 time through the course of the programme	NR	NR	1 time per week
Katsura et al. (2004), Japan[242]	N=78 60% males 67 (7.9) years old FEV1pp=36 (14.3) BMI (kg/m2) 21.7 (0.5)	Inpatient	2	Aerobic and resistance	7 times per week	Face-to-face	NR	NR	NR	NR
Jones et al. (2015), UK[108]	N=90 63% males 73 (8) years old FEV1pp=40.5 (19.6) BMI (kg/m2) 21.4 (4)	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	NR	NR	1 time per week
Kaplan et al. (2004),	N=1218 61% males	Outpatient	6-10	resistance	NR	Face-to-face	NR	NR	NR	NR

United States[83]	67 (NR) years old FEV1pp NR BMI (kg/m2) NR									
Jones et al. (2013), UK[239]	N=475 55% males 69 (10) years old FEV1pp=47.6 (20.6) BMI (kg/m2) 27.8 (6.8)	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face	NR	NR	NR	1 time per week
Kagaya et al. (2009), Japan[81]	N=40 Sex NR 70 (6) years old FEV1pp NR BMI (kg/m2) 19.3 (3.7)	Home-based	24	Aerobic and resistance	7 times per week	Face-to-face	1 time per month	IMT	NR	NR
Kanao et al. (2015), Japan[82]	N=33 90% males 73.2 (5) years old FEV1pp=51 (21.3) BMI (kg/m2) 22 (4.7)	Outpatient	12	Aerobic	2 times per week	Face-to-face	NR	Breathing exercises and mobility exercises	Aerobic	NR

Kaelin et al. (2001), United States[240]	N=50 72% males 68.4 (6.9) years old FEV1pp=39.45 (11.51) BMI (kg/m2) 25.2 (5.3)	Outpatient	6	Aerobic and resistance	3 times per week	Face-to-face	NR	Active and static stretching	NR	NR
Golmohammadi et al. (2004), Canada[74]	N=210 50% males 68.5 (8.5) years old FEV1pp=55.1 (21.9) BMI (kg/m2) NR	Outpatient	6-8	Aerobic and resistance	2-3 times per week	Face-to-face	2-3 times per week	Breathing exercises and relaxation techniques and nutritional support and IMT	NR	NR
Köhnlein et al. (2009), Germany[86]	N=40 50% males 56.8 (8) years old FEV1pp=25.5 (7.2) BMI (kg/m2) 22.3 (3.8)	Hospital - NR	NR	Aerobic and resistance	5 times per week	Face-to-face	2 times per week	Breathing exercises and bronchial hygiene	NR	NR
Kon et al. (2014), UK[87]	N=675 58% males 70 (9) years old	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face	NR	NR	NR	NR

	FEV1pp=47.6 (NR) BMI (kg/m2) 27.6 (6)									
Kon et al. (2013), UK[88]	N=430 55% males Age NR FEV1pp NR BMI (kg/m2) NR	Outpatient	8	NR	2 times per week	Face-to-face	2 times per week	NR	NR	NR
Kawagoshi et al. (2015), Japan[177]	N=15 93% males 75 (9) years old FEV1pp=60.6 (20.8) BMI (kg/m2) 22 (3.1)	Home-based	~52	Aerobic and resistance	7 times per week	Face-to-face	1 time per month	IMT and Respiratory Muscle Stretching	Aerobic and resistance	Yes
Kaymaz (2017), Turkey[244]	N=33 85% males 62.4 (5.7) years old FEV1pp NR BMI (kg/m2) NR	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face	1 time per month	Breathing and relaxation exercises	Aerobic and resistance	1 time per week
	N=191	Inpatient	8-12	NR	NR	NR	NR	NR	NR	NR

Klijn et al. (2015), The Netherlands[246]	37% males 62 (9) years old FEV1pp=33 (10) BMI (kg/m2) 25 (6)									
Katsura et al. (2003), Japan[243]	N=31 90% males 72.2 (5.6) years old FEV1pp=54.7 (13.4) BMI (kg/m2) NR	Inpatient	2	NR	7 times per week	Face-to-face	NR	NR	NR	NR
Kiongera et al. (2015), USA[245]	N=33 52% males 69.3 (13.4) years old FEV1pp NR BMI (kg/m2) 29.2 (NR)	Inpatient	6-8	Aerobic and resistance	3-4 times per week	Face-to-face	2 times per week	NR	NR	NR
Khoshkesht et al. (2015), Iran[178]	N=70 71% males 56.7 (8.8) years old FEV1pp NR	Home-based	7	Respiratory techniques and Muscle Stretchin	3 times per week	Face-to-face	NR	NR	All exercise was unsupervised	All exercise was unsupervised

	BMI (kg/m2) NR			g Exercises						
Li et al. (2018), China[96]	N=303 76% males 64.9 (8.7) years old FEV1pp=48.8 (12.9) BMI (kg/m2) 23.4 (3)	Home-based	8	Aerobic and resistance	3 times per week	Face-to-face	NR	Expiratory muscle trainning	Aerobic and resistance and IMT	3 times per week
Kozu et al. (2011), Japan[248]	N=45 84% males 67.3 (5.1) years old FEV1pp=45 (11.8) BMI (kg/m2) 20.8 (2.2)	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	Breathing exercises and bronchial hygiene	NR	NR
Lan et al. (2011), Taiwan[92]	N=22 96% males 71.4 (7.5) years old FEV1pp=51.5 (13.3) BMI (kg/m2) 25.8 (3.4)	Outpatient	12	Aerobic	2 times per week	Face-to-face	2 times per week	NR	NR	NR
	N=338	Outpatient	8					NR	NR	Everyday

Kon et al. (2014.2), UK[247]	58% males 71 (NR) years old FEV1pp=49.8 (NR) BMI (kg/m2) 27.6 (NR)			Aerobic and resistance	2 times per week	Face-to-face	2 times per week			
Li et al. (2018.2), China[264]	N=151 87% males 65.1 (8.7) years old FEV1pp=48.7 (11.7) BMI (kg/m2) 22.9 (2.1)	Outpatient	8	Aerobic and resistance	3 times per week	NR	NR	Expiratory muscle training and bronchial hygiene	Aerobic and resistance and IMT	1-3 times per week
Liang et al. (2019), Australia[181]	N=157 61% males 66.6 (10.8) years old FEV1pp=69 (20.5) BMI (kg/m2) NR	Home-based	8	Aerobic and resistance	NR	NR	NR	Smoking cessation	Aerobic and resistance	NR
Lan et al. (2013), Taiwan[90]	N=26 Sex NR 71 (10.7) years old	Outpatient	12	Aerobic	2 times per week	Face-to-face	2 times per week	Breathing exercises and bronchial hygiene	NR	NR

	FEV1pp=64.8 (23) BMI (kg/m2) 23.8 (5.1)									
Lindsay et al. (2005), China[182]	N=25 80% males 69.5 (9.3) years old FEV1pp NR BMI (kg/m2) NR	Outpatient	NR	Aerobic	7 times per week	Face-to-face	6 times per week	NR	NR	NR
Lewis et al. (2019), UK[95]	N=80 59% males 62 (11.4) years old FEV1pp=59.8 (23.9) BMI (kg/m2) 24.6 (4.8)	NR	4	Aerobic and resistance	4 times per week	Face-to-face	4 times per week	NR	NR	NR
Liacos et al. (2019), Australia [180]	N=166 60% males 69 (9) years old FEV1pp=50 (19) BMI (kg/m2) 28.3 (6.4)	Home-based and Hospital (NR)	8	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	NR	Aerobic and resistance	Most days of the week
	N=216	Outpatient	20			NR	NR	NR	NR	

Kruis et al. (2010), The Netherlands[89]	42% males 67.1 (14) years old FEV1pp=70.5 (18) BMI (kg/m2) 27.3 (6)			Aerobic and resistance	2 times per week					1 time per week
Liddell & Webber (2010), UK[270]	N=15 73% males 72 (9) years old FEV1pp=46 (18) BMI (kg/m2) NR	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face and booklet	2 times per week	NR	Aerobic and resistance	3 and times per week
Lan et al. (2014), Taiwan[91]	N=34 82% males 70.2 (9.4) years old FEV1pp=49.7 (18) BMI (kg/m2) 21.9 (3.9)	Outpatient	12	Aerobic	2 times per week	Face-to-face	2 times per week	NR	NR	NR
Lee et al. (2013), Korea[93]	N=33 96% males 66.2 (7.8) years old	Home-based	12	Aerobic and resistance	NR	NR	NR	IMT and respiratory Muscle stretching	Aerobic and resistance	NR

	FEV1pp=48.7 (16.5) BMI (kg/m2) 21.6 (3.3)									
Leleu et al. (2005), France[94]	N=100 74% males 62.1 (9.6) years old FEV1pp=53 (22) BMI (kg/m2) NR	Outpatient	NR	Aerobic and resistance	4 times per week	Face-to-face	NR	Bronchial hygiene and smoking cessation	NR	NR
Keumon et al. (2000), France[85]	N=45 82% males 63.7 (8) years old FEV1pp=48 (17) BMI (kg/m2) NR	Inpatient	4	Aerobic	5 times per week	Face-to-face	NR	Physiotherapy and water-based therapy and psychosocial support	NR	NR
Nolan et al. (2017), UK[186]	N=76 71% males 68 (8) years old FEV1pp=50.3 (21.8) BMI (kg/m2) 27.6 (4.7)	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face and booklet	2 times per week	NR	NS	NS

Ochmann et al. (2012), Germany [253]	N=34 Sex NR Age NR FEV1pp=77.9 (19.2) BMI (kg/m2) NR	Inpatient	4	Aerobic and resistance	NR	NR	NR	Gymnastics and Nordic walking and breathing exercises and relaxation techniques	NR	NR
Normandin et al. (2002), USA[187]	N=20 55% males 69 (7) years old FEV1pp=43 (16) BMI (kg/m2) 27 (6)	Outpatient	8	Aerobic	2 times per week	Face-to-face	2 times per week	NR	NR	NR
Ninot et al. (2011), France[185]	N=20 90% males Age NR FEV1pp=56 (NR) BMI (kg/m2) NR	Outpatient	4	Aerobic	2 times per week	Face-to-face	2 times per week	NR	NR	NR
Ng et al. (2014), China[184]	N=98 89% males 74.1 (6.8) years old	Outpatient	6	Aerobic	2 times per week	Face-to-face and booklet	2 times per week	NR	NR	NR

	FEV1pp=63.1 (22.12) BMI (kg/m2) 23.1 (4.4)									
O'neill et al. (2007), UK[188]	N=91 70% males 68.5 (7.9) years old FEV1pp=41.4 (17.75) BMI (kg/m2) NR	Outpatient	6	Aerobic and resistance	1-2 times per week	Face-to-face	1 time per week	NR	NR	1-2 times per week
Moullec et al. (2010), France[249]	N=14 Sex NR 64.6 (6.1) years old FEV1pp=51.6 (11.7) BMI (kg/m2) 26.9 (4)	Community	1 year	Aerobic and resistance	NR	Face-to-face	1 every 2 weeks	Psychosocial support and breathing exercises and interval training (in circuit and in team sport)	NR	NR
Moullec et al. (2008), France[250]	N=14 71% males 64.6 (6.1) years old FEV1pp=51.6 (11.7)	Community	1 year	Aerobic and resistance	NR	Face-to-face	1 every 2 weeks	Psychosocial support and breathing exercises	NR	NR

	BMI (kg/m2) 26.9 (4)									
Naseer et al. (2017), Saudi Arabia[183]	N=15 Sex NR 56.5 (5.2) years old FEV1pp=47.27 (11.07) BMI (kg/m2) NR	Outpatient and Home-based	6	Aerobic	3 times per week	NR	NR	NR	aerobic	NR
Nolan et al. (2019), UK[99]	N=154 49% males 71 (10) years old FEV1pp=45.7 (19.7) BMI (kg/m2) 28.3 (7.8)	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face and booklet	2 times per week	NR	NR	At least once a week
Ninot et al. (2007), France[252]	N=23 Sex NR 63.9 (6.6) years old FEV1pp=55.8 (13.2) BMI (kg/m2) NR	Inpatient	4	Aerobic	5 times per week	Face-to-face	2 times per week	Bronchial hygiene and nutritional support	NR	NR
	N=182	Inpatient	4				NR		NR	NR

Ninot et al. (2006), France[98]	67% males 61.5 (9.7) years old FEV1pp=53.4 (15.35) BMI (kg/m2) 26.4 (4.5)			Aerobic and resistance	5 times per week	Face-to-face		Bronchial hygiene and nutritional support		
Pande et al. (2005), India[272]	N=24 Sex NR Age NR FEV1pp=39.7 (15.3) BMI (kg/m2) NR	Home-based	6	Aerobic	5 times per week	Face-to-face	Only 1 time through the course of the programme	Breathing Exercises	Aerobic	5 times per week
Ngaage et al. (2004), UK[251]	N=14 36% males 63 (NR) years old FEV1pp NR BMI (kg/m2) NR	Outpatient	6	Aerobic and resistance	2 times per week	Face-to-face	NR	NR	Aerobic and resistance	5 times per week
Nolan et al. (2016), UK[100]	N=324 59% males 70.2 (NR) years old FEV1pp=49.8 (NR)	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	NR	NR	NR

	BMI (kg/m2) 28.3 (NR)									
Cleutjens et al. (2017), The Netherlands[73]	N=157 49% males 62.4 (8.7) years old FEV1pp=54 (22.5) BMI (kg/m2) 26.7 (6.1)	Inpatient and Outpatient	8	Aerobic and resistance	3-5 times per week	Face-to-face	NR	Daily supervised walks and occupational therapy, nutritional and pscychosocial counselling (when needed)	NR	NR
Engel et al. (2016), Australia[163]	N=15 7% males 64.5 (4.1) years old FEV1pp NR BMI (kg/m2) NR	Outpatient	24	NR	NR	Face-to-face	NR	NR	NR	NR
Seetee et al. (2016), Thailand[260]	N=33 88% males 64.8 (10) years old FEV1pp NR BMI (kg/m2) 19.9 (3.2)	Home-based	8	Aerobic and resistance	3 times per week	NR	NR	Meditation	Aerobic and resistance	3 times per week (all)

Kaymaz et al. (2015), Turkey[84]	N=27 Sex NR 62.8 (7.18) years old FEV1pp=27.33 (8.2) BMI (kg/m2) 22.4 (4.2)	Outpatient	8	Aerobic and resistance	3 times per week	Face-to-face	NR	Nutritional and psychological support	Aerobic and resistance	1 time per week
Maddocks et al. (2016), UK[97]	N=816 59% males 69.8 (9.7) years old FEV1pp=48.9 (21) BMI (kg/m2) 27.8 (6.7)	Outpatient	8	Aerobic and resistance	3 times per week	Face-to-face	2 times per week	NR	Aerobic and resistance	1 time per week
Skumlien et al. (2007), Norway[102]	N=40 55% males 63 (8) years old FEV1pp=45 (11) BMI (kg/m2) 27.0 (4.5)	Inpatient	4	Aerobic and resistance	4-5 times per week	Face-to-face	4-5 times per week	NR	NR	NR
McDonnel et al. (2014), UK[266]	N=61 46% males 68.1 (11.3) years oold	Community	8	Aerobic and resistance	3 times per week	Face-to-face	NR	NR	NR	1-2 times per week

	FEV1pp=55 (19.2) BMI (kg/m2) NR									
Vasilopoulou et al. (2017), Greece[195]	N=50 76% males 66.7 (7.3) years old FEV1pp=51.8 (17.3) BMI (kg/m2) 27.5 (5.0)	Outpatient	48	Aerobic and resistance	2 times per week	Face-to-face	NR	Nutritional support	NR	NR
Reijnders et al. (2018), Germany[255]	N=104 70% males 57.6 (7.7) years old FEV1pp=45 (14) BMI (kg/m2) 27.2 (7)	Inpatient	3	Aerobic and resistance	3-6 times per week	Face-to-face	Only 7 sessions through the course of the programme	Whole-body vibration and Bronchial hygiene and psychological interventions and social counselling and nutritional counselling and occupational therapy	NR	NR

Reijnders et al. (2019), Germany [256]	N=104 70% males 57.6 (7.7) year old FEV1pp=45.36 (14.15) BMI (kg/m2) 27.2 (7)	Inpatient	3	Aerobic and resistance	3-6 times per week	Face-to-face	Only 7 sessions through the course of the programme	Whole-body vibration and bronchial hygiene and psychological interventions and social counselling and nutritional counselling and occupational therapy	NR	NR
Revitt, et al. (2013), United Kingdom [190]	N=160 51% males 70.7 (8.9) years old FEV1pp NR BMI (kg/m2) 26.0 (5.8)	Outpatient and Home-based	4	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	NR	Aerobic and resistance	NR
Sandoz et al. (2017),	N=141 56% males 68 (7) years old	Outpatient	8-12	Aerobic and resistance	2 times per week	Face-to-face	Only 1 time through the course of the programme	NR	NR	4 times per week

Australia [101]	FEV1pp=42 (17) BMI (kg/m2) 26 (5)									
Schuler et al. (2018.2), Germany [276]	N=590 65% males 57.7 (7.4) years old FEV1pp=50.3 (15.2) BMI (kg/m2) 26.7 (6.5)	Inpatient	3	Aerobic and resistance	3-6 times per week	Face-to-face	Only 7 sessions through the course of the programme	Whole-body vibration and Bronchial hygiene and psychological interventions and social counselling and nutritional counselling and occupational therapy	NR	NR
Román et al. (2013), Spain [194]	N=22 82% males 64.1 (NR) years old FEV1pp NR BMI (kg/m2) 27.6 (NR)	Community	12	Resistance	3 times per week	Face-to-face	Only 3 sessions through the course of the programme	Breathing exercises and bronchial hygiene	NR	NR

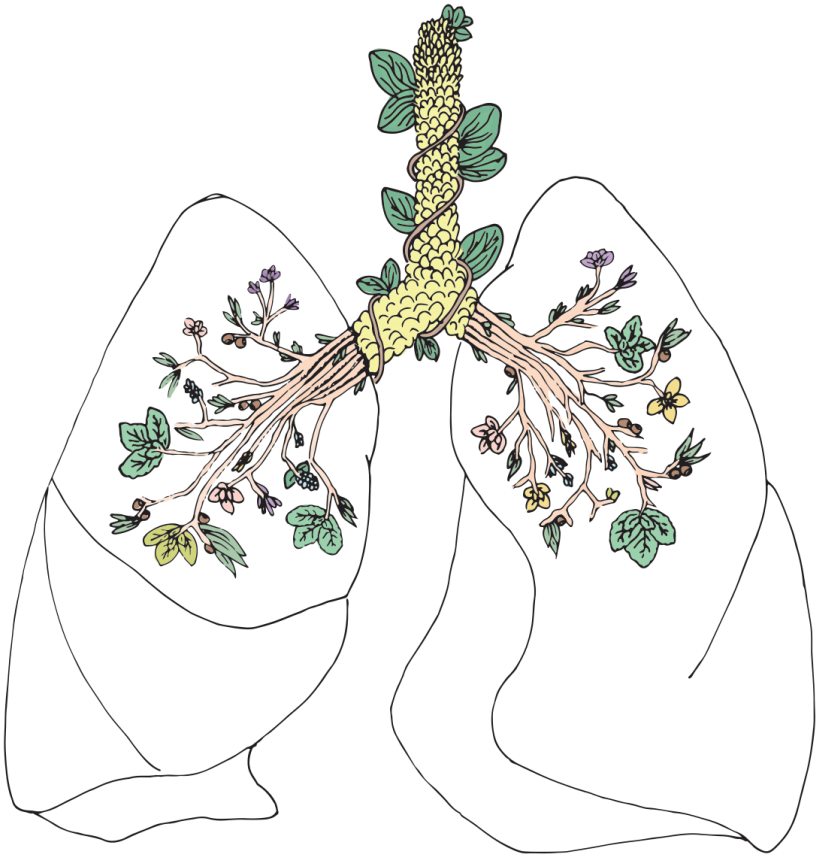
Sahin et al. (2018), Turkey[103]	N=34 34% males 61 (NR) years old FEV1pp=28 (NR) BMI (kg/m2) 25 (NR)	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face	NR	Nutritional and psychological support and breathing exercises	NR	NR
Ringbaek et al. (2013), Denmark[191]	N=22 50% males 69.4 (9.8) years old FEV1pp=32.8 (15.9) BMI (kg/m2) 26.4 (5)	Outpatient	7	Aerobic	2 times per week	Face-to-face	1 time per week	NR	Aerobic	Everyday
Romagnoli et al. (2005), Italy[193]	N=14 57% males 69 (8) years old FEV1pp=37 (9) BMI (kg/m2) 25 (3)	Inpatient	2 and (18 consecutive sessions)	Aerobic and resistance	7 times per week	Face-to-face	2 times per week	Behavioral and nutritional and psychosocial counseling	NR	NR
Rubí et al. (2010), Spain[259]	N=82 100% males 67 (8.5) years old	Outpatient	8	Aerobic and resistance	3 times per week	Face-to-face	NR	IMT and breathing techniques and	NS	NS

	FEV1pp=33 (9.8) BMI (kg/m2) 27.0 (5.9)							occupational therapy		
Ringbaek et al. (2000), Denmark [192]	N=24 6% males 61.8 (6.8) years old FEV1pp=49.5 (17.4) BMI (kg/m2) 26.1 (5.6)	Outpatient	8	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	Mobility and coordenation training and relaxation	Aerobic and resistance	NR
Ringbaek et al. (2008), Denmark [258]	N=141 36% males 69.1 (7.6) years old FEV1pp=32.5 (11.8) BMI (kg/m2) 24.6 (5.2)	Outpatient	7	Aerobic	2 times per week	Face-to-face	2 times per week	NR	Aerobic	5 times per week
Raskin et al. (2006), USA [254]	N=132 35% males 69 (8) years old FEV1pp=44 (15) BMI (kg/m2) 28 (7)	Outpatient	NR	NR	NR	Face-to-face	NR	NR	NR	NR

Riario-Sforza et al. (2005), Italy[257]	N=37 65% males 74.6 (NR) years old FEV1pp NR BMI (kg/m2) NR	Inpatient	4	Aerobic and resistance	2 times per week	Face-to-face	NR	Breathing exercises and bronchial hygiene	NR	NR
Resqueti et al. (2007), Spain[189]	N=19 Sex NR 66.9 (5.8) years old FEV1pp=27.5 (9) BMI (kg/m2) 25.3 (4.7)	Home-based	9	Aerobic and resistance	3-5 times per week	Face-to-face	Only 3 sessions through the course of the programme	IMT	Aerobic and resistance	5 times per week
Vincent et al. (2011), UK[104]	N=225 55% males 69 (8.8) years old FEV1pp NR BMI (kg/m2) NR	Outpatient	7	Aerobic and resistance	2 times per week	Face-to-face	2 times per week	NR	Aerobic	Everyday

Results are mean (SD) unless otherwise stated.

ADL, activities of daily living; BMI, body mass index; FEV1pp, forced expiratory volume in 1 sec, percentage predicted; IMT, inspiratory muscle training; NR, not reported in study; NS, not specified in study; UK, United Kingdom.



Chapter 3

Cut-off of the one-minute sit-to-stand test to detect functional impairment in people with chronic obstructive pulmonary disease

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ABSTRACT

Background: The 6-minute walking test (6MWT) is a widely used measure to assess functional status of people with chronic obstructive pulmonary disease (COPD). However, it requires a long hallway and might be time-consuming. Other simple measures might be useful as a first screening tool. We explored the predictive ability of the 1-minute sit-to-stand test (1-min STS) in discriminating people with COPD with or without functional impairment.

Methods: A receiver operating characteristics (ROC) curve analysis was performed. We determined a threshold for the 1-min STS to identify functional impairment based on different cut-offs of the 6MWT (300, 350, 400 and 450m).

Results: A total of 135 people with COPD were included. Except for the <450 m cut-off of the 6MWT, all other cut-offs identified 19.5 repetitions as the optimal cut-off point for the 1-min STS. All AUCs showed excellent discrimination (AUCs=0.812-0.901). The best AUC (<300 m cut-off) had an outstanding discrimination (0.901; 95%CI: 0.84-0.96; other AUCs 0.812-0.836) between people with or without functional impairment, with 86% specificity and 83% sensitivity.

Conclusions: A cut-off of 19.5 repetitions in the 1-min STS discriminates accurately people with COPD with a functional impairment. Future studies may validate our treatable trait candidate in other samples and investigate its utility in predicting other meaningful outcomes.

Introduction

Functional status (i.e., ability to perform daily activities required to meet basic needs, fulfil usual roles, and maintain health and well-being)[1] is known to deteriorate over time and is a strong predictor of acute exacerbations, hospitalisations and mortality in people with chronic obstructive pulmonary disease (COPD)[2,3]. Therefore, an accurate detection of functional impairment is fundamental to guide tailored interventions and improve the daily living of people with COPD.

The 6-minute walk test (6MWT) has been one of the most used measures to assess functional status[4]. However, it requires a 30m hallway and might be time consuming for routine outpatient consultations (i.e., complex instructions, time taken to conduct and repeat the test). Simple and quick, office-based field exercise tests such as the 1-minute sit-to-stand test (1-min STS)[5,6] may be a valuable option as a first screening tool before a detailed assessment of functional status, and subsequent treatment. Thus, we explored the predictive ability of the 1-min STS in discriminating people with COPD with or without functional impairment.

Material and methods

A cross-sectional study was conducted. This study was approved by the Ethics Committees of Administração Regional de Saúde do Centro (Ref. 73/2016, 16/2020, 85/2018), and Centro Hospitalar do Baixo Vouga (15-05-2019, 086892). Participants had to have a diagnosis of COPD (post bronchodilator forced expiratory volume in the first second [FEV_1]/forced vital capacity <0.70). Exclusion criteria comprised the presence of other respiratory diseases or any clinical condition that precluded participation in the assessment (i.e., signs of cognitive impairment or presence of a significant cardiovascular, neurological, musculoskeletal, immunological, or infectious disease). Eligible participants were identified during routine appointments at a hospital and primary healthcare centres, and all provided informed consent.

Sociodemographic (age and sex), anthropometric (height and weight to compute body mass index) and general clinical data (smoking status, comorbidities through the Charlson comorbidity index [CCI], use of long-term oxygen therapy and non-invasive ventilation, and number of acute exacerbations of COPD in the previous year) were collected. Additionally, activity-related dyspnoea was assessed with the modified Medical Research Council dyspnoea scale, impact of disease with the COPD assessment test, health-related quality of life with the Saint George's respiratory questionnaire, physical activity with the brief physical activity assessment tool and functional status with the 6MWT, 1-min STS, quadriceps maximal isometric voluntary contraction and handgrip strength using a handheld dynamometer. The 6MWT followed the international recommendations[7]. The 1-min STS consisted of the maximum number of complete sit-to-stands from a chair for 60 seconds, without using the hands or arms to assist movement[8].

A receiver operating characteristic (ROC) curve analysis was performed in R (v. 4.1.2). A complete case analysis was conducted with no missing data in the 1-min STS and 6MWT. All other measures collected had less than 10% missing data. We used four cut-offs of the 6MWT (300, 350, 400 and 450m) known to be associated with mortality in COPD[9]. Based on these cut-offs, a threshold for the 1-min STS was determined to identify functional impairment.

The Youden index was used to define the optimal cut-off point on the curve[10]. The area under the curve (AUC) was interpreted as: <0.5 – no discrimination, 0.5-0.69 poor discrimination, 0.7-0.79 acceptable discrimination, 0.8-0.89 – excellent discrimination, ≥0.9 outstanding discrimination[11]. People with COPD below or above the cut-off point in the 1-min STS were compared using independent samples t-test, Mann-Whitney U, chi-square, or fisher exact tests when appropriate.

Results

A total of 135 people with COPD were included. Participants were on average 68 years old, most were male (81%), with a mean FEV_1 of 57% predicted.

Except for the <450 m cut-off of the 6MWT, all other three cut-offs identified 19.5 repetitions as the optimal cut-off point for the 1-min STS (**Figure 1**). All AUCs showed excellent discrimination (AUCs=0.812-0.901). The <300 m cut-off of the 6MWT resulted in the best predictive ability in the 1-min STS with an outstanding discrimination (0.901; 95%CI: 0.84-0.96; other AUCs 0.812-0.836) between people with or without functional impairment, with 86% specificity and 83% sensitivity. A cut-off of 20, compared to 19 was superior in terms of a balanced specificity (86% vs 77%) and sensitivity (83% vs 86%).

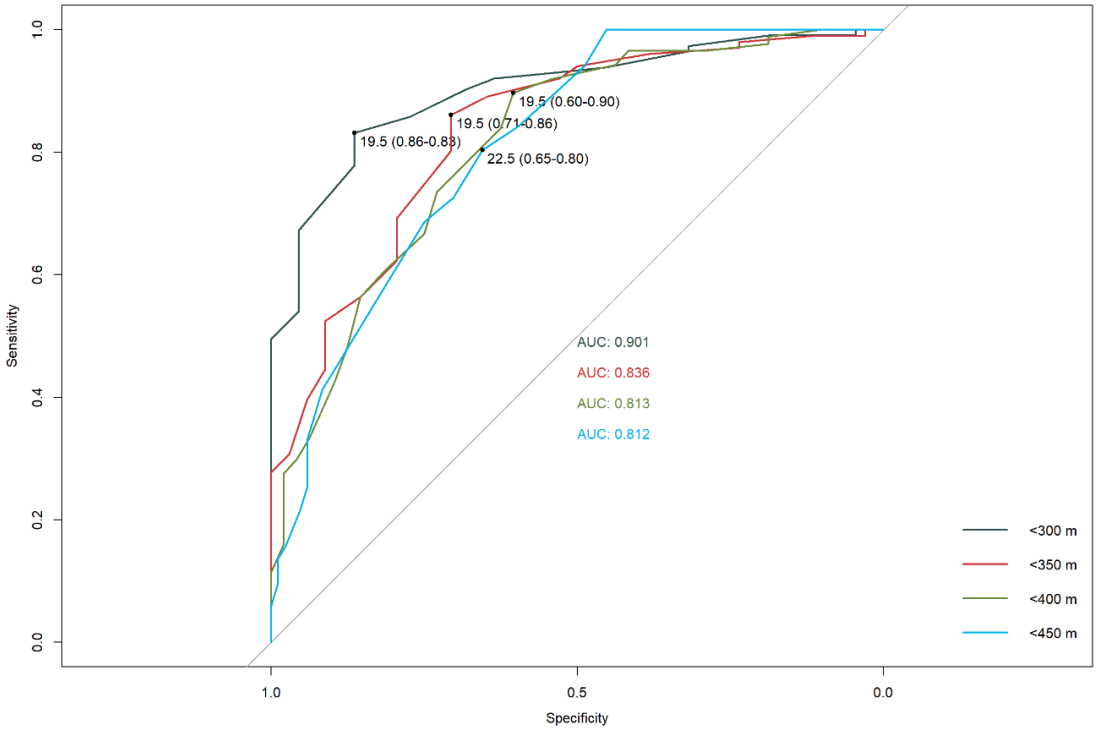

Figure 1. Receiver operating characteristics (ROC) curve to detect people with chronic obstructive pulmonary disease (COPD) with functional impairment in the 1-min sit-to-stand test, based on the different cut-offs (<300, <350, <400, 450 m) of the 6-min walk test (6MWT). AUC: Area under the

curve. The best cut-off of the 6MWT was <300 m which resulted in an AUC of 0.901 (CI% 0.84–0.96) with a specificity of 86% and sensitivity of 83%.

People with COPD below the cut-off point (n=38) had higher index of comorbidities (p=0.002), higher levels of activity-related dyspnoea (p=0.005), worse impact of the disease (p=0.004) and health-related quality of life (p=0.02), were less physically active (p=0.03), and had worse functional status in all parameters (p<0.001) compared to those with 20 or more repetitions in the 1-min STS (n=97) (**Table 1**).

Table 1. Characteristics of people with chronic obstructive pulmonary disease (COPD) (n=135) and comparison of people below (n=38) or above (n=97) the cut-off point (20 repetitions).

	Total sample (n=135)	**1-min STS <20 repetitions (n=38)**	**1-min STS ≥20 repetitions (n=97)**	**p-value**
Age, years	68.1±7.8	69.9±6.9	67.4±8.0	0.09
Sex				
Male, n (%)	109 (80.7)	27 (71.1)	82 (84.5)	0.12
Female, n (%)	26 (19.3)	11 (28.9)	15 (15.5)	
BMI, Kg/m^2	26.9 [24.5-30.8]	26.9 [17.5-31.0]	26.9 [24.5-30.8]	0.91
Smoking status, n (%)				
Never smoker	28 (20.7)	6 (15.8)	22 (22.7)	0.37
Former smoker	90 (66.7)	29 (76.3)	61 (62.9)	
Current smoker	17 (12.6)	3 (7.9)	14 (14.4)	
Pack-years, n	38.0 [12.4-67.0]	37.5 [8.0-61.5]	40.0 [13.6-70.0]	0.81
FEV_1, % predicted	56.6±19.4	52.5±18.4	58.3±19.7	0.12
GOLD grade, n (%)				

1	17 (13.3)	4 (11.1)	13 (14.1)	0.97
2	58 (45.3)	17 (47.2)	41 (44.6)	
3	45 (35.2)	13 (36.1)	32 (34.8)	
4	4 (6.2)	2 (5.6)	6 (6.5)	
CCI, score	4.0 [3.0-4.0]	4.0 [3.0-5.0]	4.0 [3.0-4.0]	0.02*
LTOT, n (%)	13 (9.6)	7 (18.4)	6 (6.2)	0.05
NIV, n (%)	17 (12.6)	4 (10.5)	13 (13.4)	0.78
AECOPD previous year, n	0.0 [0.0-1.0]	0.0 [0.0-1.0]	0.0 [0.0-1.0]	0.53
mMRC, score	2.0 [1.0-2.0]	2.0 [1.3-3.0]	2.0 [1.0-2.0]	0.005*
CAT, score	13.0 [8.0-19.0]	17.0 [10.3-21.0]	12.0 [6.0-17.0]	0.004*
GOLD groups, n (%)				
A	41 (30.4)	9 (25.0)	32 (34.8)	0.60
B	62 (45.9)	20 (55.6)	42 (45.7)	
C	2 (1.5)	0 (0)	2 (2.2)	
D	23 (17.0)	7 (19.4)	16 (17.4)	
SGRQ, score	42.0 [23.0-56.6]	51.6 [29.5-62.6]	38.2 [21.3-53.5]	0.02*
BPAAT, total score	1.0 [0.0-2.0]	0.0 [0.0-1.0]	1.0 [0.0-3.0]	0.03*
6MWT, m	420.0 [349.0-494.5]	305.0 [210.5-393.8]	461.0 [403.0-511.0]	<0.001*
1-min STS, repetitions	23.3±7.1	15.0±3.2	26.6±5.4	<0.001*
QMVC, KgF	31.1 [25.0-36.3]	27.6 [21.5-30.6]	32.8 [27.3-37.2]	<0.001*
Handgrip strength, KgF	34.2±9.2	29.3±9.5	36.2±8.3	<0.001*

Data are presented as mean±SD or median [1st quartile – 3rd quartile], unless otherwise stated. *Statistically significant ($p<0.05$).

BMI: Body mass index; FEV_1: Forced expiratory volume in the first second; GOLD: Global initiative for chronic obstructive lung disease; CCI: Charlson comorbidity index; LTOT: Long-term oxygen therapy; NIV: Non-invasive ventilation; AECOPD: Acute exacerbations of COPD; mMRC: modified Medical Research Council dyspnoea scale; CAT: COPD assessment test; SGRQ: Saint George's

respiratory questionnaire; BPAAT: Brief physical activity assessment tool; 6MWT: 6-minute walk test; 1-min STS: 1-minute sit-to-stand test; QMVC: Quadriceps maximum voluntary contraction.

Discussion

Our study showed a cut-off of 19.5 repetitions in the 1-min STS to discriminate people with COPD with or without a functional impairment accurately. This finding is consistent with a previous study which found the 1-min STS to be the best predictor of mortality in COPD with an AUC of 0.78, and an average of 19.5 repetitions in patients alive at 2 years compared to 11.8 repetitions in those who died[12]. Having less than 20 repetitions might be a good marker to identify functional impairment, hence being a good treatable trait candidate.

Although the <350 m is commonly used[13,14] and two novel sex-specific cut-offs of 6MWT have been proposed (394 m women, 404 m men)[3], in our study 300 m was the best cut-off to define functional impairment in the 1-min STS. Hence, different cut-offs of the 6MWT might be useful, depending on the endpoint of interest (e.g., mortality, functional impairment).

People with less than 20 repetitions had worse symptoms, health-related quality of life, physical activity levels and overall functional status. Therefore, it is possible that this cut-off in the 1-min STS is also a valuable predictor of these outcomes. Although we found people below the cut-off point to have a slightly higher index of comorbidities, the number of comorbidities does not provide information about the type and degree of comorbidities and therefore, an assessment of comorbidities would be of most value.

Our sample was unbalanced in terms of sex distribution (only 19% women). Hence, our cut-off might be particularly suitable for male patients with COPD and results should be further confirmed.

Conclusions

A cut-off of 19.5 repetitions in the 1-min STS detects functional impairment of people with COPD accurately. Future studies should validate our treatable trait candidate in other samples and investigate its utility in predicting other meaningful outcomes.

Acknowledgements

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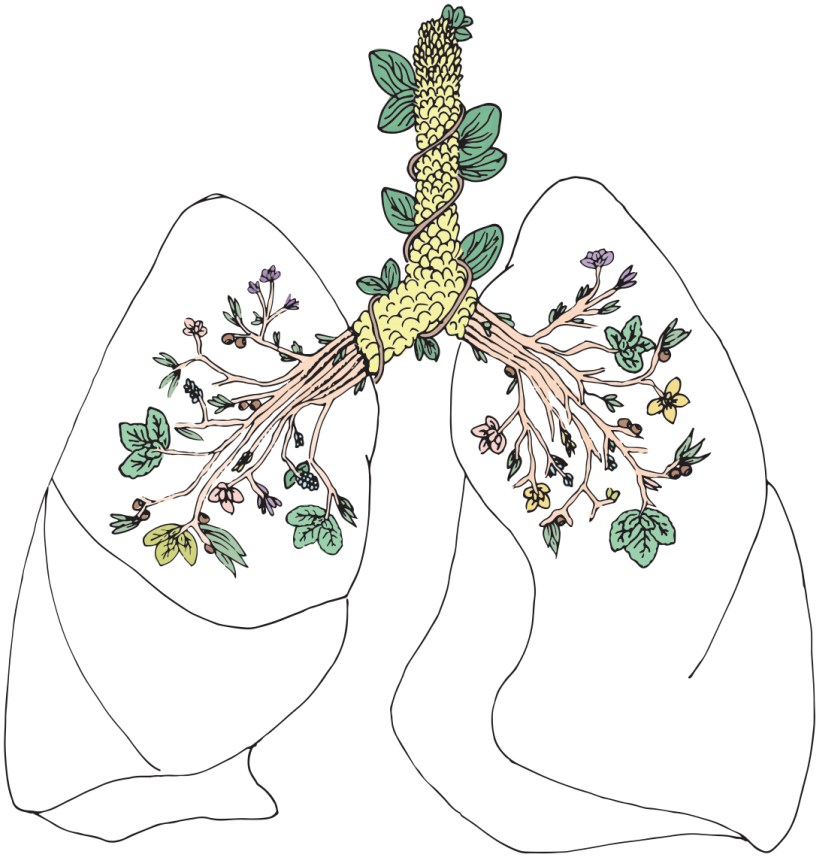

Chapter 4
Functional status following pulmonary rehabilitation: responders and non-responders

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ABSTRACT

Background: The 6-min walking test (6MWT) has been largely studied. Less is however known about responders and non-responders to pulmonary rehabilitation (PR) in other meaningful activities. We explored responders and non-responders, and predictors of response to PR in the 1-minute sit-to-stand test (1-min STS) and the 6MWT and compared both measures in classifying responders.

Methods: An observational study was conducted with 121 people with chronic obstructive pulmonary disease (COPD). Functional status was assessed before and after PR. Baseline differences between responders and non-responders were tested with Mann-Whitney U, Chi-square, or Fisher exact tests. Predictors were explored with binary logistic regressions. Agreement between both measures was assessed with Chi-square, Cohen's kappa and McNemar tests.

Results: There were 54.5% and 57.0% of responders in the 1-min STS and the 6MWT respectively. The proportion of responders was significantly different ($p=0.048$) with small agreement between the measures (kappa=0.180, $p=0.048$). Baseline 6MWT was the only significant predictor of response in 6MWT (OR=0.995, pseudo-r2=0.117, $p<0.001$). No significant predictors were found for the 1-min STS.

Conclusions: A large number of non-responders in functional status exists. The 1-min STS and the 6MWT should not be used interchangeably. Future studies should explore the added benefit of personalizing PR to this outcome and investigate other potential predictors.

Introduction

Pulmonary rehabilitation (PR) is a cornerstone for the daily management of people with chronic obstructive pulmonary disease (COPD)[1]. Improvements in physical, psychological, and social traits have been widely demonstrated with this comprehensive intervention[2]. However, there are still poor responders to PR, and this is partially influenced by the outcomes and measures selected[3].

Functional status, the individual's ability to perform normal daily activities required to meet basic needs, fulfil usual roles, and maintain health and well-being[4], is a highly valued outcome of PR by patients, informal caregivers, and healthcare professionals[5]. The 6-minute walking test (6MWT) is a widely used measure in PR[6], but its use is limited to long corridors and thus cannot be applied in all settings such as patients' homes. Furthermore, PR should be focused on improving not only people's ability to walk, but also other meaningful activities of daily living (ADL) such as sitting and standing from a chair. The 1-minute sit-to-stand test (1-min STS) has been much less used but has gained popularity in recent years, as it is a simple, reliable, and responsive test that elicits similar physiological responses to 6MWT[7-10]. Although a responder analysis for the 6MWT has been previously conducted[3,11-15], less is known about the responders in the 1-min STS and whether the type of response is similar in both measures.

Hence, this study aimed to explore the 1) responders and non-responders of PR in the 1-min STS and 6MWT, 2) predictors of response to PR in these measures and 3) agreement between both measures in classifying responders and non-responders to PR.

Materials and Methods

Study design and population

An observational study was conducted with data collected between 2017 and 2020. The study was approved by the Ethics Committee of Centro Hospitalar do Baixo

Vouga (ref. 086892) and informed consent was obtained by all participants. The study was reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement[16].

People with a spirometry-based diagnosis of COPD (Forced expiratory volume in 1 second [FEV_1]/ forced vital capacity [FVC] < 70)[17] that completed a community-based PR program were included. Those who had history of an acute cardiac/respiratory condition within the previous month; significant cardiac, musculoskeletal, or neuromuscular diseases that impaired the ability to perform tests; signs of cognitive impairment; and history of neoplasia or immunological disease were excluded. A complete case analysis was performed, with only variables with less than 5% missing data considered for the analysis[18].

Measurements

Sociodemographic and anthropometric data, such as age, sex, height, weight, and body mass index, were firstly collected. Clinical data collection consisted of smoking status, use of long-term oxygen therapy, use of non-invasive ventilation, comorbidities using the Charlson comorbidity index[19], severity of airflow limitation and symptom burden and risk of exacerbation as defined by the Global initiate for chronic obstructive lung disease (GOLD)[20], lung function with spirometry, respiratory-related hospital admissions, acute exacerbations of COPD, impact of the disease with the COPD assessment test (CAT)[21], dyspnea during activities with the modified medical research council dyspnea scale (mMRC)[22], health-related quality of life with the Saint George's respiratory questionnaire (SGRQ)[23], quadriceps maximum voluntary contraction with handheld dynamometer[24] (microFET2, Hoggan Health, The best Salt Lake City, Utah), handgrip strength with a hand dynamometer (W50174, Baseline, UK), physical activity with the Brief physical activity assessment tool (BPAAT)[25], balance with the Brief balance evaluation systems test (Brief-

BESTest)[26] and functional status with the 6MWT[27] and the 1-min STS[28]. Measurements were taken at baseline and after PR.

Participants with impairment in the 6MWT and 1-min STS were defined as those with values below 70% of the percentage predicted[29]. For the 6MWT percentage predicted was computed from the equation proposed by Marques and colleagues[30] and for the 1-min STS the reference values established by Strassmann and colleagues were used[28]. Responders were defined based on previously established minimal clinically important differences. For the 6MWT, responders were those with a pre-post mean difference of 30 meters or more and non-responders were those with a change of less than 30 meters[6]. For the 1-min STS, responders were those with a mean difference of 3 or more repetitions and non-responders were those with a mean difference of less than 3 repetitions[7].

Intervention

Participants completed a 12-week community-based PR program, with exercise training (aerobic and resistance muscle strength training) twice a week and education and psychosocial support once every 2 weeks. The program was provided by a multi-disciplinary team of physiotherapists, medical doctors, nurses, psychologists, dietitians, and social workers. Details of the program have been published elsewhere[31].

Data analysis

Descriptive statistics were computed for baseline characteristics. Effects of PR were explored through paired samples t-test, Wilcoxon, and Chi-square tests as appropriate, and effect sizes were computed using Cohen's d estimates.

Baseline differences between responders and non-responders were analyzed through independent samples t-tests, Mann-Whitney U tests, Chi-square or Fisher exact tests depending on data distribution. Normal distributed variables were reported

as mean±standard deviation, non-normal distributed variables as median [interquartile range], and frequencies as n (%).

Possible relationships between the mean difference on functional status and other outcomes were explored with Spearman correlations. Potential predictors of good response were explored with binary logistic regressions using a forward conditional model. Correlations were interpreted as <30 small, 0.30-0.49 medium and ≥0.50 large[32].

Chi-square tests were performed to compare the proportion of responders and non-responders in the 6MWT and in the 1-min STS. The agreement between the two measures in classifying responders and non-responders was assessed using Cohen's kappa and McNemar tests. Cohen's kappa was interpreted as ≤0 indicating no agreement, 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41– 0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement[33].

All analysis were performed using SPSS Statistics (v27, IBM). Plots were created using Prism (v7, GraphPad Software).

Results

Sample characteristics

One hundred and twenty-one individuals were included. Most participants were male (81.8%) with a median FEV_1 of 50% predicted, mostly GOLD grades 2 (43.0%) and 3 (38.8%) and GOLD group B (54.5%). At baseline 48.8% of participants had an impairment in the 1-min STS and 22.3% in the 6MWT. Full baseline characteristics of participants are presented in **Table 1**.

Table 1. Baseline characteristics and effects of pulmonary rehabilitation in people with chronic obstructive pulmonary disease (COPD) (n=121).

	Baseline	**Post**	**Δ Pre-post**	**Effect size (d)**	**p-value**
Age, years	69.0 [65.0-75.0]				
Sex, n (%)					
Male	99 (81.8)				
Female	22 (18.2)				
BMI, kg/m^2	26.4±4.8	26.4±4.6	-0.0±0.9	0.049	0.591
Underweight, <21, n (%)	13 (10.7)	10 (8.3)	3 (2.4)		<0.001*
Obese >30, n (%)	28 (23.1)	27 (22.5)	1 (0.6)		
Smoking status, n (%)					
Never	22 (18.2)				
Former	82 (67.8)				
Current	17 (14.0)				
Pack-years	31.2 [10.0-60.0]				
LTOT, n (%)	12 (9.9)				
NIV, n (%)	16 (13.2)				
CCI, score	4.0 [3.0-5.0]				
FEV_1 %predicted	50.0 [37.0-63.7]				
GOLD grade, n (%)					
1	9 (7.4)				
2	52 (43.0)				
3	47 (38.8)				
4	13 (10.7)				
GOLD group, n (%)					
A	32 (26.4)				
B	66 (54.5)				
C	3 (2.5)				
D	20 (16.5)				
Respiratory-related hospital admissions previous 12 months, n	0.0 [0.0-0.0]				
AECOPD previous 12 months, n	0.0 [0.0-1.0]				
mMRC, score	2.0 [1.0-3.0]	1.0 [1.0-2.0]	0.0 [-1.0-0.0]	0.39	<0.001*
CAT score, points	14.8±8.0	12.1±7.0	-2.7±5.8	0.46	<0.001*
SGRQ, total score	45.1±19.8	38.7±19.1	-6.4±12.2	0.52	<0.001*
QVC, kgF	30.6±8.4	33.4±10.2	2.7±8.7	0.31	<0.001*
Handgrip strength, KgF	34.3±9.2	34.0±10.1	-0.3±7.5	0.05	0.619

BPAAT, score	0.0 [0.0-3.0]	4.0 [2.0-6.0]	2.0 [1.0-4.0]	0.69	<0.001*
Brief-BESTest	19.0 [15.0-22.0]	21.0 [18.0-24.0]	2.0 [0.0-4.0]	0.63	<0.001*
1-min STS, repetitions	23.0 [18.0-29.0]	27.0 [21.0-33.0]	3.0 [0.0-6.0]	0.58	<0.001*
1-min STS <70% predicted, n (%)	59 (48.8)	38 (31.4)	21 (17.4)		<0.001*
6MWD, m	419.6 [331.9-508.6]	465.0 [386.7-540.3]	41.0 [7.0-75.3]	0.56	<0.001*
6MWD <70% predicted, n (%)	27 (22.3)	20 (16.5)	7 (5.8)		<0.001*

BMI: Body mass index; LTOT: Long-term oxygen therapy; NIV: Non-invasive ventilation; CCI: Charlson comorbidity index; FEV_1: Forced expiratory volume in the first second; GOLD: Global initiative for chronic obstructive lung disease; 1-4: Severity of airflow limitation, 1 – $FEV_1 \geq 80\%$ predicted, 2 – $50\% \leq FEV_1 < 80\%$ predicted, 3 – $30\% \leq FEV_1 < 50\%$ predicted, 4 - $FEV_1 < 30\%$ predicted; CAT: COPD assessment test; A-D: A – CAT < 10 points and 0-1 moderate-to-severe exacerbations (not leading to hospitalization), B – CAT ≥ 10 points and 0-1 moderate-to-severe exacerbations (not leading to hospitalization), C - CAT < 10 points and ≥ 2 moderate-to-severe exacerbations or ≥ 1 moderate-to-severe exacerbations leading to hospitalization, D - CAT ≥ 10 points and ≥ 2 moderate-to-severe exacerbations or ≥ 1 moderate-to-severe exacerbations leading to hospitalization; AECOPD: Acute exacerbations of COPD; mMRC: modified Medical research council dyspnea scale; SGRQ: Saint George's respiratory questionnaire; QVC: Quadriceps voluntary contraction; BPAAT: Brief physical activity assessment tool; Brief-BESTest: Brief-Balance evaluation system test; 1-min STS: 1-minute sit-to-stand test; 6MWD: 6-minute walking distance. Δ represents the mean or median difference according to data distribution.

General effects of PR

PR was effective in improving all outcomes ($p<0.05$), excepting BMI ($p=0.591$) and handgrip strength ($p=0.619$) (**Table 1**). Improvements, above the minimal clinically important difference, were seen in the number of repetitions on the 1-min STS ($median_{diff}$ 3.0, ES=0.58, $p<0.001$) and on the distance walked in the 6MWT ($median_{diff}$ 41.0, ES=0.56, $p<0.001$).

Negative and small to moderate correlations were found between the mean change in 1-min STS and mean change in the mMRC (r_s=-0.249; 95%CI [-0.415; -0.068], p=0.006) and the SGRQ (r_s=-0.279; 95%CI [-0.441; -0.099], p=0.002). A positive and moderate correlation was found between mean change of the 1-min STS and mean change of the 6MWT (r_s=0.317; 95%CI [0.141;0.473], p<0.001).

Small correlations were also found between mean change in the 6MWT and mean change in the SGRQ r_s=-0.197; 95%CI [-0.368; -0.013], p=0.031) and the handgrip strength (r_s=0.193; 95%CI [0.010;0.364], p=0.034). No other correlations were found (**Table SA.1** and **SA.2** of supplementary material).

Responders, non-responders and predictors of response

After PR, 54.5% of patients were responders in the 1-min STS, and 57% in the 6MWT. Differences between baseline characteristics of responders and non-responders in both 1-min STS and 6MWT, were found. Responders in the 1-min STS had higher baseline BMI (27.0 [24.3-30.1] vs non-responders 24.2 [22.1-28.3] kg/m2, p=0.008) and lower baseline performance in the 1-min STS (22.5 [18.0-27.0] vs non-responders 25.0 [20.5-31.0] repetitions, p=0.035) than non-responders. Responders in the 6MWT had lower BPAAT scores (0.0 [0.0-2.0] vs non-responders 1.0 [0.0-4.0] points, p=0.038), walked a lower distance in the 6MWT (390.0 [295.0-480.0] vs non-responders 489.2 [363.2-534.5] m, p<0.001) and had a higher percentage of people with a functional capacity impairment in the 6MWT (30.4 vs non-responders 11.5%, p=0.013) than non-responders.

When comparing the subgroups of responders and non-responders to both tests (n=43, 35.5% vs n=78, 64.5%), differences were found with responders having a higher BMI (27.5 [25.0-30.2] vs non-responders 24.6 [22.4-28.6] kg/m^2, p=0.006), worse performance in the 1-min STS (22.0 [17.5-26.5] vs 24.5 [20.0-30.0] repetitions, p=0.041), more frequently impaired in the 1-min STS (65.1 vs non-responders 39.7%, p=0.008), lower distance in the 6MWT (386.4 [287.4-478.1] vs non-responders 441.3

[356.2-523.5] m, p=0.042) and more frequently impairments in the 6MWT (34.5 vs non-responders 15.4%, p=0.014). No other significant differences were found.

Detailed comparisons of baseline characteristics between responders and non-responders can be found in **Table 2**.

Table 2. Baseline differences between responders and non-responders to pulmonary rehabilitation of people with chronic obstructive pulmonary disease (COPD) in the 1-minute sit-to-stand test and the 6-minute walking test (n=121).

	1-minute STS			**6MWT**			**1-min STS and 6MWT**		
	Responders (n=66)	Non-responders (n=55)	p-value	Responders (n=69)	Non-responders (n=52)	p-value	Responders in both measures (n=43)	Non-responders in both measures (n=78)	p-value
Age, years	69.0 [64.0-75.0]	70.0 [67.5-74.5]	0.150	69.0 [65.0-71.5]	69.0 [65.0-71.5]	0.344	69.0 [61.5-73.0]	70.0 [66.0-75.0]	0.178
Sex, n (%)									
Male	50 (75.8)	49 (89.1)	0.058	57 (82.6)	42 (80.8)	0.795	34 (79.1)	65 (83.3)	0.561
Female	16 (24.2)	6 (10.9)		12 (17.4)	10 (19.2)		9 (20.9)	13 (16.7)	
BMI, kg/m^2	27.0 [24.3-30.1]	24.2 [22.1-28.3]	0.008	27.0±4.6	25.7±5.0	0.143	27.5 [25.0-30.2]	24.6 [22.4-28.6]	0.009
Smoking status, n (%)									
Never	13 (19.7)	9 (16.4)		11 (15.9)	11 (21.2)		6 (14.0)	16 (20.5)	
Former	46 (69.7)	36 (65.5)	0.475	49 (71.0)	33 (63.5)	0.668	32 (74.4)	50 (64.1)	0.504
Current	7 (10.6)	10 (18.2)		9 (13.0)	8 (15.4)		5 (11.6)	12 (15.4)	
Pack-years, n	38.8 [12.3-64.0]	30.0 [6.1-55.0]	0.342	34.1 [13.1-60.0]	28.5 [3.2-69-0]	0.756	38.8 [17.0-60.0]	30.0 [5.9-60.8]	0.510
LTOT, n (%)	8 (12.1)	4 (7.3)	0.374	6 (8.7)	6 (11.5)	0.605	4 (9.3)	8 (10.3)	0.867
NIV, n (%)	11 (16.7)	5 (9.1)	0.221	11 (15.9)	5 (9.6)	0.309	9 (20.9)	7 (9.0)	0.063
CCI, score	4.0 [3.0-5.0]	4.0 [3.0-5.0]	0.513	4.0 [3.0-5.0]	4.0 [3.0-4.5]	0.313	4.0 [3.0-5.0]	4.0 [3.0-5.0]	0.980
FEV_1, % predicted	54.3±17.0	47.8±18.4	0.049	50.4±16.0	52.6±20.3	0.521	54.0 [41.0-63.0]	47.0 [36.0-63.7]	0.273
GOLD grade, n (%)									
1	6 (9.1)	3 (5.5)	0.054	3 (4.3)	6 (11.5)	0.180	2 (4.7)	7 (9.0)	0.064
2	33 (50.0)	19 (34.5)		33 (47.8)	19 (36.5)		25 (58.1)	27 (34.6)	

3	24 (36.4)	23 (41.8)		28 (40.6)	19 (36.5)		14 (32.6)	33 (42.3)	
4	3 (4.5)	10 (18.2)		5 (7.2)	8 (15.4)		2 (4.7)	11 (14.1)	
GOLD group, n (%)									
A	14 (21.2)	18 (32.7)		16 (23.2)	16 (30.8)		9 (20.9)	23 (29.5)	
B	39 (59.1)	27 (49.1)	0.525	42 (60.9)	24 (46.2)	0.405	28 (65.1)	38 (48.7)	0.375
C	2 (3.0)	1 (1.8)		1 (1.4)	2 (3.8)		1 (2.3)	2 (2.6)	
D	11 (16.7)	9 (16.4)		10 (14.5)	10 (19.2)		5 (11.6)	15 (19.2)	
Respiratory-related hospital admissions previous 12 months, n	0.0 [0.0-0.0]	0.0 [0.0-0.0]	0.775	0.0 [0.0-0.0]	0.0 [0.0-0.0]	0.298	0.0 [0.0-0.0]	0.0 [0.0-0.0]	0.455
AECOPD previous 12 months, n	0.0 [0.0-1.0]	0.0 [0.0-1.0]	0.083	0.0 [0.0-1.0]	0.0 [0.0-1.0]	0.983	0.0 [0.0-1.0]	0.0 [0.0-1.0]	0.399
mMRC, score	2.0 [1.0-3.0]	2.0 [1.0-3.0]	0.441	2.0 [1.0-3.0]	2.0 [1.0-3.0]	0.679	2.0 [1.0-2.5]	2.0 [1.0-3.0]	0.420
CAT, total score	15.9±8.2	13.4±7.5	0.078	15.5±7.9	13.8±8.0	0.228	13.2±7.8	14.4±8.0	0.425
SGRQ, total score	53.7 [30.2-62.8]	43.1 [30.1-53.5]	0.060	52.6 [30.1-61.8]	45.1 [30.2-56.9]	0.321	53.7 [29.6-61.1]	45.1 [30.2-57.4]	0.399
QVC, KgF		31.0±8.2	0.561	30.7±8.9	30.4±7.7	0.875	30.1±9.1	30.8±8.0	0.679
Handgrip strength, KgF	34.3±10.4	34.4±7.7	0.924	34.3±9.9	34.3±8.4	0.987	34.6±10.5	34.2±8.5	0.803
BPAAT, score	0.0 [0.0-3.0]	1.0 [0.0-3.0]	0.513	0.0 [0.0-2.0]	1.0 [0.0-4.0]	0.038	0.0 [0.0-1.0]	0.5 [0.0-3.0]	0.156

Brief-BESTest, score	19.0 [14.0-22.0]	18.0 [16.0-22.0]	0.876	18.0 [15.0-22.0]	19.0 [16.0-22.0]	0.373	19.0 [13.5-22.0]	18.0 [16.0-22.0]	0.580
1-min STS, repetitions	22.5 [18.0-27.0]	25.0 [20.5-31.0]	0.035	22.0 [18.0-28.0]	25.5 [20.0-31.5]	0.113	22.0 [17.5-26.5]	24.5 [20.0-30.0]	0.041
1-min STS <70% predicted, n (%)	37 (56.1)	22 (40.0)	0.078	37 (53.6)	22 (42.3)	0.218	28 (65.1)	31 (39.7)	0.008
6MWD, m	404.4±135.2	419.2±115.9	0.524	390.0 [295.0-480.0]	489.2 [363.2-534.5]	<0.001	386.4 [287.4-478.1]	441.3 [356.2-523.5]	0.042
6MWD <70% predicted, n (%)	17 (25.8)	10 (18.2)	0.319	21 (30.4)	6 (11.5)	0.013	15 (34.9)	12 (15.4)	0.014

BMI: Body mass index; LTOT: Long-term oxygen therapy; NIV: Non-invasive ventilation; CCI: Charlson comorbidity index; FEV1: Forced expiratory volume in 1 second; GOLD: Global initiative for chronic obstructive lung disease; 1-4: Severity of airflow limitation, 1 – FEV1 ≥ 80% predicted, 2 – 50% ≤ FEV1 < 80% predicted, 3 – 30% ≤ FEV1 < 50% predicted, 4 - FEV1 < 30% predicted; CAT: COPD assessment test; A-D: A – CAT < 10 points and 0-1 moderate-to-severe exacerbations (not leading to hospitalization), B – CAT ≥ 10 points and 0-1 moderate-to-severe exacerbations (not leading to hospitalization), C - CAT < 10 points and ≥ 2 moderate-to-severe exacerbations or ≥ 1 moderate-to-severe exacerbations leading to hospitalization, D - CAT ≥ 10 points and ≥ 2 moderate-to-severe exacerbations or ≥ 1 moderate-to-severe exacerbations leading to hospitalization; AECOPD: Acute exacerbations of COPD; mMRC: modified Medical research council dyspnea scale; SGRQ: Saint George's respiratory questionnaire; QVC: Quadriceps voluntary contraction; BPAAT: Brief physical activity assessment tool; Brief-BESTest: Brief-Balance evaluation systems test; 1-min STS: 1-minute sit-to-stand test; 6MWD: 6-minute walking distance.

A positive and moderate correlation was found between the mean difference in the 1-min STS and baseline BMI (r_s=0.32, 95%CI [0.143;0.474], p<0.001). Negative and low correlations were also found between the mean difference in the 1-min STS and baseline GOLD grade (r_s=-0.22, 95%CI [-0.390; -0.040], p=0.014) and 1-min STS (rs=-0.20, 95%CI [-0.368; -0.014], p=0.030) (**Table S.3** supplementary file).

Negative and moderate and low correlations were found between the mean dif-ference in the 6MWT and baseline 6MWT (r_s=-0.33, 95%CI [-0.483; -0.154], p<0.001) and baseline 1-min STS (r_s=-0.19, 95%CI [-0.360; -0.005], p=0.038). No other significant correlations were found (Table A.3 and SA.4 supplementary file).

No significant predictors were found for being a good responder in the 1-min STS (p=0.05) (**Table AS.5** supplementary file). Baseline 6MWD was the only significant predictor of response to PR in the 6MWT (p=0.002), with decreases of 1m in baseline 6MWT corresponding to 1.0 increased odds of being a good responder (OR=0.995 95%CI [0.992;0.998], pseudo-r^2=0.117, p<0.001) (**Table SA.6** supplementary file).

Comparison of responders and non-responders classified with the 1-min STS and 6MWT

There were significant differences in the proportion of responders and non-responders in the two measures (p=0.048); with 35.5% being responders in both measures, 24.0% non-responders in both measures, 19.0% responders only in the 1-min STS, and 21.5% responders only in the 6MWT.

There was a slight but significant agreement between the two measures (kappa=0.180, p_{kappa}=0.048, p_{McNema}r=0.755) in classifying responders and non-responders. Individual distributions of mean differences achieved in both tests across responders and non-responders can be visualized in **Figure 1**.

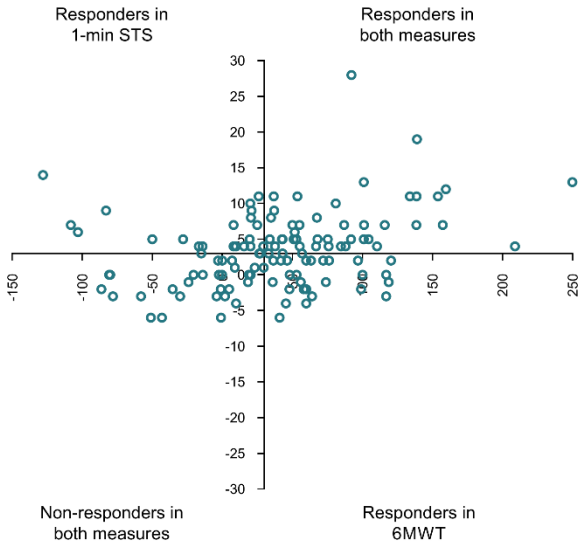

Figure 1. Scatter plot of responders and non-responders to community-based pulmonary rehabilitation of people with chronic obstructive pulmonary disease (COPD) with the mean difference achieved in the six-minute walking test (X axis) and 1-minute sit-to-stand test (Y axis). Axes are intersected at minimal clinically important differences, 6MWT: 30m and 1-min STS: 3 repetitions. 1-min STS: 1-min sit-to-stand test; 6MWT: Six-minute walking test.

Discussion

Our study has shown that although PR is effective in improving functional status, there is also a significant number of non-responders in this outcome, independently of the measure used. This result is coherent with other studies, that have shown a large and similar proportion of non-responders in the 6MWT after PR[3,34-36]. Since functional status is a highly valued outcome[5,37] and one of the goals of PR is to improve the physical condition, it is important to better understand why some patients are not responding to the intervention in several activities of daily living, and how to better tailor PR to these patients.

Including ADL-specific training to PR has been shown to further improve the impact of the disease[38], average oxygen uptake and time to perform ADL activities,

such as stair climbing, which were correlated with improvements in the 6MWT[39]. Nonetheless, authors did not perform a responder analysis and therefore the impact of such intervention in the proportion of responders is unknown. It is therefore possible that the addition of specific ADL training to the standard aerobic and resistance training is needed, at least for some people, to achieve additional benefits not only in terms of functional capacity but also functional performance, and hence, optimize each person's functional status. Furthermore, since non-responders seem to be more fit at baseline than those responding to PR, it is possible that these measures are not responsive enough for these patients, or that more challenging exercise modalities such as high-intensity functional training[40] are needed. The best way to tailor PR to this outcome is, however, yet to be determined.

Additionally, these measures might not be sufficient to have a comprehensive view of the patient functional status, as they are focused on functional capacity. In fact, only low to moderate correlations were found between both physical tests and between these tests and other important outcomes, such as health-related quality of life. Similar results have been reported during acute states of the disease[41]. Therefore, using composite measures of functional capacity and functional performance, such as the combined use of physical tests and patient-reported outcome measures might be the way forward to provide a full picture of the patient functional status.

Patients with higher baseline BMI, worse physical activity levels, worse performance in the 1-min STS and in the 6MWT seem to be better responders in functional status. Having a worse baseline status and being a good responder is a commonly observed pattern for several outcomes, and it might be due to having more room for improvement[3,36,42]. Low baseline 6MWD was the only significant predictor of good response, with little explanation of the variability in the response. Hence, reasons for being a good or poor responder in this outcome remain unclear and require further investigation.

Other patient features, such as muscle function or body composition could potentially explain why patients respond or not to the intervention. A previous study has shown isometric quadriceps muscle strength to be a predictor of response to PR in the 6MWT[43]. However, we did not find it as a predictor and a recent study found no correlations between isometric measurements of muscle function and the 1-min STS, with muscle power measured by isokinetic or the 5 times STS, being the main contributors to the 1-min STS and 6MWT performance[44]. Hence, dynamic measurements and more robust measures (e.g., isokinetic) should be further explored in the future, as they could be highly relevant to assess and predict the response to PR.

Responders and non-responders in each test shared some features at baseline, such as similar age, severity of airflow obstruction, comorbidities, symptoms, muscle strength, health-related quality of life and balance. Thus, improvements in functional status seem to occur independently of these characteristics, and therefore they should not prevent healthcare professionals from planning exercise interventions to target this outcome.

We found significant differences in the proportion of responders between the 1-min STS and the 6MWT with a small agreement between the two measures in classifying responders and non-responders. This result suggests that using the 1-min STS and the 6MWT interchangeably might not be the most appropriate approach, as it can lead to a misclassification of the person as a good or poor responder to PR in this outcome. In fact, since both tests mimic different ADL, it is possible that some people find more difficult to stand from a chair repeatedly than to do a self-paced walk and vice-versa. Although similar physiological responses (e.g., oxygen consumption) have been found between both measures[7], other factors such as muscle fatigue or mobility may play a role in explaining the differences in response to the two measures. Differences due to the different contribution of muscle strength, power, and endurance to the 1-min STS and the 6MWT might explain differences obtained[43], but this was

not tested in this study. Caution is therefore recommended when using 1-min STS as a surrogate measure of 6MWT.

This study has some limitations. Although we explored correlations between the type of response with commonly used measures, other measures such as DEXA or isokinetic muscle assessment could have provided stronger predictors of response to PR in terms of functional status. Additionally, other patient characteristics such as fatigue, objective physical activity, and mobility may influence the response to PR in this outcome and should therefore be explored in future studies.

Conclusions

Community-based pulmonary rehabilitation improves functional status of people with COPD; however, a large number of non-responders exist. Low baseline 6MWD was the only significant predictor of good response in the 6MWT, with no predictors found for the 1-min STS. Future studies should explore the added benefit of tailoring PR to this outcome (e.g., including ADL training) to maximize the response to PR. The small agreement in classifying responders and non-responders between 1-min STS and 6MWT suggests that these measures should not be used interchangeably to assess results of PR in this outcome. Future prospective studies with larger samples are needed to confirm these findings and explore other potential factors influencing the response to PR in this outcome.

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Supplementary material

Table S1. Correlation coefficients between mean difference in 1-minute sit-to-stand test and mean differences of all variables included in analysis.

Variable	Correlation coefficient	95% CI	p-value
BMI	-0.097	0.294;-0.276	0.294
mMRC	-0.249	-0.415;-0.068	**0.006**
BPAAT	-0.148	-0.324;0.037	0.106
CAT	-0.118	-0.295;0.067	0.197
SGRQ	-0.279	-0.441;-0.099	**0.002**
6MWT	0.317	0.141;0.473	**<0.001**
QVC	0.071	-0.115;0.252	0.441
Handgrip strength	0.096	-0.089;0.275	0.295
Brief-BESTest	0.023	-0.167;0.212	0.806

BMI: Body mass index; mMRC: Modified medical research council dyspnoea scale; BPAAT: Brief physical activity assessment tool; CAT: COPD assessment test; SGRQ: Saint George's respiratory questionnaire; 6MWT: Six-minute walk test; QVC: Quadriceps voluntary contraction; Brief-BESTest: Brief-Balance evaluation systems test.

Table S2. Correlation coefficients between mean difference in 6-minute walk test and mean differences of all variables included in analysis.

Variable	Correlation coefficient	95% CI	p-value
BMI	-0.075	-0.256;0.111	0.418
mMRC	-0.158	-0.333;0.027	0.084
BPAAT	0.152	-0.034;0.327	0.098
CAT	-0.025	-0.208;0.159	0.783
SGRQ	-0.197	-0.368;-0.013	**0.031**
QVC	0.059	-0.127;0.241	0.524
Handgrip strength	0.193	0.010;0.364	**0.034**
1-min STS	0.317	0.141;0.473	**<0.001**
Brief-BESTest	0.099	-0.092;0.283	0.294

BMI: Body mass index; mMRC: Modified medical research council dyspnoea scale; BPAAT: Brief physical activity assessment tool; CAT: COPD assessment test; SGRQ: Saint George's respiratory questionnaire; 1-min STS: 1-minute sit-to-stand test; QVC: Quadriceps voluntary contraction; Brief-BESTest: Brief-Balance evaluation systems test.

Table S3. Correlation coefficients between mean difference in 1-minute sit-to-stand test and baseline characteristics.

Variable	Correlation coefficient	95% CI	p-value
Sex	0.148	-0.037;323	0.106
Age	-0.060	-0.241;0.126	0.517
Smoking status	-0.138	-0.314;0.047	0.130
Pack-years	0.047	-0.140;0.231	0.612

CCI_Baseline	-0.022	-0.204;0.163	0.814
BMI	0.318	0.143;0.474	**<0.001**
LTOT	-0.039	-0.221;0.146	0.672
NIV	0.074	-0.112;0.254	0.422
Hospital admissions previous 12 months	-0.038	-0.220;0.147	0.681
AECOPD previous 12 months	0.144	-0.041;0.319	0.116
mMRC	0.062	-0.123;0.243	0.500
BPAAT	.073	-0.112;0.254	0.423
CAT	0.118	-0.067;0.295	0.198
GOLD group (A-D)	0.042	-0.143;0.224	0.647
SGRQ	0.129	-0.056;0.307	0.159
FEV1, % predicted	0.164	-0.021;0.337	0.073
GOLD grade (1-4)	-0.222	-0.390;-0.040	**0.014**
6MWT	0.011	-0.173;0.195	0.902
QVC	0.078	-0.107;0.258	0.393
1-min STS	-0.198	-0.368;-0.014	**0.030**

CCI: Charlson comorbidity index; BMI: Body mass index; LTOT: Long-term oxygen therapy; NIV: Non-invasive ventilation; mMRC: Modified medical research council dyspnoea scale; BPAAT: Brief physical activity assessment tool; CAT: COPD assessment test; GOLD: Global initiative for chronic lung disease; SGRQ: Saint George's respiratory questionnaire; FEV1: Forced expiratory volume in 1 second; 6MWT: Six-minute walk test; QVC: Quadriceps voluntary contraction; 1-min STS: 1-minute sit-to-stand test.

Table S4. Correlation coefficients between mean difference in 6-minute walk test and baseline characteristics.

Variable	**Correlation coefficient**	**95% CI**	**p-value**
Sex	0.102	-0.083;0.281	0.263
Age	0.094	-0.091;0.273	0.305
Smoking status	0.021	-0.163;0.204	0.817
Pack-years	-0.106	-0.286;0.082	0.254
CCI_Baseline	0.109	-0.076;0.287	0.234
BMI	0.114	-0.072;0.291	0.215
LTOT	-0.080	-0.260;0.105	0.381
NIV	0.000	-0.183;0.184	0.997
Hospital admissions previous 12 months	-0.032	-0.215;0.152	0.725
AECOPD previous 12 months	0.112	-0.073;0.290	0.222
mMRC	-0.010	-0.193;0.174	0.912
BPAAT	-0.109	-0.287;0.076	0.234
CAT	0.114	-0.071;0.291	0.214
GOLD group (A-D)	0.057	-0.128;0.238	0.533
SGRQ	0.091	-0.095;0.271	0.321

FEV1, % predicted	-0.009	-0.193;0.175	0.919
GOLD grade (1-4)	-0.042	-0.224;0.142	0.645
6MWT	-0.329	-0.483;-0.154	<**0.001**
QVC	-0.095	-0.274;0.090	0.300
Handgrip strength	-0.062	-0.243;0.123	0.502
1-min STS	-0.189	-0.360;-0.005	**0.038**
Brief-BESTest	-0.077	-0.260;0.113	0.414

CCI: Charlson comorbidity index; BMI: Body mass index; LTOT: Long-term oxygen therapy; NIV: Non-invasive ventilation; mMRC: Modified medical research council dyspnoea scale; BPAAT: Brief physical activity assessment tool; CAT: COPD assessment test; GOLD: Global initiative for chronic lung disease; ; SGRQ: Saint George's respiratory questionnaire; FEV1: Forced expiratory volume in 1 second; 6MWT: Six-minute walk test; QVC: Quadriceps voluntary contraction

Table S5. Logistic regression for response in 1-min STS.

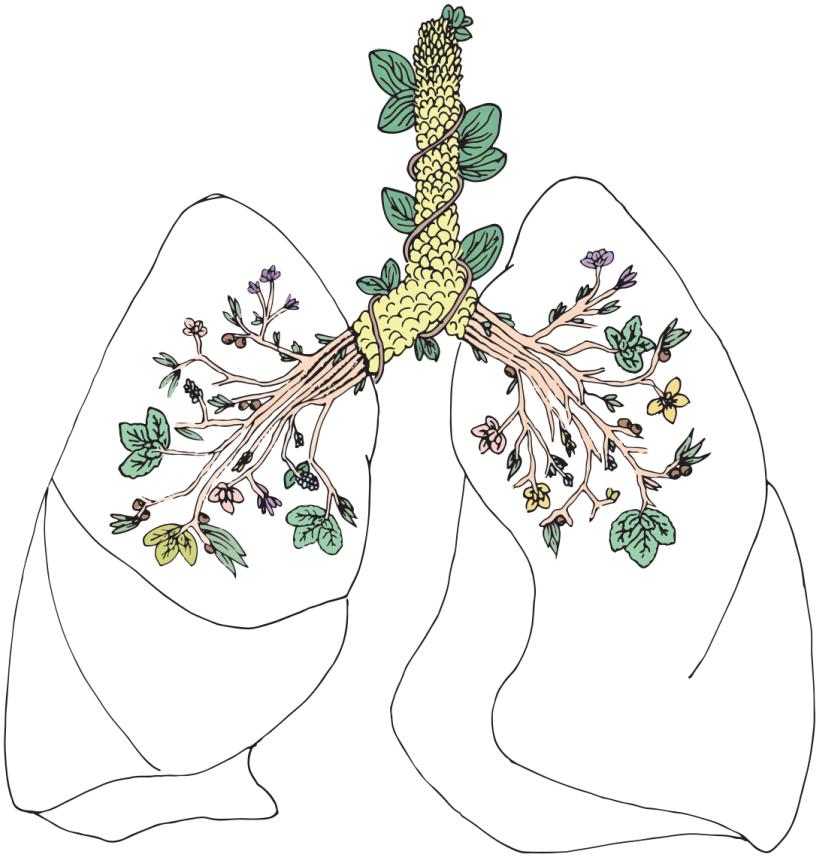
Variables in equation	**Coefficient**	**p-value**	**Odds ratio**	**95%CI**
Baseline 1-min STS	-0.042	0.050	0.958	0.919;1.000
Constant	1.233	0.030	3.433	
Variables not in equation				
Baseline BMI		0.116		

1-min STS: 1-minute sit-to-stand test; BMI: Body mass index

Table S.6. Logistic regression for response in 6MWT.

Variables in equation	Coefficient	p-value	Odds ratio	95%CI
Baseline 6MWT	-0.005	0.002	0.995	0.992;0.998
Constant	2.452	<0.001	11.613	
Variables not in equation				
Baseline 1-min STS		0.168		

6MWT: Six-minute walk test; 1-min STS: 1-minute sit-to-stand test



Chapter 5

The presence of extra-pulmonary treatable traits increases the likelihood of responding to pulmonary rehabilitation

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ABSTRACT

Background: Studies suggest that people with chronic obstructive pulmonary disease (COPD) who are worse at baseline respond better to pulmonary rehabilitation (PR). Identifying treatable traits (TT) may help to distinguish responders from non-responders. We explored the impact of PR on extra-pulmonary traits of people with COPD and whether the presence of TT influences the type of response to PR.

Methods: A comprehensive assessment of 9 TT including symptoms (dyspnoea, fatigue, anxiety and depression), functional capacity, deconditioning, balance, impact of the disease and health-related quality of life was conducted before and after a 12-week community-based PR programme. Pre-post differences between people with or without each TT at baseline were compared with independent samples t-tests or Mann-Whitney U tests. Proportion of responders between groups were explored with chi-square tests and odds ratio.

Results: 102 people with COPD were included (70 [65; 75] years old, 78% male, FEV_1 47 [36; 60] %predicted). They had a median of 3 (out of 9) TTs per person and each patient responded on average to 5 (out of 9) outcomes of PR. People with TT were more responsive than those without them in all outcomes ($p<0.05$) except for the 1-minute sit-to-stand test. The presence of TT increased 4 to 20 times the likelihood of being a good responder.

Conclusions: Identification of baseline extra-pulmonary TT in people with COPD showed the potential to inform on PR responsiveness and might therefore be an important strategy for patient prioritization, treatment personalisation (i.e., activation of the most suitable components) and optimisation.

Introduction

A treatable traits strategy has been advocated for people with chronic respiratory diseases, to personalise medicine to the individual's needs and therefore, improve outcomes of interventions[1,2]. In general, only necessary treatments are provided according to the identified treatable traits. This strategy has been shown to be more effective than usual care in improving health-related quality of life and asthma control in patient with asthma[3].

Pulmonary rehabilitation (PR) provides a unique opportunity to address various treatable traits simultaneously and to implement person-centred treatments in chronic respiratory diseases, namely chronic obstructive pulmonary disease (COPD). In fact, it is a multicomponent intervention moving towards more personalised care where ideally the best strategies are activated according to patients' needs[4].

PR has multiple benefits (e.g., less symptoms, better exercise tolerance, improved health-related quality of life) for people with COPD[5,6]. However, there are non-responders in one or more outcomes (e.g., anxiety, fatigue, functional status) and the magnitude of response to PR has been found to be greater in people who are worse at baseline (e.g., higher symptom burden)[7-10]. Despite its comprehensiveness, a recent systematic review has shown that treatable traits have been poorly addressed in PR trials[11].

Hence, identifying treatable traits might help to better personalise PR (e.g., select/activate the most appropriate components for each treatable trait), and distinguish responders from non-responders, which could aid optimisation of the intervention in the future.

This study aimed to explore the impact of PR on extra-pulmonary treatable traits of people with COPD and to explore the influence of the presence of these traits on being a responder or non-responder to PR.

Materials and Methods

This was a retrospective study of data collected between October 2017 and November 2021 and is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[12]. The study was approved by the Ethics Committees of Administração Regional de Saúde do Centro (Ref. 73/2016, 16/2020, 85/2018), and Centro Hospitalar do Baixo Vouga (15-05-2019, 086892). Participants needed to have a diagnosis of COPD (post bronchodilator forced expiratory volume in the first second [FEV_1]/forced vital capacity <0.70), be clinically stable in the previous month (i.e., no hospital admissions, acute exacerbations or changes in medication) and have participated in PR to be included. Exclusion criteria comprised the presence of other respiratory diseases or any clinical condition that precluded participation in the assessment (i.e., signs of cognitive impairment or presence of a significant cardiovascular, neurological, musculoskeletal, immunological, or infectious disease). Eligible participants were identified during routine appointments at a hospital or primary healthcare centres. All participants provided written informed consent.

Data collection and intervention

A comprehensive assessment was performed. Sociodemographic (age and sex), anthropometric (height and weight to compute body mass index) and general clinical data (smoking status, comorbidities through the Charlson comorbidity index [CCI], use of long-term oxygen therapy and non-invasive ventilation, and number of acute exacerbations of COPD in the previous year) were collected. Activity-related dyspnoea was assessed with the modified Medical Research Council dyspnoea scale (mMRC), fatigue with the functional assessment of chronic illness therapy fatigue subscale (FACIT-F), and symptoms of anxiety and depression with the hospital anxiety and depression scale (HADS). Functional capacity was assessed with the one-minute sit-to-stand test (1-min STS) and deconditioning with the six-minute walk test (6MWT). Handgrip strength and quadriceps maximal isometric voluntary contraction

(QMVC) were measured using a handheld dynamometer (W50174, Baseline, UK, and microFET2, Hoggan Health, The best Salt Lake City, Utah respectively). Balance was assessed with the Brief balance evaluation systems test (Brief-BESTest). Self-reported physical activity was assessed with the brief physical activity assessment tool (BPAAT), the impact of disease/health status with the COPD assessment test (CAT) and health-related quality of life with the Saint George's respiratory questionnaire (SGRQ).

People with COPD underwent a conventional 12-week community-based PR programme. The programme was not designed considering the prevalence of treatable traits. The exercise training was personalised to each person (e.g., functional and muscle strength capacity), but all patients received the same PR components. It consisted of exercise training (aerobic and resistance training) twice per week and education and psychosocial support once every 2 weeks. Each session lasted approximately 60 minutes. A multidisciplinary team of physiotherapists, medical doctors, nurses, psychologists, dietitians, and social workers provided the programme. Details of the programme have been published elsewhere[13].

Extra-pulmonary treatable traits and responders and non-responders to PR were identified for each outcome measure. Nine treatable traits were defined based on previously established cut-offs and responders and non-responders to PR were defined based on published minimal clinical important differences (**Table 1**).

Table 1. Cut-offs and minimal important clinical differences used to define treatable traits and response to pulmonary rehabilitation in each outcome measure in people with chronic obstructive pulmonary disease.

Treatable trait	**Cut-off used for the treatable trait**	**Minimal clinical important difference**
Severe dyspnoea	mMRC ≥2 points[14]	Difference in mMRC ≥1 point[15]
Clinically relevant fatigue	FACIT-F ≤43 points[16]	Difference in FACIT-F ≥4.7 points
Symptoms of anxiety	HADS sub score ≥8 points[17]	Difference in HADS ≥1.5 points[18]

Symptoms of depression	HADS sub score ≥8 points[17]	Difference in HADS ≥1.5 points[18]
Poor functional capacity	1-min STS <70 % predicted [19]	Difference in 1-min STS ≥3 repetitions[20]
Deconditioning	6MWT <70% predicted[19]	Difference in 6MWT ≥30 m[21]
Poor balance	Brief-BESTest ≤16.5 points[22]	Difference in Brief-BESTest ≥3 points[23]
Poor health status	CAT ≥18 points [24]	Difference in CAT ≥2 points[25]
Poor health-related quality of life	SGRQ ≥46 points [24]	Difference in SGRQ ≥4 points[26]

mMRC: Medical Research Council dyspnoea scale; FACIT-F: functional assessment of chronic illness therapy fatigue subscale; HADS: hospital anxiety and depression scale; 1-min STS: one-minute sit-to-stand test; 6MWT: six-minute walk test; Brief-BESTest: Brief balance evaluation systems test; CAT: COPD assessment test; SGRQ: Saint George's respiratory questionnaire.

Data analysis

A multivariate imputation by chained equations was performed as some variables (i.e., HADS, FACIT-F) had more than 5% but less than 30% of missing data[27]. A sensitivity analysis with the original dataset (not imputed) was performed to check if results were similar to the ones of our main analysis.

Descriptive statistics were used to characterise the sample. Effects of PR were explored using paired samples t-tests or Wilcoxon signed-rank tests. Differences in mean/median between people with COPD with or without the treatable trait were explored using independent samples t-tests or Mann-Whitney U tests. Responders with or without the treatable trait were compared using chi-square tests for two proportions.

Odds ratios were computed to explore the probability of being a responder in each outcome, by having the presence of each treatable trait.

Adherence of responders was compared with the adherence of non-responders considering the absence or presence of the treatable traits using non-parametric two-way ANOVA. Normality of residuals was explored with Shapiro-Wilk test and homogeneity of variance with Levene's test.

All statistical analysis were performed in R (v. 4.1.2).

Results

Of the initial 140 database entries, 102 people with COPD were included. 38 entries were excluded after applying inclusion and exclusion criteria (repeated PR programmes, FEV_1 ≥70% predicted). No differences were found in the interpretation of results with or without imputed data (analysis with the original dataset provided in **Supplementary material**).

Patients were mostly male (78%), had a median FEV_1 of 47% predicted, and were predominantly from GOLD grades 2 and 3 (43%, 42% respectively) and group B (57%). Patients had 85±14.3% adherence to the PR sessions. Full characteristics of the sample are presented in **Table 2.**

Overall, PR was effective in improving all outcomes ($p<0.05$) (**Table 2**).

Table 2. Baseline characteristics and outcomes of pulmonary rehabilitation in people with chronic obstructive pulmonary disease (n=102).

	Baseline	**Post**	**Mean/Median diff**	**95% CI**	**p-value**
Age, years	69.5 [65.0;75.0]	N.A.	N.A.	N.A.	N.A.
Sex, n (%)					
Female	23 (22.5)	N.A.	N.A.	N.A.	N.A.
Male	79 (77.5)	N.A.	N.A.	N.A.	N.A.
Smoking status, n (%)					
Never smoker	21 (20.6)	N.A.	N.A.	N.A.	N.A.
Former smoker	65 (63.7)	N.A.	N.A.	N.A.	N.A.
Current smoker	16 (15.7)	N.A.	N.A.	N.A.	N.A.
Pack-years, n	30.0 [9.4;57.0]	N.A.	N.A.	N.A.	N.A.
FEV_1, % predicted	47.0 [36.0;60.0]	N.A.	N.A.	N.A.	N.A.
GOLD grade, n (%)					
1	7 (7.0)	N.A.	N.A.	N.A.	N.A.
2	43 (42.6)	N.A.	N.A.	N.A.	N.A.
3	42 (41.6)	N.A.	N.A.	N.A.	N.A.

4	9 (8.9)	N.A.	N.A.	N.A.	N.A.
GOLD group, n (%)					
A	27 (26.5)	N.A.	N.A.	N.A.	N.A.
B	58 (56.9)	N.A.	N.A.	N.A.	N.A.
C	2 (2.0)	N.A.	N.A.	N.A.	N.A.
D	15 (14.7)	N.A.	N.A.	N.A.	N.A.
CCI, total	4.0 [3.0;5.0]	N.A.	N.A.	N.A.	N.A.
LTOT, n (%)	10 (9.8)	N.A.	N.A.	N.A.	N.A.
NIV, n (%)	13 (12.7)	N.A.	N.A.	N.A.	N.A.
No. AECOPD previous 12 months, n	0.0 [0.0;1.0]	N.A.	N.A.	N.A.	N.A.
BMI, kg/m^2	26.4±4.8	N.A.	N.A.	N.A.	N.A.
mMRC, score	2.0 [1.0;3.0]	1.0 [1.0;2.0]	0.0 [-1.0;0.0]	N.A.	<0.001
FACIT-F, total score	36.1±9.0	39.3±8.5	3.2±6.7	1.9; 4.5	<0.001
HADS, Anxiety score	5.9±4.1	5.2±3.7	-0.7±3.2	-1.3; -0.1	0.02
HADS, depression score	6.0 [3.0;9.8]	6.0 [3.0;8.0]	-1.0 [-3.0;1.0]	N.A.	<0.001
1-min STS, repetitions	22.5 [18.3;27.8]	26.0 [21.0;31.0]	4.0 [0.0;6.0]	N.A.	<0.001
6MWT, m	405.1±127.3	448.8±123.1	43.7±61.9	31.5; 55.9	<0.001
Handgrip strength, Kg	34.0 [26.0;40.0]	N.A.	N.A.	N.A.	N.A.
QMVC, Kg/F	30.7±7.9	33.2±8.4	2.5±6.2	1.2; 3.7	<0.001
Brief-BESTest, score	18.0 [15.0;22.0]	21.0 [18.0;23.0]	3.0 [0.0;4.0]	N.A.	<0.001
BPAAT, score	0.0 [0.0;2.8]	4.0 [2.0;6.0]	2.0 [1.0;4.0]	N.A.	<0.001
CAT, total score	14.7±8.0	11.6±7.1	-3.1±6.1	-4.3; -1.9	<0.001
SGRQ, total score	46.0 [28.4;59.5]	40.0 [20.1;51.8]	-7.5 [-14.3;0.5]	N.A.	<0.001

N.A. Not applicable; FEV_1: forced expiratory volume in the first second; GOLD: Global initiative for chronic obstructive lung disease; CCI: Charlson comorbidity index; LTOT: long-term oxygen therapy; NIV: non-invasive ventilation; BMI: body mass index; mMRC: modified Medical Research Council dyspnoea scale; FACIT-F: functional assessment of chronic illness therapy fatigue subscale; HADS: hospital anxiety and depression scale; 1-min STS: one-minute sit-to-stand test; 6MWT: six-minute walk test; QMVC: quadriceps maximal isometric voluntary contraction; Brief-BESTest: Brief balance evaluation systems test; BPAAT: brief physical activity assessment tool; CAT: COPD assessment test; SGRQ: Saint George's respiratory questionnaire.

At baseline, people with COPD had a median [min-max] of 3 [0-7] extra-pulmonary treatable traits per person, and responded on 5 [0-9] outcomes of PR.

People with the presence of treatable traits responded to a greater extent than those without treatable traits in all outcomes except for the 1-min STS (**Table 3**). Indeed, the pre-post mean differences of each outcome were significantly higher in those with a baseline mMRC ≥2 points ($p<0.001$), FACIT-F ≤43 points ($p<0.001$), HADS ≥8 points ($p<0.001$ both anxiety and depression symptoms), 6MWT <70% predicted ($p=0.005$) and Brief-BESTest <16.5 points ($p<0.001$), CAT ≥18 points ($p<0.001$), and SGRQ ≥46 points ($p=0.005$). Accordingly, people with the treatable trait were more frequently responders than those without the treatable trait (**Table 3 and Figure 1**). There was a significantly higher proportion of responders to mMRC ($p=0.003$), FACIT-F ($p<0.001$), HADS ($p<0.001$, $p=0.001$), 6MWT ($p=0.009$), Brief-BESTest ($p<0.001$), CAT ($p<0.001$) and SGRQ ($p=0.003$), in people with the respective treatable trait - severe dyspnoea, clinically relevant fatigue, symptoms of anxiety and depression, deconditioning, poor balance, poor health status and poor health-related quality of life - compared to those without the treatable trait at baseline (**Table 3 and Figure 2**). People with the treatable traits were more likely responders than those without the treatable traits (OR=4.25-19.95) with the exception of people with less than 70% predicted in the 1-min STS (**Table 3)**.

No significant differences related to adherence were found between responders and non-responders nor in the interaction between the 2 factors (i.e., treatable trait, no treatable trait; responder, non-responder) for all outcomes ($p>0.05$). A significant difference was found in adherence rates between people with or without depression symptoms ($p=0.013$).

Table 3. Response to pulmonary rehabilitation defined by the minimal important clinical differences of each outcome measure, according to the presence or absence of each treatable trait in people with chronic obstructive pulmonary disease (n=102).

Treatable trait	Mean/Median$_{diff}$	p-value	Non-responders, n (%)	Responders, n (%)	p-value	OR [95%CI]	Non-responders % adherence	Responders % adherence	p-value[a]
mMRC, score									
<2 points	0.0 [0.0; 0.0]		29 (76.3)	9 (23.7)			88.0 [71.0; 92.0]	100.0 [83.0; 100.0]	
≥2 points (severe dyspnoea)	-1.0 [-1.0; 0.0]	<0.001	28 (43.8)	36 (56.3)	0.003	4.14 [1.69; 10.15]	81.0 [74.0; 89.0]	88.0 [75.0; 96.0]	0.182
FACIT-F, score									
≤43 points (clinically relevant fatigue)	5.0 [0.0; 8.8]		40 (48.8)	42 (51.2)			88.0 [75.0; 96.0]	85.5 [72.0; 95.0]	
>43 points	0.0 [-3.0; 1.2]	<0.001	19 (95.0)	1 (5.0)	<0.001	19.95 [2.55; 156.05]	88.0 [77.0; 92.0]	67.0 [67.0; 67.0]	0.819
HADS, Anxiety score									
<8 points	0.0 [-2.0; 2.0]		50 (73.5)	18 (26.5)			88.0 [75.0; 96.0]	88.0 [73.0; 94.3]	
≥8 points (symptoms of anxiety)	-2.5 [-5.0; 0.0]	<0.001	10 (29.4)	24 (70.6)	<0.001	6.67 [2.67; 16.62]	79.0 [69.0; 94.3]	81.0 [70.0; 89.0]	0.362
HADS, Depression score									

<8 points	0.0 [-2.0; 2.0]		41 (69.5)	18 (30.5)			88.0 [83.0; 96.0]	88.0 [75.0; 95.0]		
≥8 points (symptoms of depression)	-3.0 [-4.0; -1.0]	<0.001	15 (34.9)	28 (65.1)	0.001	4.25 [1.84; 9.82]	79.0 [67.5; 88.0]	81.0 [70.0; 95.3]		0.767
1-min STS, % predicted										
<70% (poor functional capacity)	4.0 [2.0; 7.0]		21 (39.6)	32 (60.4)			79.0 [71.0; 88.0]	88.0 [81.0; 96.0]		
≥70%	2.0 [-1.0; 5.0]	0.046	26 (53.1)	23 (46.9)	0.245	1.72 [0.78; 3.78]	90.0 [79.0; 96.0]	83.0 [71.0; 93.0]		N.A.
6MWT, % predicted										
<70% (deconditioning)	81.0 [43.5; 117.0]		4 (17.4)	19 (82.6)			81.0 [79.0; 86.3]	83.0 [71.0; 94.0]		
≥70%	29.6 [2.5; 65.4]	0.005	40 (50.6)	39 (49.4)	0.009	4.87 [1.52; 15.62]	83.0 [74.0; 93.0]	88.0 [75.0; 95.0]		0.729
Brief-BESTest										
<16.5 points (poor balance)	4.0 [3.0; 6.0]		9 (21.4)	33 (78.6)			83.0 [75.0; 88.0]	83.0 [71.0; 95.0]		
≥16.5 points	1.0 [0.0; 3.0]	<0.001	39 (65.0)	21 (35.0)	<0.001	6.81 [2.75; 16.89]	88.0 [73.0; 92.0]	92.0 [79.0; 100.0]		0.251
CAT, score										
<18 points	-1.6±6.0	<0.001	32 (46.4)	37 (53.6)	<0.001	8.65 [2.41; 31.03]	88.0 [79.0; 97.0]	88.0 [71.0; 96.0]		0.281

≥18 points (poor health status)	-6.2±5.1		3 (9.0)	30 (90.9)			79.0 [77.0; 85.5]	81.0 [71.0; 92.0]		
SGRQ, score <46 points	-6.0 [-11.4; 4.0]		37 (72.5)	14 (27.5)			92.0 [80.0; 100.0]	83.0 [75.0; 92.0]		
≥46 points (poor health-related quality of life)	-10.4 [-15.4; -5.1]	0.005	2 (4.0)	49 (96.1)	0.003	9.27 [1.98; 43.32]	91.5 [87.3; 95.8]	88.0 [71.0; 95.0]		0.193

[a]p-value of ANOVA for differences between responders and non-responders; no interaction effects found for all variables. Results are presented as mean±SD, median [1st; 3rd quartile] or n (%). The presence of the treatable trait is presented in bold. mMRC: modified Medical Research Council dyspnoea scale; FACIT-F: functional assessment of chronic illness therapy fatigue subscale; HADS: hospital anxiety and depression scale; 1-min STS: one-minute sit-to-stand test; 6MWT: six-minute walk test; Brief-BESTest: Brief balance evaluation systems test; CAT: COPD assessment test; SGRQ: Saint George's respiratory questionnaire; N.A.: Not applicable.

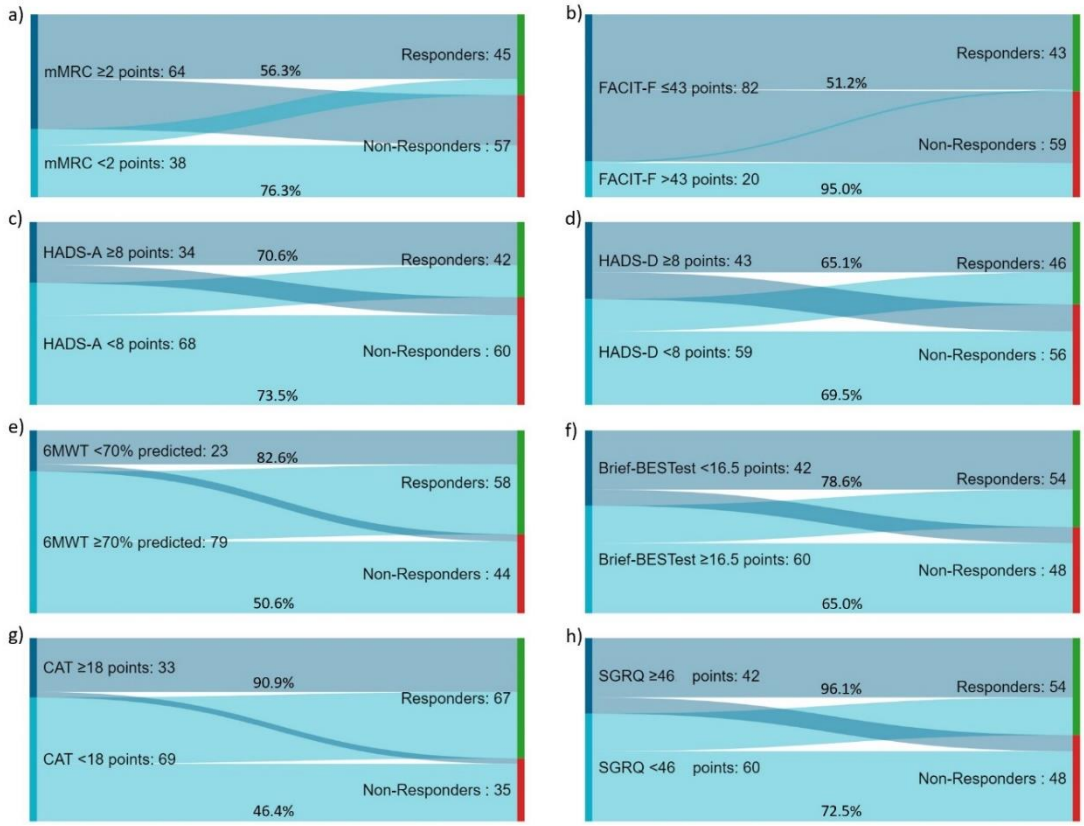

Figure 1. Flow of responders and non-responders to pulmonary rehabilitation with or without each treatable trait a) treatable trait – severe dyspnoea mMRC ≥2 points; b) treatable trait – clinically relevant fatigue FACIT-F ≤43 points; c) treatable trait – symptoms of anxiety HADS ≥8 points; d) treatable trait – symptoms of depression HADS ≥8 points; e) treatable trait - poor functional capacity 6MWT <70% predicted; f) treatable trait – poor balance Brief-BESTest <16.5 points; g) treatable trait poor health status CAT≥18 points; h) treatable trait - poor health-related quality of life SGRQ ≥46 points;. Dark blue represents people with the treatable trait and light blue people without the treatable trait. Green represents responders and red represents non-responders. Percentages are represented for responders with the treatable trait and non-responders without the treatable trait.

mMRC: modified Medical Research Council dyspnoea scale; FACIT-F: functional assessment of chronic illness therapy fatigue subscale; HADS: hospital anxiety and depression scale; 6MWT: six-minute walk test; Brief-BESTest: Brief balance evaluation systems test; CAT: COPD assessment test; SGRQ: Saint George's respiratory questionnaire.

Discussion

This study showed that PR was generally effective in addressing extra-pulmonary traits of people with COPD, and that people who exhibit treatable traits at baseline are more responsive than those without the treatable traits.

Our findings are consistent with several recent studies which demonstrated that people with COPD who are clinically worse at baseline are usually those responding better to the intervention[7-9,28]. This might be due to having more room for improvement in those more severe, and an absence of abnormal values in some measures or a delayed response to PR in people that are functionally better at baseline. Therefore, early identification of these patients and referral to PR considering their treatable traits seems to be of paramount importance.

A recent study has demonstrated different stakeholders to believe that when necessary people with chronic respiratory diseases who are more symptomatic and with worse functional status should be prioritised for PR[29]. Considering these findings and the present study, it might be appropriate to prioritise patients who exhibit a higher number of treatable traits. Nonetheless, this requires further investigation.

Overall, for most outcomes, the group of patients with absence of each treatable trait did not achieve clinically relevant benefits (within the established minimal clinical important differences) with PR. Therefore, it seems crucial to conduct a comprehensive assessment at baseline to identify the multiple treatable traits of each person and only activate the necessary PR components (e.g., exercise, education, psychological support, and/or balance training) accordingly. Indeed, designing the PR programme for each individual based on the treatable traits that need to be targeted could enhance the programme personalisation and cost-effectiveness, especially considering the lack of resources commonly available[5]. Healthcare professionals should be however aware of the need of a multidimensional assessment, as narrow baseline assessments may lead to a misinterpretation of the lack of need of PR for some patients. In fact, it is unlikely for a person with COPD to exhibit no

treatable traits[30,31], and therefore to have no need to be integrated, at least partially, in PR.

The present study did not aim to explore the effectiveness of a treatable trait strategy for PR. Similar to a randomized controlled trial of a treatable traits strategy vs. usual care in asthma[3], future studies could compare conventional PR with a treatable traits based programme in terms of their effectiveness for people with COPD.

Even though most responders were those who had the treatable traits at baseline, our findings still showed a large proportion of people with the treatable traits who did not respond to PR. We found no influence between adherence to PR and responding to the intervention, independently of the presence or absence of treatable traits. Therefore, whether these patients are truly non-responders or if a higher intensity or frequency of treatment is necessary, requires further research.

In our sample the response in the 1-min STS was not significantly different between those with or without the treatable trait. Most of our patients were responders in this outcome and therefore this fact is likely to have impacted the group comparisons. Nevertheless, responders to PR in the 1-min STS have been found to exhibit a lower capacity at baseline than non-responders[8]. Therefore, similar to other outcomes, a pattern of better response to PR with the presence of poor functional capacity in the 1-min STS at baseline is expected.

Although we identified multiple traits through a comprehensive assessment, it might also be important to identify other treatable traits that are relevant for PR, such as respiratory muscle dysfunction, lack of disease-specific knowledge, poor nutritional status, and poor social status, to decide the most suitable PR path for each patient. A recent study has provided a clinical decision tree for the quick allocation of people with COPD to a profile, which might enable a fast clinical decision on the best treatment regimens, following the profile treatable traits[31]. Future studies could also develop a PR-specific clinical decision tool to rapidly decide the PR components to

be activated for each patient according to their treatable traits (based on a comprehensive treatable trait assessment).

Our sample was mainly composed of men and elderly people. Studies have shown women to have a higher prevalence and more severe treatable traits than men with COPD, which also seem to increase with progression of disease[32]. Hence, comparison of the impact of PR on the treatable traits of men versus women, and also in younger and less severe samples should be further explored. Holland and colleagues concluded that treatable traits have been poorly addressed in PR trials[11]. However, most of the traits were identified based on previous literature[33] and were non-relevant outcomes for PR, such as emphysema or persistent systemic inflammation. Future studies need to identify rehabilitation-specific treatable traits for which patients and clinicians can expect improvements[34]. Finally, the cut-offs used in this study to define the treatable traits seem to be suitable to differentiate responders from non-responders to PR. Nevertheless, these candidate treatable traits should be externally validated for PR.

Conclusions

Identification of extra-pulmonary treatable traits in people with COPD showed the potential to inform on PR responsiveness and might therefore be an important strategy for patient prioritization (when/if needed), treatment personalisation and optimisation. Future trials are needed to compare the use of a treatable traits' strategy within PR (identification of each patient's treatable traits to trigger the most suitable PR components accordingly) with conventional PR.

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Supplementary materials

Analysis without data imputation. Results are similar with or without data imputation.

Table A1. Baseline characteristics and outcomes of pulmonary rehabilitation in people with chronic obstructive pulmonary disease with the original dataset (not imputed) (n=102).

	Baseline	**Post**	**Mean/Median$_{diff}$**	**95% CI**	**p-value**
Age, years	69.5 [65.0; 75.0]	N.A.	N.A.	N.A.	N.A.
Sex, n (%)					
Female	79 (77.5)	N.A.	N.A.	N.A.	N.A.
Male	23 (22.5)	N.A.	N.A.	N.A.	N.A.
Smoking status, n (%)					
Never smoker	21 (20.6)	N.A.	N.A.	N.A.	N.A.
Former smoker	65 (63.7)	N.A.	N.A.	N.A.	N.A.
Current smoker	16 (15.7)	N.A.	N.A.	N.A.	N.A.
Pack-years, n	30.0 [9.4; 57.0]	N.A.	N.A.	N.A.	N.A.
FEV_1, % predicted	47.0 [36.0; 60.0]	N.A.	N.A.	N.A.	N.A.
GOLD grade, n (%)					
1	7 (6.9)	N.A.	N.A.	N.A.	N.A.
2	43 (42.6)	N.A.	N.A.	N.A.	N.A.
3	42 (41.6)	N.A.	N.A.	N.A.	N.A.
4	9 (8.9)	N.A.	N.A.	N.A.	N.A.
GOLD group, n (%)					
A	27 (26.5)	N.A.	N.A.	N.A.	N.A.
B	58 (56.9)	N.A.	N.A.	N.A.	N.A.
C	2 (2.0)	N.A.	N.A.	N.A.	N.A.
D	15 (14.7)	N.A.	N.A.	N.A.	N.A.
CCI, total	4.0 [3.0; 5.0]	N.A.	N.A.	N.A.	N.A.
LTOT, n (%)	10 (9.8)	N.A.	N.A.	N.A.	N.A.
NIV, n (%)	13 (12.7)	N.A.	N.A.	N.A.	N.A.
No. AECOPD previous 12 months, n	0.0 [0.0; 1.0]	N.A.	N.A.	N.A.	N.A.
BMI, kg/m^2	26.4±4.8	N.A.	N.A.	N.A.	N.A.
mMRC, score	2.0 [1.0; 3.0]	1.0 [1.0; 2.0]	0.0 [-1.0; 0.0]	N.A.	<0.001*

[ł]FACIT-F, total score	35.8±9.1	39.1±8.6	3.3±6.9	1.86; 4.71	<0.001*
[ł]HADS, Anxiety score	5.0 [3.0; 9.0]	4.0 [2.3; 8.0]	-1.0 [-3.0; 1.0]	N.A.	0.008*
[ł]HADS, depression score	6.0 [3.0; 9.0]	5.0 [3.0; 7.8]	-1.0 [-3.0; 1.0]	N.A.	0.004*
[ł]1-min STS, repetitions	22.0 [18.0; 27.5]	26.0 [21.0; 31.0]	4.0 [0.0; 6.5]	N.A.	<0.001*
6MWT, m	405.1±127.3	448.7±123.1	43.7±61.9	31.54; 55.86	<0.001*
Handgrip, Kg	34.0 [26.0; 40.0]	N.A.	N.A.	N.A.	N.A.
QMVC, Kg/F	30.7±7.9	33.2±8.4	2.5±6.2	1.24; 3.69	<0.001*
[ł]Brief-BESTest, score	18.0 [15.0; 22.0]	21.0 [18.0; 23.0]	3.0 [0.0; 4.0]	N.A.	<0.001*
BPAAT, score	0.0 [0.0; 2.7]	4.0 [2.0; 6.0]	2.0 [1.0; 4.0]	N.A.	<0.001*
CAT, total score	14.7±8.0	11.6±7.1	-3.1±6.1	-4.29; -1.90;	<0.001*
SGRQ, total score	46.0 [28.4; 59.5]	40.1 [20.1; 51.8]	-7.5 [14.3; 0.5]	N.A.	<0.001*

[ł]n=90 for HADS, n=99 for 1-min STS, n=94 for FACIT-F, n=98 for Brief-BESTest. N.A. Not applicable; FEV_1: forced expiratory volume in the first second; GOLD: Global initiative for chronic obstructive lung disease; CCI: Charlson comorbidity index; LTOT: long-term oxygen therapy; NIV: non-invasive ventilation; BMI: body mass index; mMRC: modified Medical Research Council dyspnoea scale; FACIT-F: functional assessment of chronic illness therapy fatigue subscale; HADS: hospital anxiety and depression scale; 1-min STS: one-minute sit-to-stand test; 6MWT: six-minute walk test; QMVC: quadriceps maximal isometric voluntary contraction; Brief-BESTest: Brief balance evaluation systems test; BPAAT: brief physical activity assessment tool; CAT: COPD assessment test; SGRQ: Saint George's respiratory questionnaire.

Table A2. Response to pulmonary rehabilitation according to the minimal important clinical differences, for each treatable trait of people with chronic obstructive pulmonary disease with the original dataset (not imputed) (n=102).

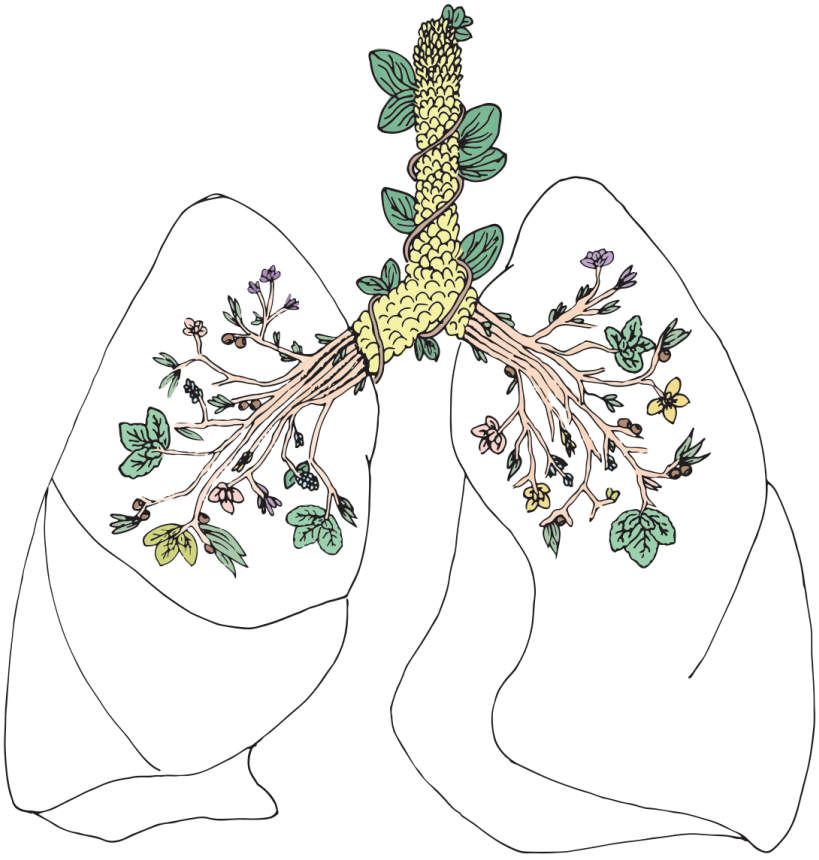
Treatable trait	Mean/Median$_{diff}$	p-value	Non-responders, n (%)	Responders, n (%)	p-value	OR [95%CI]
mMRC, score						
<2 points	0.0 [0.0; 0.0]	<0.001*	29 (76.3)	9 (23.7)	0.003*	4.14 [1.69; 10.15]
≥2 points	-1.0 [-1.0; 0.0]		28 (43.8)	36 (56.3)		
[1]FACIT-F, score						
≤43 points	5.0 [0.0; 9.0]	<0.001*	35 (46.7)	40 (53.3)	<0.001*	19.43 [2.46; 153.53]
>43 points	0.0 [-3.0; 1.0]		17 (94.4)	1 (5.6)		
[1]HADS, Anxiety score						
<8 points	0.0 [-2.0; 1.0]	<0.001*	42 (72.4)	16 (27.6)	<0.001*	6.89 [2.54; 18.68]
≥8 points	-2.0 [-5.0; 0.0]		8 (27.6)	21 (72.4)		
[1]HADS, Depression score						
<8 points	0.0 [-2.0; 2.0]	<0.001*	36 (69.2)	16 (30.8)	0.006*	3.81 [1.54; 9.40]
≥8 points	-3.0 [-4.0; -1.0]		13 (37.1)	22 (62.9)		
[1]1-min STS, % predicted						
<70%	4.0 [2.0; 7.0]	0.053	20 (38.5)	32 (61.5)	0.290	1.67 [0.75; 3.71]
≥70%	3.0 [-1.0; 5.5]		24 (51.1)	23 (48.9)		
6MWT, % predicted						
<70%	81.0 [43.5; 117.0]	0.005*	4 (17.4)	19 (82.6)	0.009*	4.87 [1.52; 15.62]
≥70%	29.6 [2.5; 65.4]		40 (50.6)	39 (49.4)		
[1]Brief-BESTest						
<16.5 points	4.0 [3.0; 5.5]	<0.001*	9 (23.1)	30 (76.9)	<0.001*	6.03 [2.41; 15.07]
≥16.5 points	1.0 [0.0; 3.0]		38 (64.4)	21 (35.6)		
CAT, score						
<18 points	-2.0 [-5.0; 2.0]	<0.001*	32 (46.4)	37 (53.6)	<0.001*	8.65 [2.41; 31.03]
≥18 points	-5.0 [-8.0; -4.0]		3 (9.0)	30 (91.0)		
SGRQ, score						
<46 points	-6.0 [-11.4; 4.0]	0.005*	14 (27.5)	37 (72.5)	0.003*	9.27 [1.98; 43.32]
≥46 points	-10.4 [-15.4; -5.1]		2 (4.0)	49 (96.1)		

[1]n=90 for HADS, n=99 for 1-min STS, n=94 for FACIT-F, n=98 for Brief-BESTest. The presence of the treatable trait is presented in bold. mMRC: modified Medical Research Council dyspnoea scale; FACIT-F: functional assessment of chronic illness therapy fatigue subscale; HADS: hospital anxiety and depression scale; 1-min STS: one-minute sit-to-stand test; 6MWT: six-minute walk test; Brief-BESTest: Brief balance evaluation systems test; CAT: COPD assessment test; SGRQ: Saint George's respiratory questionnaire.

Table A3. Odds ratio for the probability of being a responder with the presence of the treatable trait with the original dataset (not imputed).

Trait, measure	Odds ratio	95%CI	p-value
Severe dyspnoea, mMRC	4.1	1.7; 10.6	0.002
Clinically relevant fatigue, [1]FACIT-F	19.4	3.7; 359.0	0.005*
Symptoms of anxiety, [1]HADS	6.9	2.6; 19.6	<0.001*
Symptoms of depression, HADS	3.8	1.6; 9.6	0.004*
Functional capacity, [1]1-min STS	1.7	0.8; 3.7	0.209
Deconditioning, 6MWT	4.9	1.7; 18.0	0.008*
[1]Balance, Brief-BESTest	6.0	2.5; 15.8	<0.001*
Poor health status, CAT	8.6	2.8; 38.5	<0.001*
Poor HRQoL, SGRQ	7.6	2.3; 25.5	<0.001*

[1]n=90 for HADS, n=99 for 1-min STS, n=94 for FACIT-F, n=98 for Brief-BESTest *p<0.05. mMRC: modified Medical Research Council dyspnoea scale; FACIT-F: functional assessment of chronic illness therapy fatigue subscale; HADS: hospital anxiety and depression scale; 1-min STS: one-minute sit-to-stand test; 6MWT: six-minute walk test; Brief-BESTest: Brief balance evaluation systems test; CAT: COPD assessment test; SGRQ: Saint George's respiratory questionnaire.



Chapter 6

International perspectives on outcome measurement in pulmonary rehabilitation of people with COPD: a qualitative study

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ABSTRACT

Background: There is high heterogeneity of outcomes and measures reported in the literature for pulmonary rehabilitation (PR), which might limit benchmarking and an effective evidence synthesis. A core outcome set (COS) can minimise this problem. It is however unclear which outcomes and measures are most important and suitable for different stakeholders.

Methods: A multicentre qualitative study with one-to-one semi-structured interviews with people with chronic obstructive pulmonary disease (COPD), healthcare professionals (HCPs), researchers and policy makers was conducted. Manifest content analysis was conducted to explore the frequency of outcomes viewed as crucial or not. Thematic analysis was performed to better understand stakeholders' views.

Results: 37 participants (17 people with COPD and 20 HCPs/researchers/policy makers) from 14 countries and 4 continents were included. Participants expressed that i) core outcomes need to be meaningful to people with COPD and show PR benefits; ii) there should be comprehensive assessment and similar outcomes across settings; iii) a balance between optimal and practical measures is needed; iv) the COS is needed to benchmark PR and advance knowledge; and v) reluctance to change outcomes/measures used by HCPs and using the COS as a maximum set of outcomes might be the pitfalls. 28 outcomes were identified as crucial, and 12 as not crucial.

Conclusions: This study provided important insights into outcome measurement in PR from the perspectives of different key international stakeholders and a list of outcomes that will inform a future consensus study.

Introduction

Pulmonary rehabilitation (PR) is a safe and effective intervention for the management of chronic obstructive pulmonary disease (COPD)[1]. Nevertheless, some patients still respond poorly to the intervention. This depends partially on the outcomes and measures selected, which commonly consider only the views of healthcare professionals (HCPs) or researchers[2-4].

A recent systematic review identified 163 outcomes and 217 measures reported in the literature, revealing high heterogeneity in outcome measurements during PR[5]. This is of most importance as measuring different outcomes and using different measures between centres and studies hinders benchmarking PR efficacy, an effective evidence synthesis, and effective marketing strategies to foster PR amongst payers, clinicians, and patients[6,7].

Heterogeneity can be minimised with a core outcome set (COS), defined as a standardised set of outcomes that is agreed by different stakeholders, and that should be measured and reported, as a minimum in PR trials and programmes[8,9]. A consensus in reporting outcomes of PR in patients with COPD has been advocated by international societies[10,11] and renowned researchers[12-15], and should include international perspectives to promote its worldwide applicability[8]. Although a Portuguese qualitative study has been previously conducted on perspectives of different stakeholders on outcomes of PR[16], international perspectives and views on the measures are unknown. Thus, this study aimed to explore international perspectives of people with COPD and HCPs, researchers and policy makers on outcomes and measures of PR.

Methods

A multicentre qualitative study with individual interviews was conducted. This study was approved by the Ethics Committee of the Research Unit of Health Sciences at the School of Nursing in Coimbra (UICISA), Portugal (P466-10/2017).

All participants gave informed consent to participate in this study. The study is reported following the Consolidated Criteria for Reporting Qualitative Research (COREQ)[17]. This study is part of a COS that will include outcomes and measures to assess the effectiveness of PR programmes and is registered in the Core outcome measures in effectiveness trials (COMET) initiative database at https://www.comet-initiative.org/Studies/Details/1151.

Participant selection

People with COPD were recruited through HCPs using the snowballing technique, researchers' network, and a patient organisation (Respira) using purposive sampling.

HCPs, researchers, and policy makers (i.e., guideline developers) were invited through researchers' network and by disseminating the study via the European Respiratory Society group 1.02 (Rehabilitation and Chronic Care). A maximum variation strategy was used to recruit stakeholders from different countries with different backgrounds and gender[18].

Invitations occurred face-to-face or were sent by e-mail. A short explanation of the study and a short video "What are Core Outcome Sets" developed by COMET initiative, were provided to participants (https://youtu.be/g1MZi2mzK1U). Those interested to participate filled a sociodemographic and consent form (either online or face-to-face) and the interview with the researcher was scheduled according to participants' preferences.

People with COPD were included if they had a diagnosis of COPD and had participated or were participating in a PR programme.

HCPs, researchers, and policy makers were included if they had been involved in the design, assessment and/or implementation of PR programmes and were able and comfortable speaking in English.

A total sample size of 10-20 interviews has been suggested for this type of study[18].

Data collection

An online or paper-based sociodemographic data form was completed by all stakeholders. The form was developed using Qualtrics (XM, Seattle, USA) and provided onsite or sent by email to participants. People with COPD provided information on sex, age, country of origin, occupation, time since diagnosis, and for how long they have been doing PR. HCPs, researchers, and policy makers provided information on sex, age, country of origin, professional group (e.g., HCP, researcher, guideline developer) and profession, and for how long they had been involved in PR.

Interviews with HCPs/researchers/policy makers were conducted online, through Zoom (California, USA), in English, by one English-proficient speaker and were recorded with the system's recorder. Interviews with people with COPD occurred in 2 formats: 1) online for people that were able to speak in English or Portuguese or 2) face-to-face in PR facilities of different countries with a local HCP in their native language.

One-to-one interviews were conducted by four researchers and followed a semi-structured guide (**Appendix A**) with open-ended questions about outcomes essential to be measured, preferences on the measures, perspectives on outcome measurement in different settings and different phenotypes, and of having a COS for pulmonary rehabilitation.

A rapport was established with participants, by keeping an informal environment and allowing short non-related conversations to the topics during the interviews.

After the interviews, audio files were saved to a computer with access restricted only to the researchers. Names of participants were replaced with

pseudonyms to ensure confidentiality. Field notes were taken during and after each interview with reflections about the data collection process and ideas for analysis.

Orthographic transcription of audios was performed and followed a notation system previously proposed[18]. Interviews that were not conducted in English were first transcribed and then translated to English before the analysis by English proficient researchers.

Data analysis

The sample characteristics were analysed using Excel (Microsoft, Washington, USA).

Qualitative data were managed and analysed in Atlas.ti (v9, Berlin, Germany). Firstly, manifest content analysis was conducted to identify the frequency of outcomes reported as crucial or not for the COS, and the most common outcome measures for each outcome[19]. No list of outcomes or measures was provided to participants. Outcomes were defined as crucial if they were spontaneously mentioned by participants after the question "Of all the outcomes mentioned [by you], can you share which ones are more important/crucial to you?". Similarly, they were categorized as non-crucial if participants mentioned that they should not be part of the COS. Outcomes were defined in clinical concepts through the interpretation of participants' own words.

Then, data were analysed by one author with thematic analysis with a primary inductive approach in 6 phases: transcription, generating initial codes, searching for themes, reviewing themes and defining and naming themes and producing the report[20]. S.S-M generated the initial codes using organic coding and the codes were then merged and interpreted as themes, when there were common patterns within the data[18]. During the analysis, memos were used to register decisions and other meaningful notes. Themes were discussed with the research team until consensus was

reached. A negative case analysis was performed to ensure that there were no views of participants contradicting the overall interpretation of data.

Validation of results was performed with member checking, by one HCP and one person with COPD who revised the results to ensure they did not misrepresent their perspectives.

Trustworthiness was ensured through procedures of credibility, transferability, dependability and confirmability as recommended (**Table A.3.**)[21]. The research team reflexivity can be found in **Appendix A.**

Results

A total of 37 participants were interviewed. People with COPD (n=17) were 53% males, on average 66 years old, diagnosed for about 14 years, mostly retired (74%) and from six countries and 2 continents. The other stakeholder group (n=20) was composed of HCPs (95%), researchers (75%), and policy makers (20%). They were mostly females (55%), on average 43 years old, with 14 years of experience with PR on average, from six professional backgrounds of 11 countries and 3 continents. A total of 14 countries from 4 continents were covered. Interviews lasted 41 [17-82] minutes. Details of participants' characteristics are presented in **Table 1**.

Table 1. Characteristics of participants (n=37).

	People with COPD (n=17)	**Healthcare professionals/Researchers/Policy makers (n=20)**
Sex, n (%)		
Male	9 (53)	9 (45)
Female	8 (47)	11 (55)
Age, mean±SD	65.9±7.3	43.9±9.6
Country, n (%)		

Portugal	4 (24)	---
Netherlands	4 (24)	3 (15)
UK	1 (6)	3 (15)
Norway	3 (18)	2 (10)
Germany	3 (18)	---
Sweden	---	2 (10)
Belgium	---	3 (15)
Switzerland	---	1 (5)
Italy	---	1 (5)
France	---	1 (5)
Denmark	---	1 (5)
Brazil	2 (12)	---
Australia	---	2 (10)
Canada	---	1 (5)
Occupation, n (%)		
Retired	12 (71)	N.A.
Self-employed	1 (6)	N.A.
Retired due to incapacity	3 (18)	N.A.
Employed	1 (6)	20 (100)
Healthcare professionals	N.A.	19 (95)
Physiotherapists	N.A.	7 (35)
Medical doctors	N.A.	3 (15)
Psychologists	N.A.	2 (10)
Nurses	N.A.	2 (10)
Occupational therapists	N.A.	3 (15)
Dietitians	N.A.	2 (10)

Researchers	N.A.	15 (75)
Policy makers	N.A.	4 (20)
Experience with pulmonary rehabilitation, months	40.4±48.1	164.1±99.6

N.A.: Not applicable

A total of 28 outcomes were identified by both stakeholder groups as crucial to be measured (**Table B.2**, **Appendix B**). HCP/researchers/policy makers identified 12 outcomes as non-crucial (**Table B.3, Appendix B**) and were uncertain to include 14 outcomes (**Table B.4, Appendix B**). People with COPD only expressed opinions about crucial outcomes (could not identify outcomes that should be excluded from the COS) hence, non-crucial outcomes were not identified by these stakeholders. When combining data from both stakeholder groups, the outcomes most frequently defined as crucial were exercise capacity, dyspnoea, anxiety and depression. The most frequent non-crucial outcomes mentioned by HCPs/researchers and policy makers were lung function, handgrip muscle strength, physical activity and cognitive function.

Conflicting views were found for eight outcomes within and between stakeholder groups, i.e., considered by some people as crucial to be included in the COS and by others as non-crucial – lung function, muscle strength, physical activity, self-efficacy, anxiety and depression, exercise capacity, body mass index and balance. Both stakeholder groups did not report some outcomes (i.e., did not mention them spontaneously), hence the percentage of people not reporting, or reporting as crucial and/or non-crucial each outcome can be visualised in **Fig. 1** and **Table B.1 (Appendix B)**.

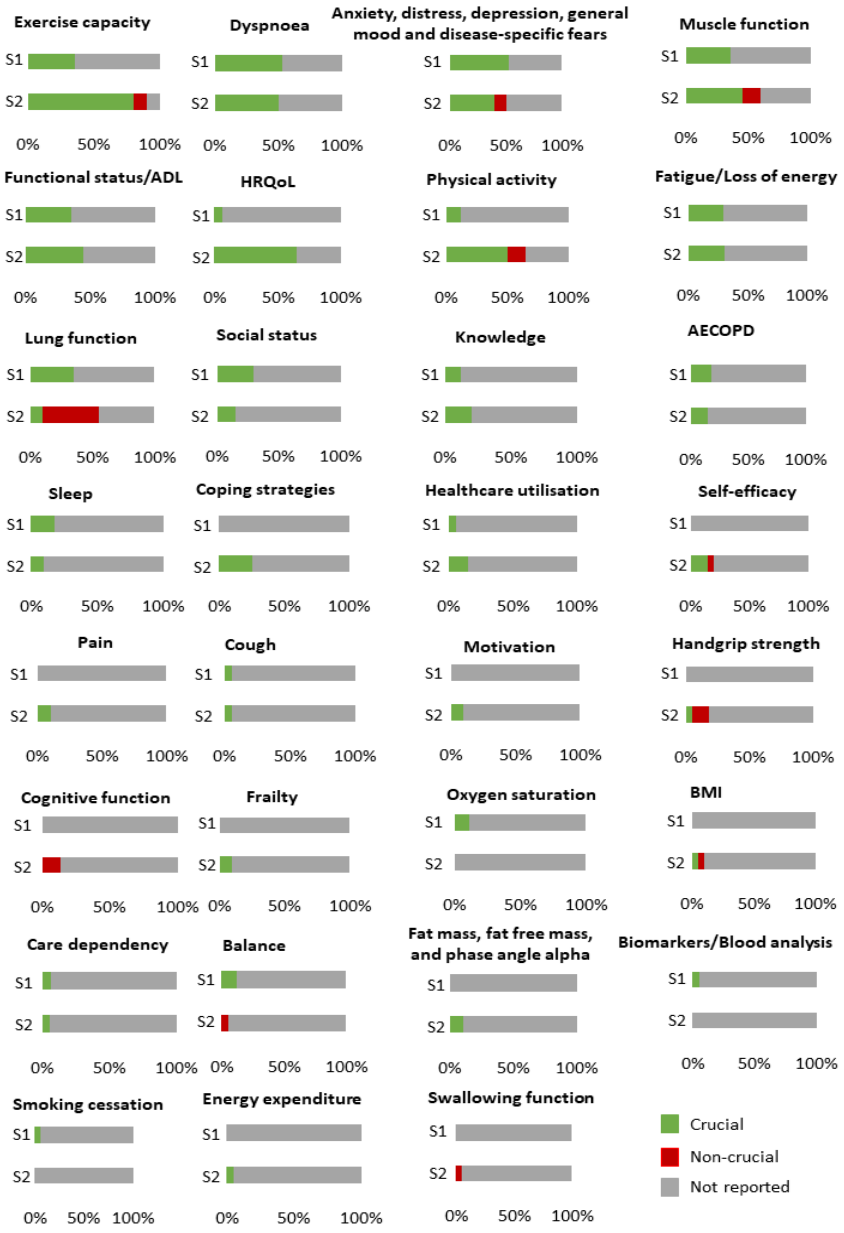

Figure 2. Percentage of people with COPD (Stakeholder group 1 [S1], n=17) and healthcare professionals/researchers/policy makers (Stakeholder group 2 [S2], n=20) not reporting (not spontaneously mentioning the outcome - grey bars) or reporting each outcome as crucial (spontaneously

mentioning the outcome as crucial - green bars) and/or non-crucial (spontaneously mentioning that the outcome should be excluded from the core outcome set - red bars).
COPD: chronic obstructive pulmonary disease; HCP: Healthcare professionals; ADL: Activities of daily living; HRQoL: Health-related quality of life; AECOPD: Acute exacerbations of COPD; BMI: Body mass index.

A total of 68 measures, with their advantages and disadvantages from the perspectives of both stakeholders, were identified. Overall, people with COPD were less vocal about measurements, most had no strong opinions on the best measures and felt their assessments were well-chosen by their own HCPs. For 25 measures only advantages were identified, whilst for 5 only disadvantages were stated. A summarised list of the mentioned measures can be found in **Table 2** with the full table with the views of stakeholder in **Appendix C**.

Table 2. List of measures with advantages and disadvantages mentioned by both stakeholder groups (stakeholder group 1, 17 people with COPD; and stakeholder group 2, 20 healthcare professionals/researchers/policy makers).

Domain/Measure	Advantages	Disadvantages
AECOPD and healthcare utilisation		
GOLD ABCD assessment tool	• Developed by experts	Not mentioned
No. AECOPD previous year	• Important to have a long-term view	• Not robust enough
No. AECOPD during PR	• Recall is not too bad	Not mentioned
No. hospitalisations	• Can be improved with PR	Not mentioned
Anxiety and distress		
AIR	• Distinguishes anxiety symptoms from respiratory ones • Measures panic	• Not as convenient as other measures (does not measure depression)
DASS-21	• Also measures stress • Available for free	Not mentioned
GAD-7	• Good for primary care • Available for free	Not mentioned
HADS	• Does not have somatic items • Psychometrically robust • Frequently used • Also assesses depression • Short and easy to use	• It should be discussed with a trained professional • It is outdated • Not available for free • Not disease-specific
Balance		
BBS	Not mentioned	• Does not allow personalising treatment
BESTest (full version)	Not mentioned	• Time consuming
Brief-BESTest	• Allows personalising treatment	Not mentioned
Mini-BESTest	• Allows personalising treatment	Not mentioned
TUG	• Easy to use as a first screen measure • Can also measure functional status	Not mentioned
Body composition		

Bioelectrical impedance	• Quick to use	• Some equipment is not very accurate
DEXA	• Psychometrically robust • Important to detect comorbidities	• Not feasible for most settings/countries
Cognitive function		
MoCA	• It is the measure with most information for COPD	• Not comprehensive enough
Depression		
DASS-21	• Also measures anxiety and distress • Available for free	Not mentioned
HADS	• Does not have somatic items • Psychometrically robust • Frequently used • Also assesses anxiety • Short and easy to use	• It should be discussed with a trained professional • It is outdated • Not available for free • Not disease-specific
PHQ-9	• Available for free • Good for primary care	Not mentioned
Disease-specific fears		
BBQ	• Available in English	Not mentioned
CAF	• Comprehensive	• Needs translation/cultural adaptation
Dyspnoea		
Borg scale	• Possible to measure more than intensity of dyspnoea • Good to use during physical activity/exercise • The original is more precise than the modified	• Very generic • Takes time to get familiarised
CRQ dimension	• Psychometrically robust	Not mentioned
D-12	• Comprehensive assessment • Short and easy to use	Not mentioned
mMRC	• Frequently used	• Not very responsive to PR

	• More functional than other measures • Psychometrically robust • Short and easy to use	• Difficult for some patients to understand
MDPI	• Comprehensive	Not mentioned
Energy expenditure		
Indirect calorimetry	• Psychometrically robust	• Most are not mobile
Exercise capacity		
6MWT	• Affordable • More functional than other tests • Psychometrically robust • Shows the benefits of PR • Meaningful to patients • Familiar • Complements CPET • Better for more impaired patients • Feasible in clinical practice • Easy to perform • Useful to adjust oxygen therapy • Useful for exercise prescription	• Needs a long corridor • Might scare patients and cause dropouts • Needs a practice test • It's self-paced so it does not show real endurance capacity • Not meaningful for daily activities • Not the most responsive measure for PR • Not very comprehensive compared to other tests • Type of floor might influence the results • Not possible to use in patients with some disabilities
CPET	• Complements the 6MWT • Good to assess safety of the intervention • Gives a lot of information	• Difficult to do for some patients • Not feasible for most settings/countries • It might not reflect endurance capacity • Not very responsive to PR • Not functional enough
ESWT	• Not self-paced • Good for exercise prescription	• Difficult to implement • It is necessary to also do an ISWT
ISWT	• Measures maximum exercise capacity • Good for patients with more capacity • Feasible in clinical practice • Good for exercise prescription	• Might scare patients and cause dropouts • Time consuming • Does not complement CPET • It is also necessary to do an ESWT

	• Not self-paced	• Not very good for patients with low capacity
Step tests (not specified)	• Complements a walking test	• Not feasible for most settings/countries (human resources) • Not meaningful to patients
Fatigue		
CIS-F	• Short and easy to use	• There are not enough studies
FACIT-F	• Comprehensive	Not mentioned
Frailty		
FI-CGA		• Not responsive to PR
Fried's phenotype	• Responsive to PR	• Not comprehensive enough
Handgrip dynamometry	• Quick and easy to use • Correlates with other strength measures	Not mentioned
TUG	• Quick and easy to use • Correlates with other strength measures	Not mentioned
Functional status/ADL		
CDS	• Easy to use • Comprehensive	• Has a ceiling effect
COPM	• Allows personalising treatment • Good for the home setting	• Requires a trained occupational therapist • Difficult to use in research • Time consuming
Glittre ADL test	• Comprehensive • Meaningful to patients	• Causes high levels of fatigue
Londrina ADL protocol	• Easy to perform • Patient-friendly	Not mentioned
MRADL	• Comprehensive • Responsive to PR	Not mentioned
Sit-to-stand tests (not specified)	• Good for small spaces/home • Meaningful to patients	• There are not enough studies • Need to be standardised

	• Good for people with low capacity • Feasible for different settings/countries	
1-minute STS	• Easy to do • Patient-friendly • Can be used to also assess muscle function	• Might scare patients
30-seconds STS	• Can be used to also assess muscle function • Good for home/tele-rehabilitation • Meaningful to patients	Not mentioned
SPPB	Not mentioned	• Has a ceiling effect • Not feasible for all settings
6PRT	• Meaningful to patients	• Might cause pain
HRQoL		
CAT	• Feasible for most settings • Can be used to assess risk change in the ABCD assessment tool • Can be used to assess each symptom	• Not comprehensive enough • Difficult for some patients • Not good enough to assess the impact of dyspnoea on quality of life • Does not really assess quality of life • Scores depend on how the patient feels at the moment • Not very personalised
CRQ	• Not too long • Psychometrically robust • Frequently used • Has personalised questions • It is respiratory-specific • Comprehensive	Not mentioned
EQ-5D	• Also assesses pain	• Not disease-specific

	• Measures well the construct of quality of life • Helps with cost-effectiveness analysis	
MRFQ	• Good for several respiratory diseases	Not mentioned
SF-12	• Measures well the construct of quality of life	Not mentioned
SGRQ	• Psychometrically robust • Can be used in respiratory diseases other than COPD • Good for research • Respiratory-specific	• Time consuming • Needs help of an HCP • Too generic • It is an old measure
VQ-11	• Quick and easy to use	Not mentioned
Motivation		
PAM	• Overall good measure	• Time consuming
Muscle function		
HHD	• Quick and easy to use	• Only good for weak patients • Does not reflect endurance which is important
Isokinetic system	• Psychometrically robust	• Not feasible for most settings/countries
Maximum repetitions	• Possible to measure strength and endurance • Important to prescribe exercise • Improves with PR – can be a motivator	• Not feasible for all settings • Not meaningful for daily life • Difficult to measure in some patients with disability
Maximum respiratory mouth pressures	• Quick and easy to use	• Does not reflect endurance which is important
Strain gauge	• Valid measure	• Not commercially available
Pain		
BPI	• Comprehensive	Not mentioned
Physical activity		
Accelerometery	• Frequently used	• Not feasible for most settings

	• Optimal way to measure physical activity	
IPAQ		• Subjective
Pedometers	• Objective measure • Reliable • Inexpensive	• Not valid enough • Not comprehensive enough • Not patient-friendly
PROactive instruments	• Psychometrically robust	Not mentioned
Smartphones and wearables	• Generate a lot of useful data • More valid than a questionnaire • Easy to wear • Will become more psychometrically robust in the future • Useful to motivate patients	• Not psychometrically robust enough • Data is difficult to analyse • Might be difficult to use for some patients •
Self-efficacy		
CSES	• Familiar	• Might be outdated
PRAISE	Not mentioned	• Might not be responsive to PR
Sleep		
PSQI	• Good measure for PR	Not mentioned
Social status		
DJGLS	• It's familiar	Not mentioned

Some measures related with previously identified outcomes (Figure 1) were not mentioned by participants and are therefore not displayed in this table.

AECOPD: Acute exacerbations of COPD; GOLD: Global initiative for chronic lung disease; PR: Pulmonary rehabilitation; AIR: Anxiety inventory for respiratory disease; DASS-21: 21-item Depression, anxiety and stress scale; GAD-7: Generalised anxiety disorder-7; HADS: The hospital anxiety and depression scale; BBS: Berg Balance scale; BESTest: Balance evaluation systems test; TUG: Timed up and go; DEXA: Dual-energy x-ray absorptiometry; MoCA: Montreal cognitive assessment; PHQ-9: Patient health questionnaire-9; BBQ: Breathlessness beliefs questionnaire; CAF: COPD Angst Fragebogen; CRQ: Chronic respiratory disease questionnaire; D-12: Dyspnoea-12 questionnaire; mMRC: Modified medical research council dyspnoea questionnaire; MDPI: Multidimensional dyspnoea profile; 6MWT: Six-minute walk test; CPET: Cardiopulmonary exercise testing; ESWT: Endurance shuttle walk test; ISWT: Incremental shuttle walk test; CIS-F: Checklist of individual strength – fatigue scale; FACIT-F: Functional assessment of chronic illness therapy fatigue scale; FI-CGA: Frailty index-Comprehensive geriatric assessment; CDS: Care dependency scale; COPM: Canadian

occupational performance measure; ADL: Activities of daily living; MRADL: Manchester respiratory activities of daily living questionnaire; STS: Sit-to-stand test; SPPB: Short physical performance battery; 6PRT: Six-minute pegboard and ring test; CAT: COPD assessment test; EQ-5D: EuroQol - 5 Dimension; MRFQ: Maugueri respiratory failure questionnaire; SF-12: 12-Item short form survey; SGRQ: Saint George's respiratory questionnaire; VQ-11: Chronic obstructive pulmonary disease-specific health-related quality of life questionnaire; PAM: Patient activation measure; HHD: Hand-held dynamometry; BPI: Brief pain inventory; IPAQ: International physical activity questionnaire; CSES: COPD self-efficacy scale; PRAISE: Pulmonary rehabilitation adapted index of self-efficacy; PSQI: Pittsburgh sleep quality index; DJGLS: De Jong Gierveld Loneliness Scale.

Five themes with perspectives of both stakeholder groups were identified. Perspectives were concordant between stakeholder groups and no discrepancies related with the geographical area of participants were found.

Theme 1: Core outcomes need to be meaningful to people with COPD and show the benefits of PR

Stakeholders felt outcomes to be included in the COS needed to i) be meaningful to people with COPD and related to their daily life, as otherwise the intervention could be beneficial but lead to no significant daily difference; and ii) show PR benefits and cost-effectiveness, for advocacy and funding purposes.

It was perceived that core outcomes should help to personalise treatment, cover commonly impaired aspects at baseline, be related to prognosis, correspond to patients' goals for PR and be directly connected to the foundations of PR (e.g., exercise training).

"(…) like strength is so specific but it doesn't mean anything to the patient's life. Ability to get off the toilet is what matters to patients, so I think the reason why these [outcomes] should be included is because they matter to patients.", Diana, female, Physiotherapist

"And I think that it is important to also look to what is relevant for a patient. Like I said, for me it is not that important if I can cycle longer on the cycle test, but it is important that I have for example more energy and that I can do more without getting breathless.", Willow, female, person with COPD

"(…) I think it's playing a game a little bit, but I think that we do have to use outcomes that are going to show that it works, if we are going to talk that rehab is beneficial.", Caleb, male, Physiotherapist

Theme 2: Comprehensive assessment and similar outcomes across settings

Stakeholders felt it was necessary to have a comprehensive assessment (multiple and distinct domains) in the COS, as it would allow to have a broad picture of the patient's health and their improvements with PR. Furthermore, they thought outcomes should be similar across settings to enable comparisons and provide patients with same quality assessment and treatment.

"(...) given that they [i.e., the set of outcomes] are broad enough, that they try to target different aspects of what people with COPD would need, so I would say a core outcome set of 3 to 5 [outcomes] would be ideal to be implemented across different settings, I feel.", Tobias, male, Psychologist

"Not only one or two physical variables, but a set of different ones. Of course, each person is different so it needs to be adjusted, but I think you should assess all dimensions, the physical part, the nutritional part, the psychological part. All of those dimensions and variables, but of course in some people some are more important than others, but they should always be present.", Elizabeth, female, person with COPD

"The disadvantage [of not assessing the same outcomes in different settings] is that the disease is the same so, if one person does one thing and the other does another, this treatment was better for who? Me or him/her?", George, male, person with COPD

Theme 3: Balance between optimal and practical measures

A great concern, for both stakeholder groups, was to include measures feasible for all, reasonably priced, short and simple, available in different languages

(i.e., questionnaires), patient-friendly and preferably already commonly used by clinicians and researchers. Nonetheless, they thought the COS needed to strike the right balance between practicality and rigor and should contain psychometrically robust and comprehensive measures which reveal patients' treatable traits. Most people also recognised that although the outcomes should ideally be the same for different settings, having the same measures would be challenging and adapting them to the context/resources might be therefore necessary.

"Minimal equipment, that you don't have massive requirements on space and things like that, or the staffing required to do those tests. In an ideal world, I'm just, especially considering I guess the kind of virtual models that we're having to work with at the moment, even something that can be done sort of safely remotely, for example, might be quite important.", Lily, female, Researcher

"Not too expensive, yet valid. So that our results are trustworthy, outcomes are trustworthy. So, both economical perspective and practical perspective. And user-friendly. It should not be hard for the patient, it's one of the most important things.", Norah, female, Dietitian

"*Now, a hospital or a rehabilitation centre are different. The hospital has one way to do things and the conditions are different. In a clinic the conditions are different, because sometimes they don't have the machines, the treadmills, other things.",* Charles, male, person with COPD

Theme 4: A COS is needed to benchmark PR and advance knowledge

Participants thought the COS was important for benchmarking PR, as this would improve the quality of care for people with COPD, by acknowledging centres with best practices through audits. Furthermore, the COS was also perceived to

advance knowledge in the field, by pooling data and facilitating comparisons across studies, producing meta-analysis, defining the optimal PR model, and generating new research questions. Participants also vocalised that a COS could help people with COPD to navigate through the health system, by transporting their results and avoiding repetition of assessments, and facilitating comparisons of their results with their peers.

Clarification why the final outcomes and measures were chosen and endorsement by a credible source, such as recognised international societies, were perceived as fundamental for COS uptake by both stakeholders.

Additionally, they thought it should be disseminated locally, nationally, and internationally through various means, such as organisations (patients and professionals), social media, websites, directly to PR centres and HCPs, industry partners and researchers (e.g., publications, scientific meetings). Nevertheless, some concerns about having strict rules in outcome measurement were raised, as these could hinder personalisation of assessments and PR.

"There needs to be consistent standards for lung clinics to qualify for doing pulmonary rehabilitation. And there needs to be something like a quality assurance institution that controls clinics for that.", Simon, male, person with COPD

"Well, one thing is the metadata to get the bigger picture of how this kind of treatment is helping patients. A group of 15 is a too small population for measuring or saying something about the outcome. (…) And therefore, a core list of outcomes is of course improving the population and the ability for the scientist to actually provide good recommendations. (…) And I think it's a good thing to make this kind of core parameters so that people around the world can learn from each other and make these kind of treatments and programs the best possible.", Harrison, male, person with COPD

"I think the thing that to me makes the biggest impact locally, and I don't know what it's like in other countries, but if you get societal approval in different countries, and it goes into societal or, you know, thoracic societies, respiratory societies, as recommended practice, as opposed to just publishing a paper on it, I don't think the publication actually changes the practice, but if then it comes into your national or local guidelines, that's the thing that it will cause people to change.", Caleb, male, Physiotherapist

Theme 5: Reluctance to change outcomes/measures used by HCPs and using the COS as a maximum set of outcomes might be the pitfalls

Participants highlighted reluctance to change routine clinical practice by HCPs as the most probable barrier for COS uptake. They thought that changing the measures and equipment of different centres and countries would be challenging as people might refuse to change their practice due to tradition, ownership of choice of assessment, lack of knowledge on the advised measures or simply because they would not see the advantage of having a minimum standardised set of outcomes.

Moreover, stakeholders showed concern with the implementation of the COS, as some centres could end up viewing the COS as a maximum number of measurements, not measuring other important outcomes for specific situations/patients.

"'Hey, I've been in this field for 30 years and I know what the hell I'm doing'. (…) And I don't know if that's real or not, but some [professionals] may feel actually threatened by it. Like, 'are we actually delivering the product, we say we're delivering?'.", Patrick, male, person with COPD

"I mean, you ask for a behaviour change, and we all know how difficult it is to induce behaviour change. It's not different from making people move and that's very challenging so, if they been doing something for years, maybe decades, and a core outcome set might ask them to maybe change their practice, so that might be a pitfall. Healthcare providers will not be willing to change their practice, and I think there the challenge is to find the right communications, to target the right people.", Connor, male, Physiotherapist

"The only thing is, when we have a core outcome set, it should be a minimum, and you should be able to do broader assessments and it should not be 'okay we only have to do this'.", Delilah, female, MD

Discussion

This study provided important insights into outcome measurement in PR from the perspectives of different international stakeholders. It informed the development of a COS by defining that the COS should include outcomes that are meaningful to patients and show PR benefits, and measures that are feasible for different settings but psychometrically robust.

This study included four continents, and people from different backgrounds, hence providing an international picture of which outcomes are meaningful to key PR stakeholders, advantages, and disadvantages of using different measures, and usefulness and possible pitfalls of the COS.

The most frequent crucial outcomes identified in this study were exercise capacity, dyspnoea and anxiety and depression. It is likely they will end up in the final COS since these are also some of the most measured outcomes in PR trials[5]. This is partly in line with a recent expert consensus that advised exercise capacity, dyspnoea, quality of life, nutritional status and occupational status as the essential components to be assessed in PR[22], and with a COS developed for COPD in primary care

physiotherapy practices which included exercise capacity, muscle strength, physical activity, dyspnoea and quality of life as core outcomes[23]. However, it is important to note that the expert consensus gathered mostly HCP, overlooking patients' perspectives, which is fundamental for the development of a COS.

Conflicting views were observed regarding the inclusion of lung function, muscle strength, physical activity, self-efficacy, anxiety and depression, exercise capacity, body mass index and balance. Moreover, some outcomes were not identified as crucial by both stakeholder groups (i.e., swallowing function, cognitive function) and others were only identified as crucial by one of the stakeholder groups (i.e., coping strategies pain, motivation, frailty, oxygen saturation, fat mass, fat free mass and phase angle alpha, balance, biomarkers/blood analysis, smoking cessation, energy expenditure). These findings highlight the importance of conducting a Delphi survey with all key stakeholders to achieve consensus on what should be measured as a minimum in PR.

Furthermore, although it is known that resting lung function remains unchanged and is not a goal of PR[24,25], stakeholders, particularly patients seem to value it as an outcome of PR. This result in combination with the fact that patients were less comfortable naming non-crucial outcomes and discussing measures due to lack of knowledge, underlines the need of clarifying to patients what is being measured with which measure, why and what effects can be expected from PR. In fact, studies have highlighted the need to promote health literacy for people with COPD, with up to 59% of patients with limited health literacy[26,27].

In the present study no list of outcomes was provided to participants, i.e., they had to think about the crucial outcomes for them. Therefore, it is possible that when confronted with the outcomes to be scored in a Delphi survey, some outcomes that were rarely reported especially by patients (e.g., health-related quality of life) will be classified as important.

This study also revealed future challenges for the COS uptake. Firstly, the choice of the most suitable measure for each outcome will be highly challenging, as stakeholders emphasized the COS only to be useful if measures are practical across different settings and resources. Hence, it is possible that some gold-standards will not be recommended and an additional consensus-method might be needed[28] to have a balance between quality and feasibility. Furthermore, although advantages and disadvantages of measures are displayed in this manuscript and might be useful in the future to decide "how to measure" the COS, a systematic review of their measurement properties before drawing recommendations is necessary.

Additionally, due to the importance of the COS for benchmarking PR and conducting more robust studies, strategies are needed to minimise the possible reluctance of HCPs to change and its misuse as a maximum rather than a minimum set of measurements. Strategies such as having the COS advised by a trusted source (i.e., internationally recognised respiratory society), advising measures that are already commonly used, and explaining the importance of the COS, might be important to minimise reluctance to change among HCPs. Although the use of the COS as a maximum of measurements for PR cannot be avoided, the number of outcomes to be included in the COS should be carefully thought. Five to nine outcomes have been advised by COS initiatives in other fields[29], but this may need to be further discussed for PR, as with too little outcomes the assessment might not be comprehensive enough and with too many outcomes, people might not have time to assess other relevant aspects for their patients or research. Some of these advantages and challenges, such as the COS being useful for meta-analysis, and the difficulty on 'how' to measure once the 'what' has been defined, have also been previously recognised on a study exploring the uptake of COS in Cochrane systematic reviews[30]. Furthermore, in an era of personalised medicine, the outcomes and measures to be included in the COS should not preclude conducting more comprehensive and

personalised assessments of people with COPD, nor tailoring PR to each individual's needs.

This study provided a list of outcomes, that combined with those reported in the literature[5], will inform a future Delphi survey to achieve consensus on what should be measured as a minimum in PR.

Some limitations need to be acknowledged. The interviews were conducted in several languages, and some were translated to English (only forward translation), hence it is possible that some cultural inherent expressions and meanings got lost. Nonetheless, all translations and English-speaking interviews were conducted by English proficient speakers. Similarly to published COS in other areas, Africa and Asia were underrepresented in this study[31]. Additionally, although we had participants from the American continent, there was a lack of views from large countries such as the United States of America or Argentina. Hence, future research for this COS (i.e., Delphi survey), should include people from these continents, as resources and PR practices may vary and therefore their perspectives are important to consider. Additionally, views of informal carers although previously explored[16], could be important, but were not included in this study due to difficulties in recruitment. Hence, future steps of the COS (e.g., Delphi and consensus meeting) should include these participants.

Conclusion

This study provided important insights into outcome measurement in PR from the perspectives of different international stakeholders and provided a list of outcomes that combined with outcomes prevenient from the literature will inform a future consensus study. Future studies should include informal carers in the process and achieve consensus on 'what' to measure and 'how' to measure in PR.

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Supplementary materials

Appendix A – Interview guides, procedures of trustworthiness and research team reflexivity

Table A.1. Interview guide used with people with chronic obstructive pulmonary disease.

Topics	Sub-topics	Questions	Probes
Essential outcomes	• Experienced outcomes of PR • Positive outcomes • Negative outcomes • Outcomes perceived as most important	Can you share outcomes (positive or negative) you perceived during or after finishing a pulmonary rehabilitation programme?	- Can you elaborate further on that outcome? - What sort of effects did you perceive?
		Of all the outcomes mentioned, can you share which ones (positive and negative) are more important/crucial to you?	- What outcomes should always be measured? - Why are those outcomes important? - Why are does outcomes more important than others?
		Is there any outcome that should not be	

		included in the core outcome set?	
Outcome measures	• Importance of measuring outcomes • Measurements perceived as positive • Measurements perceived as negative • Outcome measures perceived as important/meaningful	How do you feel about measuring those outcomes? How do you feel about the outcome measures to assess those outcomes? Can you share which measure or measures (test or questionnaires) you consider essential for PR? Is there any measure you consider not essential to be used in PR?	- Is it meaningful to you? Why? - If needed, give examples (physical tests, questionnaires) - What does it mean to you? - Why do you consider them essential? - Can you tell me advantages and disadvantages of using it? - Why?

Different settings	• Outcomes in different settings • Outcome measures in different settings • Different recommendations for different settings	What are your thoughts about having specific outcomes for specific settings? Is there any outcome we did not talk before that you consider essential for a specific setting? Why? What are your thoughts about having specific outcome	- Give examples of outcomes talked before - Explain settings (hospital, community, home) - What do you think of the relevance of outcomes according to each setting? - Is there anything specific for a setting that you think we should pay attention to? Why? - What do you think of the relevance of outcome

		measures/tests in each setting?	measures according to each setting?
Phenotypes and the COS	• Different outcomes for different phenotypes of patients • Different outcome measures for different phenotypes of patients	What are your thoughts about measuring specific outcomes for different types of patients? What are your thoughts about having specific outcome measures (same outcome) for different types of patients?	- Give examples of outcomes talked before - Explain different groups of patients (oxygen dependent, frail, etc) - Is there anything specific for a type of patient that you think we should pay attention to? Why?

The COS itself	• Advantages of having a COS • Enablers to accomplish a COS • Disadvantages of having a COS • Barriers to accomplish a COS • Recommendations	Can you tell me any advantage of having a core outcome set in this field?	- Why do you think that is an advantage? - How do you feel about having a COS for pulmonary rehabilitation and COPD? Why?
		Do you see any disadvantage of having a COS?	- What? - Why is that a disadvantage?
		Is there anything you can perceive as a barrier to accomplish this COS?	- *Rephrase if needed.* What do you think that can make this COS not useful in the future? - Why?
		Is there anything that can help this COS to be successful?	- *Rephrase if needed.* What do you think can make this COS applicable in the future? - Why?

		Is there any other recommendation you would like to give?	- Is there anything else you would like to say about this topic? - Do you have any advice for the developers?

COS: Core outcome set; PR: Pulmonary rehabilitation

Table A.2. Interview guide used with healthcare professionals, researchers and policy makers.

Topics	Sub-topics	Questions	Probes
Essential outcomes	• Perceived outcomes of PR • Positive outcomes • Negative outcomes • Outcomes perceived as most important	Can you share outcomes (positive and negative) of pulmonary rehabilitation experienced by patients with COPD?	- Can you elaborate further on that outcome? - Did you perceive any effect/outcome that was not measured?
		Of all the outcomes mentioned, can you share which ones (positive and negative) are more important/crucia	- What outcomes should always be measured? - Why are those outcomes important? - Why are those outcomes more

		l to you as a healthcare professional/researcher/policy maker? Is there any outcome that should not be included in the core outcome set?	important than others?
Outcome measures	• Importance of measuring outcomes • Measurements perceived as positive • Measurements perceived as negative • Outcome measures perceived as important/meaningful	How do you feel about the outcome measures used to assess those outcomes? Can you share which measure or measures (test or questionnaires) you consider essential for PR?	- If needed, give examples (physical tests, questionnaires) - What does it mean to you? - Why do you consider them essential? - Can you tell me advantages and disadvantages of using it?

		Is there any measure you consider not essential to be used in PR?	- Why?
Different settings	• Outcomes in different settings • Outcome measures in different settings • Different recommendations for different settings	What are your thoughts about having specific outcomes for specific settings? Is there any outcome we did not talk before that you	- Give examples of outcomes talked before - Explain settings (hospital, community, home) - What do you think of the relevance of outcomes according to each setting? - Is there anything specific for a setting that you think we should pay attention to? Why?

		consider essential for other setting? Why? What are your thoughts about having specific outcome measures/tests in each setting?	- What do you think of the relevance of outcome measures according to each setting?
Phenotypes and the COS	• Different outcomes for different phenotypes of patients • Different outcome measures for different phenotypes of patients	What are your thoughts about having specific outcomes for different phenotypes of patients? What do you think about	- Give examples of outcomes talked before - Explain different phenotypes (less symptomatic, oxygen dependent, different comorbidities, etc) - Is there anything specific for a type of patient that you think we should pay attention to? Why?

		having specific outcome measures (same outcome) for different phenotypes of patients?	
The COS itself	• Advantages of having a COS • Enablers to accomplish a COS • Disadvantages of having a COS • Barriers to accomplish a COS • Recommendations	Can you tell me any advantage of having a core outcome set in this field? Do you see any disadvantage of having a COS? Is there anything you can perceive as a barrier to accomplish this COS?	- Why do you think that is an advantage? - How do you feel about having a COS for pulmonary rehabilitation and COPD? Why? - What? - Why is that a disadvantage? - *Rephrase if needed.* What do you think can make this COS not useful in the future? - Why?

		Is there anything that can help this COS to be successful?	- *Rephrase if needed.* What do you think can make this COS applicable in the future? - Why?
		Is there any other recommendation you would like to give?	- Is there anything else you would like to say about this topic? - Do you have any advice for the developers?

Table A.3. Criteria and procedures used to ensure trustworthiness.

Criteria	Description of the procedures performed
Credibility	Ensured by i) data triangulation – data were collected from different stakeholders, different countries, by different researchers and methods (e.g., interviews and field notes); ii) researchers triangulation – different perspectives on the analysis were discussed and agreed between team members; iii) member-checking to test findings with participants.
Transferability	Ensured by describing the study in detail; sampling strategies, characteristics of researchers (their role and background), participants and contexts of data acquisition as well as all procedures of the analysis.
Dependability	Ensured by having the research process explained, well documented and traceable (i.e., records of raw data, field notes, transcripts, memos, codebook were kept).

Confirmability	Ensured by providing participants quotes to confirm researchers' findings, and by ensuring credibility, transferability, and dependability.

Research team and reflexivity

S.S-M is a PhD student with experience in conducting qualitative studies and has been involved in assessment of people with COPD and implementing PR programmes for about 6 years. S.S-M conducted the interviews with the HCPs, several interviews with people with COPD, transcribed most interviews and first analysed all the data. S.S-M is aware of the multiple benefits of PR and has her own general views of some outcomes being more important than others but tried to set her experience aside and remain neutral. Participants were aware of her motivations to conduct the research, but no personal opinions were revealed to the participants.

A.W.V, R.G. and A.G conducted, transcribed and translated interviews of non-English speaking people with COPD. They are experienced researchers and have been involved in the design, assessment and implementation of PR programmes. They are aware of the several outcomes of the intervention and of their own preferences but remained neutral throughout the interviews without disclosing their own perspectives.

M.A.S. and A.M are experienced researchers with expertise in the field of PR and qualitative studies and discussed and refined the analysis and report with S.S-M. They too had their own preferences of top outcomes and measures but made an effort to remain neutral through the analytical process.

Appendix B – Crucial, non-crucial outcomes and outcomes healthcare professionals were not sure about including in the core outcome set.

Table B.1. Outcomes reported by the two stakeholders as crucial, non-crucial, and outcomes with discrepant views.

Crucial outcomes			**Non-crucial outcomes**	
Outcome	No. people with COPD that reported outcome	No. of HCP/researchers /policy makers that reported the outcome	Outcome	No. participants that reported (only reported by HCPs/researchers/policy makers)
Exercise capacity	6 (35%)	16 (80%)	Lung function	9 (45%)
Dyspnoea	9 (53%)	10 (50%)	Handgrip strength	3 (15%)
Anxiety, distress, depression, general mood, and disease-specific fears	9 (53%)	8 (40%)	Physical activity	3 (15%)
Muscle strength/function	6 (35%)	9 (45%)	Cognitive function	3 (15%)
Functional status and ADL	6 (35%)	9 (45%)	Muscle strength	2 (10%)
Health-related quality of life	1 (6%)	13 (65%)	Anxiety and depression	2 (10%)
Physical activity	2 (11.8%)	10 (50%)	Exercise capacity	2 (10%)
Fatigue/Loss of energy	5 (29.4%)	6 (30%)	Respiratory muscle function	1 (5%)
Lung function	6 (35%)	2 (10%)	Self-efficacy	1 (5%)
Social status	5 (29.4%)	3 (15%)	Body mass index	1 (5%)
Knowledge	2 (11.8%)	4 (20%)	Balance	1 (5%)
AECOPD	3 (17.6%)	3 (15%)	Swallowing function	1 (5%)
Sleep	3 (17.6%)	2 (10%)		
Coping strategies	N.R	5 (25%)		
Healthcare utilisation	1 (6%)	3 (15%)		
Self-efficacy	N.R	3 (15%)		
Pain	N.R	2 (10%)		
Cough	1 (6%)	1 (5%)		
Motivation	N.R	2 (10%)		
Frailty	N.R	2 (10%)		

Oxygen saturation	2 (11.8%)	N.R
Care dependency	1 (6%)	1 (5%)
Fat mass, fat free mass and phase angle alpha	N.R	2 (10%)
Balance/Agility	2 (11.8%)	N.R
Body mass index	N.R	1 (5%)
Energy expenditure	N.R	1 (5%)
Smoking cessation	1 (6%)	N.R
Biomarkers/blood analysis	1 (6%)	N.R

N.R.: Not reported.

Table B.2. Crucial outcomes from the perspectives of both stakeholder groups (people with COPD and healthcare professionals)

Outcomes	Number of times reported	Summary of reasons given	Citations	Speaker
Exercise capacity	22 • 35% people with COPD • 80% HCP/researchers/policy makers	Objective, reflects the treatment effect and the ability of what patients can do, might translate to their ability to do more activities of daily living, important predictor of function and participation in society	"I do think that exercise capacity should always be measured. (...) because that's showing what a patient can do, it doesn't show what a patient will do, but it shows what a patient can do and so, what we also can expect after the rehab programme from a patient."	Delilah, 41yo, MD
			"(…) exercise capacity as well because it's like the bulk of the training that you do so, it might be interesting to have an outcome of that as well. (…) I think because it might be one of the most proximal measures, because, like I said like if the balk of what you do is exercise training and you do it with the intention of improving exercise capacity, then measuring something that is really closely related to what you're trying to improve. And also, I do feel it's helpful to have a more or less objective outcome measure as well. (...) Of course if it would be, and we know that is not the case, but you know, in a hypothetical situation where exercise capacity wouldn't matter at all in COPD long-term outcomes, like mortality or exacerbations, then I would say it's not important to measure it, but since it's something that you really focus on your intervention I do feel like it's important on different levels to just looking at the quality of your programme, like are you achieving what you hoped to achieve in your programme, or be able to compare with other interventions or other type of outcomes. So, there I do, I do feel very strongly that it's an important outcome."	Tobias, 46yo, Psychologist
			"The most important outcome for me is exercise capacity. So that I can manage my daily life easier again. This is my greatest motivation for pulmonary rehabilitation."	Simon, male, 61yo, person with COPD
Dyspnoea	19	One of the main COPD symptoms,	"It's the main thing that patients talk about in terms of their symptom management and what affects them in terms of their health-related quality of life."	Sarah, 36yo, Physiotherapist

	• 53% people with COPD • 50% HCP/researchers/policy makers	important for patients, impairs their quality of life, one of the goals of PR	"If we think of a core outcome for everyone, I think is dyspnoea and fatigue could be the most important ones. (..) they matter to patients. They will define whether the patient thinks the rehabilitation programme was successful. This is also the aim of the rehabilitation programme, to make the patients feel better. Of course, we have a lot of secondary aims that we want to achieve as a healthcare provider, but in the end the patient wants to feel better, so I think that's the crucial part."	Connor, 40yo, Physiotherapist
			"One thing that is absolutely noticeable is our capacity to breathe. Breathing better and stop having, sometimes I still do have breathlessness." (…) Less breathlessness. From the top of my head, and by far breathlessness [is the most important outcome]. Breathlessness is a terrifying experience, very, very scary. When you have a programme that reduces that sensation of not breathing, the value is their in the first place, right? Breathlessness is a frightening situation. It's psychologically devastating, even if one has a great control over himself."	Elizabeth, female, 71yo, person with COPD
Anxiety, distress, depression, general mood and disease-specific fears	17 • 53% people with COPD • 40% HCP/researchers/policy makers	Affects other outcomes, impacts behaviour change, can be improved with PR	"Then as a psychologist, of course, would always recommend to collect main psychological symptoms, whether they have been improved, anxiety for example, depression, and hm, disease-specific fears, that the participants or the patients might have. (…) Well, because we know that, hmm, general levels of negative affect, such as general anxiety for example, they are already doing not very good to the patients, in other words they contribute to worse outcomes. (...) So you assess them [disease-specific fears] at the beginning of PR and you see 'well this person has a specific fear, let's say, of moving', then you can directly address that in your treatment, whereas in other patient maybe not have any fears of movement but he or she might be very afraid of the progress of the disease, that that will soon be very, very bad, and that might be her or his problem, and so you want to tackle this specific problem."	Anthony, 46yo, Psychologist
			"For me mental health outcomes have to be a core, for me are extremely important, so anxiety, depression, as the most simplistic sense of looking at it. Because I feel that is still a, unfortunately, not underrecognized but	Caleb, 40yo, Physiotherapist

			underappreciated aspect of the benefits of pulmonary rehab in this group. So that has to be in there in my opinion."	
			"You feel a lot better mentally wise. Feel as though you can sort of do a lot more than you could before. A lot of people find it hard to do the programme, but if you stick at it is very beneficial, definitely. It stimulates you, because you can actually see 'well there is a bit of a life afterwards', you know? There's hope."	Grace, female, 71yo, person with COPD
Muscle function/strength	15 • 35% people with COPD • 45% HCP/researchers/policy makers	Improve other outcomes (e.g., functional status, ADL), important for HCP, can be the cause of symptoms, it can be improved with PR,	"We know that about one third of the COPD population have muscle dysfunction so, when they feel dyspnoea and they feel out of breath could be related to their function of the muscles. So this is why I also think this should be something that we have to look at. (...) So, if you have a patient that you suspect this patient is limited by muscle strength, then we should measure the strength. But if you have patient that you don't suspect strength is the problem, then measuring the strength and targeting the strength with pulmonary rehabilitation makes no sense. And then, perhaps other aspects, for example endurance or muscle power. We have seen that in healthy elderly, power seems to be important for many aspects of daily life. So, I think power is coming more and more, and I believe that several research groups are looking into the power of the muscle, but I wouldn't say that 'okay you should do, you should always do strength or always do endurance or always power'."	Aaron, 36yo, Physiotherapist
			"Lower limb strength I think we should be assessing (…) I don't think it's something that patients always say 'oh I have weak leg muscles', sometimes they do, but then you see that they struggle to get up from a chair, they struggle climbing stairs, so again I think that's something that we need to improve so they can go about their daily life."	Sarah, 36yo, Physiotherapist
			"But also, the test to measure the strength, this is also important. Well, look, at start of pulmonary rehabilitation these tests are performed, and also at the end. And then you can see how much you improved. I think it is important to measure improvement in relevant outcomes of	Hannah, female, 64yo, person with COPD

				pulmonary rehabilitation, and these tests reflect the progress made through rehabilitation."	
Functional status/ADL	15 • 35% people with COPD • 45% HCP/researchers/policy makers		It matters to patients, impacts other important outcomes (e.g., HRQoL)	"They are not important for me, but they are important for the client, for the rehabilitant, yeah, so, that's why it depends on what is his life about. So, for some patients, they experience problems with hmm, with dressing. And that's very important, but there also patients who experience problems with dressing but don't think is that important, because they want to spend their energy hmm, on their children or grandchildren. So, it's the problematic activities that are important for them and then is important for me."	Nicole, 34yo, Occupational therapist
				" (…) And getting dressed, showering, eating, all these things are so private, so if you need help with them, your quality of life decreases. So that's why it's so important for us to kind of help them to help themselves. "	Helen, 40yo, Occupational therapist
				"I think we should [measure it], because nobody likes to admit that, you know, it's hard brushing your teeth, you know what I'm saying? Or it's like 'Oh God, getting out of the bathtub. Oh, Jesus Christ.' You know? (…) If you're going to live independently, it's important that you're able to do the necessary things to live independently. For independent living, it's important that you're able to do that or get the type of help, support, whether it's a stool for your shower or... so that you're able to live independently as long as you can."	Patrick, male, 75yo, person with COPD
Health-related quality of life	14 • 6% people with COPD • 65% HCP/researchers/policy makers		It's important for patients, it's impaired in a lot of patients, shows the impact of the disease on daily life, it's one of the aims and can	"I think, one of the main things that I think about is whether they, they feel better or not, as a, as an outcome, I think you would either just conceptualise it as self-rated health or go a bit more into detail and conceptualise it as quality of life, but I think, at least from a patient perspective, I think that's the first thing that comes to mind and if you want to, also from healthcare providers perspective, if you want to convince people of why they should try and participate into pulmonary rehabilitation, I think the idea that has an impact on how you feel on a day-to-day basis might be really important. (...) pulmonary rehabilitation is a quite intense, extensive treatment, and so I feel like it	Tobias, 46yo, Psychologist

		be improved with PR	only should matter or has the potential to matter if you can have this positive impact on the lives of the patients. (...) My main motivation is because this is a patient-centred outcome that really tries to take into account the effects of the treatment on what matters for them."	
			"I would say quality of life, mm, and why, I think because the reason we practice is to improve well-being and the lives of people that we're working with. So, if we can achieve improved quality of life that makes a huge difference to overall well-being. So, that's highly important."	Victoria, 49yo, Nurse
			"When you have less dyspnoea, you have a better quality of life. If I continue at home, I can reach a level where I do not always only sit at home. And as a consequence, quality of life is improving more or less automatically. (…) The whole quality of life is all about what I used to do before my COPD or what I liked to do and being with other people is important for me, because with COPD you isolate yourself a bit."	Christine, female, 68yo, person with COPD
Physical activity	12 • 12% people with COPD • 50% HCP/researchers/policy makers	It's important to maintain the benefits of PR, it matters to patients, it's related to other outcomes and prognosis	"I think that physical activity is so important to maintain the benefits of the rehab programme after the rehab programme. (...) And I think that when we measure that frequently, you can also identify problems early. So, 'I see that you're moving less, what's going on?', and I think that we don't do that enough."	Delilah, 41yo, MD
			"(...) several reasons, I think. So, when you talk with patients with COPD they tell you they have troubles in being physically active. So patients tell you this, and the other one is, it is really linked to the prognosis of patients. The more active the patients are, the less likely they need to be hospitalized in the next future and the best is the prognosis. Also when you use mortality as an outcome. So, I think we have good reasons to put them in a core outcome set for pulmonary rehab."	Andrew, 59yo, Physiotherapist
			"That is one of the most important things that I've learned from all my stays, which is, the best thing you can do for yourself is to be physically active according to your level. (…) And I knew that in order to remain fit, you have to keep active. Otherwise, you, all creatures I would assume, you know, use it or lose it, right? So that's important."	Patrick, male, 75yo, person with COPD

Fatigue/Loss of energy	11 • 29% people with COPD • 30% HCP/researchers/policy makers	One of the main COPD symptoms, important for patients, it can be improved with PR	"(...) because in the end symptoms, especially if they are linked to activities of daily life, they're directly what the patient is feeling. I mean, this what the patient is limited by and these are the aspects that directly limit the quality of life of patients. If you experience symptoms, you're not feeling well and then you feel the disease impact. So, I think improving symptoms is one of the core aims of a rehabilitation programme, and therefore is a very important measure to do. And then, not only focus on dyspnoea, but I think we should focus on dyspnoea but also on fatigue. I think these 2 are the most important ones in general, for every patient, and then we should look for individual patients, what other symptoms they also suffer from, and of course we also have to follow them up. If we think of a core outcome for everyone, I think is dyspnoea and fatigue could be the most important ones. (...) they matter to patients. They will actually define whether the patient thinks the rehabilitation programme was successful. This is also the aim of the rehabilitation programme, to make the patients feel better. Of course, we have a lot of secondary aims that we want to achieve as a healthcare provider, but in the end the patient wants to feel better, so I think that's the crucial part."	Connor, 40yo, Physiotherapist
			"And another main symptom which have not received, I think, the attention that should receive is fatigue. (...) It's the second main symptom. When we talk to patients with COPD, 'what bothers you?', they come up with dyspnea and three seconds later they come up with fatigue. And sometimes they use them interchangeably, they call it dyspnoea, but they mean fatigue, and when they call it fatigue they mean dyspnoea."	Andrew, 59yo, Physiotherapist
			"Physical exercise gives you energy, right? At least to me it does. I can enter [the session] more tired, but I leave energised, physical exercise gives me energy, physical energy and affective energy, intellectual. It gives me energy. (…) When I don't have energy, when I am very tired, I stay in sofa-bed bed-sofa mode. I can't read, I can't work, I can't do absolutely nothing. It's an absolute state of apathy, looking at the TV	Elizabeth, female, 71yo, person with COPD

				like a zombie, not even seeing what is happening on the tv. And this a very uncomfortable feeling. Being energised means that I work, I am a volunteer. And that is very important for me, to maintain this level of activity, read a lot, I always have, didn't need a lockdown to read. Also with my grandchildren. Basically, energy is important so I can do my volunteer activities and to feel better about myself."	
Lung function	8 • 35% people with COPD • 10% HCP/researchers/policy makers		Good to know especially if pharmacotherapy has not been optimized, important for patients to track their disease	"Well, to control for it, you want to know how severely impaired the patients' lungs are before you start the rehab and want to also see how that develops over the course of PR, especially if you start often PR with optimizing the pharmacological therapy, for example."	Anthony, 46yo, Psychologist
				"I feel that it should have to do with lung function, something that patients may be able to improve or at least to not further reduce due to rehabilitation."	Tobias, 46yo, Psychologist
				"The spirometry [is important]. If we can keep our stability, to stabilize the disease, it's great. The later the disease progresses the better for us." Int: "But do you think this should be done specifically in pulmonary rehab?" "Yes, to make sure the values don't go up and down, being always between those parameters is wonderful for a COPD patient."	Charles, male, 49yo, person with COPD
Social status	8 • 29% people with COPD • 15% HCP/researchers/policy makers		Patients tend to isolate themselves, everyone needs somebody, it's a human need to be able to contribute to society	"Because social support can be super supportive and helpful for affective patients if you have somebody that helps you with, let's say daily little things, like go shopping, that motivates you to go out for a little walk, someone to talk to, someone to have the feeling that shares the concerns and the problems that you have yourself. (…) And a related concept is actually loneliness. Which describes how people experience their isolation and whether they have or not somebody to talk to, and the feeling that there is somebody who cares for them, for the problems."	Anthony, 46yo, Psychologist
				"(…) humans first of all to survive need food, water and to be kept safe. Then they need love. Then they need to feel self-esteem and then right at the top is being involved and to be able to contribute to society."	Emma, 57yo, Nurse
				"Being with other people is important for me, because with COPD you isolate yourself a bit because first you feel inhibited to go outside, then depending on the weather and mobility. (…) The social aspect [is the	Christine, female, 68yo, patient

				most important outcome]. Because without friends or social contact there is no quality of life."	
Knowledge	6 • 12% people with COPD • 20% HCP/researchers/policy makers	It might influence response to treatment, impacts other outcomes (i.e., self-management), improves with PR		"Also, like learning styles and knowledge they have, so, how your treatment should be built. (…) yes, I think a different learning style or coping style will influence [the treatment] or could divide groups."	Nicole, 34yo, Occupational therapist
				"Another important is knowledge. Another outcome would be to measure knowledge, before and after. (…) Yeah, knowledge about the disease and management of the disease. Knowledge about exercise, the importance of managing, self-care."	Diana, 54yo, Physiotherapist
				"As I learned from you about how to breath when I got scared and started to hyperventilate, that was important and that has been stuck with me. Also learning how to use medications, that was also very important. "	Theresa, female, 73yo, person with COPD
AECOPD	6 • 18% people with COPD • 15% HCP/researchers/policy makers	Important for long-term benefits, impact other important outcomes and prognosis		"The other impacts that are really crucial and have to be there: exacerbations or hospitalizations, however you want to phrase that. If we are not trying to break the cycle, then I say it's fundamentally a flaw, if we are not able to achieve some long-term change."	Caleb, 40yo, Physiotherapist
				"Yeah, exacerbations. Exacerbations of all kinds and not just hospitalisations as well. I would say moderate as well as severe exacerbations, again because of the impact that exacerbations have on other outcomes."	Victoria, 49yo, Nurse
				"It's difficult to say [why it's important to measure], but it's important because I forget that I have COPD. I feel good, like I don't have any problem. (…) It's very important, it's essential, it's one of those results that I want to know when there is a new action."	Cameron, male, 77yo, person with COPD
Sleep	5 • 18% people with COPD • 10% HCP/researc	Important for patients, might improve with PR		"So these are symptoms that are very common, have major affects but again understudied and underdiagnosed as well. (…) Really valuable in terms of measuring the things that are really important to patients."	Victoria, 49yo, Nurse
				"Because many with COPD have problems lying down sleeping because the breathing gets so hard. So there are some technical aids that they can have on their bed, so they can sleep in their bed because many of them maybe sit in a chair and the rest is so poor. So when you don't have so	Helen, 40yo, Occupational therapist

		hers/policy makers		much energy and you sleep poorly you hardly have any energy to do anything at all. And also because many with COPD after a while, maybe have some cognitive symptoms and if you don't even sleep they will be worse. So that's why sleep is so important."	
				"Because if you don't [sleep well], you're not going to have the energy that you need to have during the day. It's going to affect you physically, poor sleep, me, facts. And energy-wise cognitively, I'm groggy. I don't know how you measure it, but that's your problem, right? ((laughs))"	Patrick, male, 75yo, person with COPD
Coping strategies	5 • Not reported by people with COPD • 25% HCP/researchers/policy makers		It can be improved with PR, it affects other outcomes, allows personalising intervention	"So, you can train the people, help them to cope better with their disease, to find more sense in other parts of their life, so they can deal better with the disease and can improve the quality of life."	Anthony, 46yo, Psychologist
				"[pulmonary rehabilitation] is also how to learn to cope with their life with a chronic disease, is so they can handle their everyday life, with fatigue and loss of energy and shortness of breath. I think it's important for the patient because it's what gives them, I would say, their quality of life, that they can cope with their disease"	Martha, 40yo, Occupational therapist
Healthcare utilisation	4 • 6% people with COPD • 15% HCP/researchers/policy makers		It's a source of financial burden, it's important to show the intervention is cost-effective	"So, hospitalizations for instance, not only hospitalizations due to exacerbations of COPD but also for other reasons. Many patients with COPD have other conditions as well, I don't know many patients with COPD as the only diagnosis they have. They have many, many other physical, social, psychological troubles which prone them to hospitalizations. (...) They spend 6000 euros per year more [than the average person]. And when you look where they spend that money on, where they spend the 8000 euros on, they spend only 2000 euros on their COPD and they spend 6000 euros on the other conditions. Especially hospitalizations for other conditions, chronic, usually chronic conditions. So I think pulmonary rehabilitation could be a strong intervention also to help patients to care better for themselves, to improve their set of management skills, which can help to prevent hospitalizations, not only for their respiratory disease but also for the other conditions. When we do it well, when we design our pulmonary	Andrew, 59yo, Physiotherapist

				rehabilitation programmes well, I think we have the ability, we have the power to have a positive effect on that outcome."	
				"I would also say from a healthcare payer perspective, we should be looking at healthcare utilisation, because if we want to be able to advocate for these programmes, then we need to be able to show that it's a cost-effective intervention. So, reductions in hospitalisations."	Victoria, 49yo, Nurse
Self-efficacy	3	• Not reported by people with COPD • 15% HCP/researchers/policy makers	Especially good for the home setting, can be improved with PR	"People talk about improvements (...) and feeling better about themselves, or feeling more confident in their abilities, and I guess some of that is with how pulmonary rehabilitation can sometimes challenge people's perceptions of what they can safely do, so, those are some of the big things"	Lily, 28yo, Researcher
				"But to be honest I don't have a preferred measure. I think you should look at the evidence and see which one has more validity and reliability but should measure self-efficacy for sure. And self-efficacy has become so much more important with tele-rehab because, you know, it gives you an idea of how much they can do at home."	Diana, 54yo, Physiotherapist
Pain	2	• Not reported by people with COPD • 10% HCP/researchers/policy makers	Common symptom, important for patients, improves with PR	"Which I think is also really important, but not something that is routinely measured in many pulmonary rehab programmes, is things like fatigue, sleep and pain (…) So these are symptoms that are very common, have major affects but again undertested and underdiagnosed as well. (...) And they are really valuable in terms of measuring the things that are really important to patients."	Victoria, 49yo, Nurse
				"It's a physical well-being, the person feels well physically, not having pain for example in the back. It's a very typical thing in people of my age, isn't it? And being a whole day working without back pain or very residual one, that's very important right?"	Elizabeth, female, 71yo, person with COPD
Cough	2	• 6% people with COPD • 5% HCP/researc	Important, embarrassing symptom, improves with PR	"Well, I think so, because for some patients that's more relevant, for others may be less, but one should assess it, and if it's a major problem they should get in contact with techniques for example that relief cough, so, they could learn to cough more efficiently, for example. (...) because I think for some patients it's relevant, they don't like this urge to cough in public."	Anthony, 46yo, Psychologist

		hers/policy makers		"[it's important] because it holds you to breathe, you need to control your breathing and you need to cough up when you can. And then, the exercises, the breathing exercises help you with the control of that really, you know, I can't really explain it."	Grace, female, 71yo, person with COPD
Motivation	2 • Not reported by people with COPD • 10% HCP/researchers/policy makers		Important to tailor PR to those less motivated, might be improved with PR	"I personally, I think it might be good to have some sort of motivation measure so you can target those who have low motivation."	Emma, 57yo, Nurse
				"It's very interrelated with the physical side, particularly with anxiety as well, but that kind of, people talk about improvements in motivation (...) and I guess some of that is with how pulmonary rehabilitation can sometimes challenge people's perceptions of what they can safely do, so, those are some of the big things."	Lily, 28yo, Researcher
Frailty	2 • Not reported by people with COPD • 10% HCP/researchers/policy makers		It's related to other important outcomes, it acknowledges other comorbidities	" I think, because frailty, if you can measure frailty and you can improve frailty, frailty correlates with so many other things like hospital admission, quality of life, mortality, comorbidities, etc. If we can show that we're improving their frailty, then we're actually ticking a lot of boxes."	Emma, 57yo, Nurse
				"I guess one of the things that I'm conscious of is although we're, sometimes we're doing studies and we're recruiting people because they have COPD, they will often have multiple other conditions that they're living with, and sometimes what's the most important to us as a researchers is their COPD, but actually for them it's kind of 'I'm now going to pulmonary rehabilitation' yes it helps with their COPD but it's also helping with their broader picture of their health, and not the conditions that they're living with. So, and that's why I think frailty is particularly useful as a kind of a global measure of health regardless of diagnosis and also, I guess because a lot of, you know in some of our measures, I think with some of the physical measures that we do, or some of the quality measures that we have for people with COPD, are quite tied up in their experience of breathlessness and their experience with their respiratory condition which is very important, but I think	Lily, 28yo, Researcher

				measures like frailty kind of acknowledge the global impact of multiple health conditions that they may likely be living with."	
Oxygen saturation	2 • 12% people with COPD • Not reported by HCP/researchers/policy makers		It's not visible/felt, might hinder independency	"Well because these things are not visible, you can't see it if something is wrong, and it is also important. For example, I know that I have an impaired endurance and also my strength is decreased. I know that because I notice that in daily life, but I don't know if my saturation is low. So, it is also important to measure these outcomes."	Kevin, male, 63yo, person with COPD
				"It's the oxygen saturation that has been important to me. I lost my driver's license due to low oxygen saturation. So that is important to notice."	Theresa, female, 73yo, person with COPD
Care dependency	2 • 6% people with COPD • 5% HCP/researchers/policy makers		It affects other outcomes and impacts caregivers' burden	"Hmm, care dependency is also important, I think. (…) Because care dependency also has a major impact on quality of life, but also on survival and also has practical consequences, such as the help you need to organize the home environment, and also for the loved ones, how much family caregiving burden can be."	Delilah, 41yo, MD
				"Yes, it should be assessed before and after. If he has family support, how is his social structure at home, the environment, a lot of things are hidden, and nobody asks. I think this is a really big negative point. Nobody cares about this part. Because everyone [friends] would ask 'don't you have anyone that helps?'. No, I never did. And there were times when I was struggling and I didn't have any help, I had to look for it. And those that can't… is the worst thing."	Charles, male, 49yo, person with COPD
Fat mass, fat free mass and phase angle alpha	2 • Not reported by people with COPD • 10% HCP/researchers/policy makers		It's related to the aim of the nutritional intervention; it shows a more comprehensive view of the patient	"For those who have a lower BMI there is the aim to increase both the fat free mass but also the fat mass. So then comes the second methodology, to measure the body composition. So that is also lacking right now, mostly in the clinical work, for most of the dietitians. Obviously, we get much more information if they have gone up in increasing weight by 2 kg, 'was it the muscle mass or the fat mass, or was it the water only?' Because you're not giving the therapy that their body water should increase, they should get more fat free mass or muscle mass. So, definitely, from that point of view".	Norah, 51yo, Dietitian

				"I want to look into, I don't know if you've heard about something called phase angle alpha. (…) so, it's the bioelectrical impedance scale that can assess this. And that looks more at cells in the body actually, and how they will be affected by the nutritional situation. But we don't do it now, but I want to look into it, because weight is only one small part of a nutritional assessment."	Taylor, 35yo, Dietitian
Balance/Agility	2 • 12% people with COPD • Not reported by HCP/researchers/policy makers	It helps with confidence for ADL		"Yes [I value agility], because I am in a house that has stairs, and climbing up and down stairs without fear and without having to hold the handrail is something that I value a lot."	Elizabeth, female, 71yo, person with COPD
				"Oh yes [it's important]. I can't, you know what is a drunk? I can't go around like a drunk person, right?"	Harold, 73yo, person with COPD
BMI	1 • Not reported by people with COPD • 5% HCP/researchers/policy makers	It's important for prognosis, affects other outcomes		"You can see that a BMI below twenty-one is not really good for the patients. They, in a sense if they have a little, if they have more, it will reduce the mortality risk, morbidity and mortality risk. That's for undernutrition, and for overweight it makes it easier to breathe if you don't have that much weight, if you're overweight or obese and, and of course it will reduce the cardiovascular risk as well. (...) So at least like weight, BMI and weight change, I think that should be assessed everywhere."	Taylor, 35yo, Dietitian
Energy expenditure	1 • Not reported by people with COPD • 5% HCP/researchers/policy makers	It's necessary to individualise and adjust the intervention		"Hmm, we do have just body weight and height. But to be able to know how much they, we have, we know at the group level how much energy require they have and so on, but at individual level we don't have the methods to measure. So, as a dietitian I would absolutely want to measure their energy expenditure. (...) I feel that I don't have appropriate instruments to measure, in this case energy expenditure, so that I could give much more individualized nutritional therapy. So, by measuring energy expenditure I will be looking just at that patient's expenditure, which would help me to calculate how much do they need to eat."	Norah, 51yo, Dietitian

Smoking cessation	1 • 6% people with COPD • Not reported by HCP/researchers/policy makers	Important for patients, impacts other outcomes	"Well, the most important thing for me was that I quit smoking, I was able to accomplish this goal. I think this is important for me as [smoking] is the start of a vicious circle. If I continue to smoke after completing my rehabilitation, then, I guess that everything I have achieved will be for nothing, that my endurance and strength will soon be back to the level before I started rehabilitation. Now that I quit smoking, I am able to do a lot more at home and without getting out of breath."	Kevin, male, 63yo, person with COPD
Biomarkers/blood analysis	1 • 6% people with COPD • Not reported by HCP/researchers/policy makers	Because these are parameter that cannot be seen/felt	"…and the blood analysis. Well because these things are not visible, you can't see it if something is wrong, and it is also important. For example, I know that I have an impaired endurance and also my strength is decreased. I know that because I notice that in daily life, but I don't know if my, for example cholesterol level is too high. So, it is also important to measure these outcomes."	Kevin, male, 63yo, person with COPD

Table B.3. Non-crucial outcomes from the perspectives of healthcare professionals/researchers/policy makers.

Outcomes	Number of times reported	Summary of reasons given	Citations	Speaker
Lung function	9 (45%)	It's not an aim of PR, it does not change with PR, we might give false expectations to patients by measuring it	"I think that measuring lung function after rehab is not very useful. (...) well, we are not targeting, pulmonary rehabilitation is not usually improving lung function, of course when people are medically not optimally treated, then you optimize their medical treatment during pulmonary rehab, you can have an influence. But pulmonary rehab is not usually focused on improving lung function. So, I think that's a measure that is not so relevant afterwards."	Delilah, 41yo, MD
			"No, because I think that pulmonary rehab doesn't aim to change and probably doesn't change pulmonary function and I think that patients, I	Sarah, 36yo, Physiotherapist

			think we confuse patients in terms of their expectations. So I don't think focusing on lung function is much useful."	
Handgrip strength	3 (15%)	It doesn't change with PR, it's not an aim of the intervention, it's more important to know the functional activities they can('t) do.	"(...) handgrip strength as an outcome I think it's a bit useless for rehabilitation because we are not targeting to change it and could be interesting in general, as a general screening for people to look at general weakness but is way not specific enough to use as a targeted outcome for rehabilitation so, I think it's totally useless to use as a follow-up measure."	Connor, 40yo, Physiotherapist
			"I don't' care so much about strength itself, like, I don't care about handgrip measure, I don't think we should have handgrip as part of our core set, because it's not really about the handgrip but is about whether they can function and move around society and do their exercise and so on. (...) we just did a systematic review about handgrip and it is predictable of survival, it is related to exercise capacity, but I don't think we should be measuring it instead of the other measures, because there's too many confounders. So, that's another one that I would put on should not measure, is handgrip."	Diana, 54yo, Physiotherapist
Physical activity	3 (15%)	It's difficult to measure in a reliable way that is feasible, PR doesn't always improve it	"Because we know self-reported physical activity isn't that accurate anyway. And we also know pulmonary rehab doesn't always result in a behaviour change and improved physical activity. So if I was going to get rid of one I would get rid of that. If you have an objective measure of physical activity, and there's many, to give people activity monitors it would be great, but we don't have that for sure."	Sarah, 36yo, Physiotherapist
			"I might sound controversial, I don't think physical activity should be in there, in my opinion. (…) because I think that to do it properly, to do it justice, you need the equipment and the access and the technology, and that's just such a practical challenge for a lot of places, and the evidence isn't even very strong that we affect it through pulmonary rehab."	Caleb, 40yo, Physiotherapist
Cognitive function	3 (15%)	Since not all patients have problems it's	"Again this is personal, cognition, balance, those sort of areas, I don't think they are, or the outcome measures related to them, that are important enough to do for everyone. I think that's the sort of things that	Caleb, 40yo, Physiotherapist

		only good for screening, we don't know enough about it and there's a lack of good outcome measures	if screening detects a problem, then you may do it, but not as across the board everyone has them."	
			"I think it's difficult. When you look at the amount of studies, again this is to my on the topic very limited knowledge, but the amount of studies that have done, have found quite a high amount of prevalence of at least mild cognitive dysfunction in COPD, and this is two to three times as common as in healthy older adults and it's very very closely linked to the prognosis of the patient. You have a patient with COPD that we know has not a good prognosis, but if you have COPD and mild cognitive dysfunction your prognosis is quite a lot worse. But I think when we discuss core outcome measures, or what should we assess, we also need to have a valid way of assessing it, we need to have a reliable way of accessing it, we need to hopefully have normative values so we can compare, and we need to know what is significant or what is a clinically relevant. And I don't think we have that yet when it comes to cognitive dysfunction, but I do think this is important, but perhaps not part of the core outcome set today based on what we know. But people with a specific knowledge in this topic, I guess would argue otherwise."	Aaron, 36yo, Physiotherapist
Muscle strength (not specified)	2 (10%)	Not meaningful for patients, it's more important to know the functional activities they can('t) do.	"Because for a person who is able to do the leg press on 8Kg it will not say if they are able to climb the stairs. So what's important? Climbing stairs, not leg press, I think."	Nicole, 34yo, Occupational therapist
			"And the other one is strength, I don't know if I would be doing, handheld, I would recommend as part of the core data set, handheld (dynamometer) on different muscles, quads and hems, and upper extremity, I think I would focus more on function and mobility measures rather than those. So I've put 3 on the no list."	Diana, 54yo, Physiotherapist
Anxiety and depression	2 (10%)	Not all patients have problems, it should be reassessed only in those who	"I think that everything that turns out pretty normal at the start and therefore you are not really going to tackle, well I don't see the reason why you should reassess it. I mean, you could have a normal HADS score and with exercise training you make it even more normal but what does that mean? Nothing. I mean, it's not wrong to do it, but it's a bit of a waste of time."	Connor, 40yo, Physiotherapist

		were impaired at the beginning	"not routinely because when we discussed the patient's characteristics and the programme at a multidisciplinary level, we are used to have a consultant which is a psychologist so, after the discussion with the psychologist we decide whether to test these characteristics of the patient in order to include in the course of pulmonary rehabilitation specific meetings for dealing with the problems of the patients. We do measure anxiety and depression in case the patient is already known to be depressed." Int: So you wouldn't measure in all patients, you would only measure if the patient had already signs of… "Of an alteration, yes."	Elliot, 58yo, MD
Exercise capacity	2 (10%)	It can't be always improved and might frustrate patients who still respond in other outcomes, not meaningful for patients	"I'm going to be very brave here, because my opinion won't be popular, but I don't think the walking test tells us very much. So, I would get rid of that. (…) And what we're saying to these patients by using the exercise tolerance tests is, they feel that if they don't improve their exercise tolerance they failed. (...) because by making it an exercise programme where this successful/failure is based predominantly in an improvement in walking distance, then to my mind, that programme becomes very exclusive, and instead of capturing the people who really need pulmonary rehab, what you're doing is only focusing, it's exclusive to people who are very motivated, and don't mind, are not afraid of doing physical exercise."	Emma, 57yo, Nurse
			"But when they want to walk like 15 minutes to their daughter, I don't care about the 6-minute test, because I want to know if they are able to walk 15 minutes to their daughter. And as an occupational therapist I think they should slowly walk for 6 minutes so they are able to walk 15 minutes in total, so I think that is not an important test as well. And I think there are more examples like that, but now all the physical therapists are mad at me, I think."	Nicole, 34yo, Occupational therapist
Respiratory muscle function	1 (5%)	Not all patients have respiratory muscle	"I think, respiratory muscle function, it's interesting to use as a screening tool and if a patient has weak inspiratory muscles you want to train it and then you want to test it again. But in patients that you don't do	Connor, 40yo, Physiotherapist

		weakness, it can't be improved in all patients	respiratory muscle training, I think it's pretty useless to measure it again after 3 or 6 months. And I have done that a lot, I have done that a lot myself, 3-month measurements, 6-month measurements of respiratory muscles, but the only thing you can see is that it remains the same."	
Self-efficacy	1 (5%)	It doesn't always change with PR	"Well, it doesn't always change with pulmonary rehab and that's either because of the measure, or it's because we don't really focus on behaviour change very much with pulmonary rehab and it's just because we are not experts in that and we often don't have access to people who are. So, I just, yeah, if I was to get rid of two it would be physical activity and self-efficacy."	Sarah, 36yo, Physiotherapist
BMI	1 (5%)	Not all patients need to improve it	"(…) and I don't think all patients need that. It's more individualised, just when they have the problem [underweight or overweight] we have to work with it. "	Martha, 40yo, Occupational therapist
Balance	1 (5%)	Not all patients have problems, it should be reassessed only in those who were impaired at the beginning	"Again this is personal, cognition, balance, those sort of areas, I don't think they are, or the outcome measures related to them, that are important enough to do for everyone. I think that's the sort of things that if screening detects a problem, then you may do it, but not as across the board everyone has them."	Caleb, 40yo, Physiotherapist
Swallowing function	1 (5%)	Should be used only for screening	"Yes, it is a screening. But it's not a thing that you measure before and after. Just a screening to see if we can help them."	Norah, 51yo, Dietitian

Table B.4. Outcomes that healthcare professionals weren't certain about including in the core outcome set.

Outcomes	**Number of times reported**	**Summary of reasons given**	**Citations**	**Speaker**

Balance	5 (25%)	Important for long-term but not every patient is limited, especially important for telerehab	"(…) And maybe that's too what we do about balance. Balance we screen everybody, and if they come out with a problem then you go to the next level."	Diana, 54yo, Physiotherapist
			"But I think that Balance it's really really important when using the telemedicine. (...) Because normally, for example in the training, they were in the training room and now they were training in their own for example in the living room or the kitchen or where they were, and they were not thinking about their environment. And how it could be good or bad, so I saw that some of them had loss of balance."	Martha, 40yo, Occupational therapist
Anxiety and depression	2 (10%)	Might be important only for patients who show an impairment at the beginning	"I think sometimes there can be, like when you're having a conversation with the patient in the beginning if they bring up that they felt they had low mood or you're picking up signals like heart rate and anxiety, I think we can use as outcome measures, but I'm not sure is something that we need to do with everybody."	Sarah, 36yo, Physiotherapist
			"What I think we should do is put a screen of depression and anxiety in the core dataset. And the ones that you do get evidence that they're depressed or anxious, then you would do a full measure."	Diana, 54yo, Physiotherapist
Muscle function	2 (10%)	Not all patients are affected and therefore not all need training and reassessment, assessment might scare patients	"Let me take the example of COPD patients with quite some level of muscle weakness, for that patient you want to see that they improved the muscle function, so you measure it before and afterwards. If you have a patient, another patient that has super good muscle function, no weakness at all, in those patients it may not help a lot to train those muscles if they are very well trained, and then you don't need to assess that in the end again."	Anthony, 46yo, Psychologist
			"I know some of my colleagues, pulmonary rehab colleagues would argue about measures of muscle strength. I know quadriceps strength, possibly, the 1-minute sit-to-stand, but again, I think we might be frightening our patients when they first come, and you know, it's one of those things, do we want a programme that is patient-friendly or do we want to be really scientific and pass the audit every year, you know?"	Emma, 57yo, Nurse
Dietary intake	2 (10%)		"Maybe it's more important in the second meeting, if there isn't much change. Even if you individualised the therapy, then we would like to	Norah, 51yo, Dietitian

		The measures are not robust enough	know, or I would like to know, how does the patient eat, what do they eat, how often do they eat, what are the portions, because we know that dietary intake methods as of now, all of them have flaws."	
			"And of course, we want to affect the nutritional adequacy of the diet as well, but we don't really measure it in any way."	Taylor, 35yo, Dietitian
Knowledge	2 (10%)	It's targeted within PR but patients might feel they are doing an exam	"(...) what I think is of course, also a good outcome, something to tackle at least in pulmonary rehabilitation, is of course knowledge about the disease that you have. So, that's the patient education element that a good PR programme always has. I don't know whether that is a real outcome measure but, of course you want to include that in your treatment, and I mean, you can hope that they improve their knowledge by this, and yeah, you can also ask that. But on the other hand side you don't want to having them sitting there and doing an exam and saying 'well now I have 10 questions about the disease, so what's the right answer?'"	Anthony, 46yo, Psychologist
			"I think it's important when you have a pulmonary rehabilitation that they get the knowledge, how to handle their lung disease so they will feel less inhibited by the COPD in their daily life. (…) I think it's a lot about that patient education that we make sure that they get, the knowledge so they can understand, the knowledge is a lot of things, it could be for example how the lungs function, how they manage the shortness of breath, but also diet, nutrition. How they can do their medication is also important. (...) In a way I could say yes because then you could measure it, in another way I would like to say no because it would be like an exam for them."	Martha, 40yo, Occupational therapist
Pain	1 (5%)	Might be important only for patients who show an impairment at the beginning	"So, I think, perhaps not for every patient, but if a patient brings up issues with pain or balance, I think they should be assessed as well."	Sarah, 36yo, Physiotherapist

Loss of appetite	1 (5%)	Not as important as other outcomes	"It would be an addition. It might not be as important as measuring energy expenditure. You can ask the patient, like, one can ask the patient 'how do you feel? How is…?' You can dabble a bit. You can ask like 'how would you say your appetite is?' and if they say it's not good' 'how good do you get hungry?', so that you can dabble when we meet a patient in a meeting. But I think that measuring energy expenditure is much more important."	Norah, 51yo, Dietitian
BMI	1 (5%)	It's better to measure it than nothing, but it has flaws (e.g., doesn't allow personalising much the intervention)	"Even if I say that BMI doesn't give us all the information, yet it has still been shown to be a good predictor of mortality. So, it's better to measure something which can still predict their outcome. So, despite the disadvantages of BMI, it's still a good measure. (...) It also important to know what is their BMI so how much can you push them in terms of physical activity."	Norah, 51yo, Dietitian
Fat free mass	1 (5%)	The measures are not feasible for all	"I guess it's not that necessary, as BMI and weight change. But ultimately that's what we want to see a difference in. But it's, we lacked a bit equipment, if you're going to do it like really accurate it can be quite expensive."	Taylor, 35yo, Dietitian
Frailty	1 (5%)	We still don't know enough about this outcome, not relevant for all patients	"Personally, while it is not a current area that we are looking into, I do think also frailty, is in a subset of patients, something that is really crucial, because, I feel that pulmonary rehab can be of value for people with frailty, but we are not yet sticked in evidence-based practice in that area."	Caleb, 40yo, Physiotherapist
Self-management skills	1 (5%)	Important but probably not core	"I think it's really necessary to measure things like self-management skills that include inhaler technique and adherence and things like that. But I don't know if they need to be an outcome for the programme. I mean it would be nice to know that you've improved self-management skills like inhaler technique, cause that's really important, but whether or not it needs to be within an outcome set or just rather part of the programme, I am not sure."	Victoria, 49yo, Nurse

Social status	1 (5%)	More important on long-term, it's not something we are actively trying to change	" I don't think it's an outcome per se or if it's more kind of the experience of it, but there are social aspects of pulmonary rehabilitation I think sometimes people find, because they can become quite isolated or lonely as a result of living with COPD, and particularly with the impacts of breathlessness, that the opportunity to kind of go and be in a place with other people who are experiencing similar things to them, and again, that can kind of contribute to kind of psychological things like their mood, but also just the feeling of being less isolated or lonely as they see there are others in a similar position as them. (...) I don't know, I think, one of my things that I'm thinking about is that I know that the overall aim of pulmonary rehabilitation is sort of mapping out the mechanisms and what we are trying to do with pulmonary rehabilitation. I guess improving people's kind of social connections and things like that is like, it feels quite secondary, it's kind of an unintended benefit for some people. But it is very important to people that's the other thing, and I think it can be kind of a forgotten aspect, we often use words like psychosocial, but actually we are really just talking about psychological. (...) because I think it's actually more the longer-term consequences where that might become more important, because, I guess what we would hope is that people are feeling better about themselves and feeling fitter they may be more able to engage with other people socially, it may be, you know, they would be able to move so they're actively daily living and connecting with people potentially in their community a bit more. But if it's more about the immediate kind of impact of that, you know initial 6 to 8 weeks, then what you might be measuring is the actual contact of that social group which will be stopping. So, it's tricky. I think it's definitely something worth considering, and I wonder if it's more about people's kind of subjective feelings of loneliness, rather than the kind of more objective social connection measures."	Lily, 28yo, Researcher
HRQoL	1 (5%)	It might not be needed because	"it's a difficult concept, quality of life. It is often used as an outcome, but I doubt whether we should put it in the core outcome set, because I think it's the result of all the others, which finally at the end of the day, perhaps	Andrew, 59yo, Physiotherapist

		it's a result of other outcomes	may improve the quality of life. So I'm not really sure if we should put it on the core outcome set. It's a soft multidimensional outcome."	
Personal goals	1 (5%)	It's important to have a patient-centred intervention but there is a lack of measures	"I think, but I don't have a solution for that, but in pulmonary rehab we are sometimes not paying attention enough to the personal goals of patients, and preferably we should have a very good measure to assess personal goals, at the beginning of the rehab programme and to assess personal goals at the end of the programme. But I don't have a perfect solution for that, at this moment. How you can assess that in a constructive and comparable way in different settings and for different patients."	Delilah, 41yo, MD

Appendix C – Advantages and disadvantages of different measures from the perspectives of different stakeholders.

Table C.1. Advantages and disadvantages of using different measures, from the perspectives of people with COPD and healthcare professionals.

Exercise capacity	
Six-minute walking test (n=25)	
Advantages	**Disadvantages**
Affordable *"I mean given that you have also some settings where the technical, organisational, hmm, yeah, conditions settings are not very good, I would say 'well if you have a poor country, a rehab center that has no cycle ergometer, but they have a corridor that is long enough, well then you go for a 6-minute walking test'"*, Anthony, 46yo, Psychologist More functional *"I do prefer it above the CPET, yeah. I think a CPET is very important at the beginning of a rehab programme to assess how safe it is to exercise, but to assess outcomes afterwards, I think the 6-minute walking distance is a more functional measure, also showing more what a patient can do on daily life"*, Delilah, 41yo, MD *"So, in this context I feel that walking tests are more useful. Because everybody wants to be able to walk as long as possible."*, Christine, 68yo, person with COPD Psychometrically robust *"We use the 6-minute walking test (…) and also because scientific literature informs us that it is a reliable measure to use and so, I think*	Needs a long corridor *"Sometimes you have to look for an alternative, if you are doing home-based rehab it will be difficult to perform a 6-min walk distance."*, Delilah, 41yo, MD *"And also, the walking test in the hallway where you have to walk a certain distance and turn, how long is it?" "Int: Thirty meters." "Well, that is not possible at my physiotherapist, but probably not in other settings either."*, Benjamin, 67yo, person with COPD Might scare patients and cause dropouts *"So, I've used both the 6-minute walking distance and shuttle walk test, I think, I have very strong views about it because my patients, when they come to their initial assessment, they do that test and loads of them drop out, because they think, it makes them so tired and so distressed and they think it's all going to be like that. So, I find that it causes a lot of dropouts."*, Emma, 57yo, Nurse Needs a practice test *"My other thing about field walking tests is that actually, having to do the practice test before, from a very objective point of view, in a pulmonary rehab*

this would be very easy to apply to different categories of patients.", Elliot, 58yo, MD

It shows the benefits of rehabilitation, meaningful to patients

"The 6-minute walking distance test is able to catch what the patients may obtain from a rehabilitation course.", Elliot, 58yo, MD

"Because they count how many meters you do in six minutes, and then you can see from the first test to this one how many meters you improved. It's important.", George, 68yo, person with COPD

"Especially with the six-minute, yeah. Because they can see how they're getting better.", Martha, 40yo, Occupational therapist

It's familiar

"I like the 6-minute as a personal preference, yeah. But that's probably because it's what I've done like for a long long time, and you know, the familiarity is there. And there's a lot of data, a lot of data that supports the use of 6-minute walk test in a COPD population as well.", Victoria, 49yo, Nurse

Complements cardiopulmonary exercise testing

"If you have a maximal exercise test, I think it would be stupid to combine that with a shuttle walk test because you're measuring the same concept of exercise, and it would be more interesting to complement that with a 6-minute walk test in my view.", Connor, 40yo, Physiotherapist

Better for patients who are more impaired

"So, in patients who can hardly walk I don't think the incremental shuttle would be great, I think the 6-minute would be better, and I think class, you just haven't got time and it's, you know, it's not very practical.", Emma, 57yo, Nurse

It's self-paced so it doesn't show real endurance capacity

"I think, a problem with the 6-min walk test is that it's self-paced. So, I think it's not the best test to investigate the type of interventions that we do, that are related to more endurance and aerobic capacity.", Aaron, 36yo, Physiotherapist

"Because on the treadmill I felt I had to use myself more compared to when I walked in the corridor. (...) on the treadmill you increase, increase, increase while on the walking test you just walk in the same speed. Even if I walked 30 meters more this time on that walking test, I don't know, I did not push myself, you know?", Theresa, 73yo, person with COPD

Not meaningful for daily activities

"But when they want to walk like 15 minutes to their daughter, I don't care about the 6-minute test, because I want to know if they are able to walk 15 minutes to their daughter. And as an occupational therapist I think they should slowly walk for 6 minutes so they are able to walk 15 minutes in total so, I think that is not an important test as well", Nicole, 34yo, Occupational therapist

Not the most responsive measure for pulmonary rehabilitation

"Well, some argument not to do the 6-minute walk test is that is less responsive to the intervention, right? Patients typically have their critical walking speed and they don't change it that much.", Connor, 40yo, Physiotherapist

Not very comprehensive

"When we have the possibility with all the measurements on the treadmill and all that, I clearly think that that is the best. (...) It gives more results. It shows more parameters of how you're doing or ho w bad you're doing. And the six

the incremental would be greater in others.", Diana, 54yo, Physiotherapist Feasible in clinical practice *"I probably would say if this is a core outcome set then something that's feasible for most programmes that would be important, so that would be something like a 6-minute walk test or incremental shuttle walk test.",* Victoria, 49yo, Nurse Easy to perform *"The other one [6-minute walking test] is easy, it's very easy to do.",* Harrison, 59yo, person with COPD It's useful to adjust oxygen therapy *"It's a way to see if the patient with COPD needs anything else, if he needs oxygen or other medication. It's really good, you can see a lot of things.",* Charles, 49yo, person with COPD It's useful for exercise prescription *"It tests my maximum in that moment, and as I said, if it helps you [prescribe exercise] I think it should be done.",* Cameron, 77yo, person with COPD	*minutes testing just measures how long I could walk for six minutes. I don't think it measures anything else.",* Harrison, 59yo, person with COPD Type of floor might influence results *"I don´t know if there is a standardized procedure for the 6-minute walk test, but if so, I would suggest to use that everywhere. (...) is the floor also standardized? Because it can be slippery sometimes depending on your shoes.",* Simon, 61yo, person with COPD Not possible to measure in patients with some disabilities *"There are people sitting in a wheelchair, I walk past those people, I can imagine that you will use other outcomes compared to me. Maybe the six-minute walk test will be less important in that case.",* Willow, 63yo, person with COPD
Cardiopulmonary exercise testing (n=11)	
Complements the six-minute walking test *"Let me say if you have a maximal exercise test, I think it would be stupid to combine that with a shuttle walk test because your measuring the same concept of exercise, and it would be more interesting to complement that with a 6 min walk test in my view.",* Connor, 40yo, Physiotherapist It's good to assess safety of the intervention	Difficult to do for some patients *"As a researcher I would say before and after, and as a clinician I would say before. How we evaluate the effect with others. Because, well, it's a tough test also for the patient.",* Connor, 40yo, Physiotherapist *"(...) well, some are not pleasant. (...) that on that bike. Maybe because these are difficult to perform for me, but also for other lung patients. Because of the dyspnoea.",* Willow, 63yo, person with COPD

"It's some kind of security for tolerance effort and also coronary problems.", Frank, 57yo, MD *"For me that was very important, I did not know this blood gas analysis during exercise. It took my fear that my CO_2 levels increase too high, since my CO_2 increases in the night. That's why I wear this mask during the night. (...) I found this very valuable. "*, Sandra, 56yo, person with COPD It gives a lot of information *"Yes, the treadmill test I had, when I had all this stuff connected to my body, that test gave me a lot of useful information. At least I thought that test told me a lot even if the test was exhausting, and I think that test is very important."*, Theresa, 73yo, person with COPD	Not feasible for most settings/countries *"Cardiopulmonary exercise testing (…) requires a lot of investments in terms of opportunity to have this test in the lab, so, it's not easy to have it all over the world, or all over the labs within the same country."*, Elliot, 58yo, MD *"But it's very expensive, I think. Because you'll need a specialist and I assume he's a cardiologist, right? Yeah. So, you know, mucho dinero."*, Patrick, 75yo, person with COPD It might not reflect endurance capacity *"(..) and CPET measures maximal exercise capacity, but we have also, of course, endurance, general endurance capacity, and CPET might not reflect that very well."*, Andrew, 59yo, Physiotherapist It's not very responsive to pulmonary rehabilitation *"(…) another argument against CPET is that the improvement in most studies is relatively small. 5%, 10%, perhaps 15% on average but that's it."*, Andrew, 59yo, Physiotherapist Not functional enough *"(…) but to assess outcomes afterwards, I think the 6-minute walking distance is a more functional measure, also showing more what a patient can do on daily life."*, Delilah, 41yo, MD *"For me I think it is not [essential to measure] the one on the cycle ergometer, because I never cycle. I never cycle and I didn't have any cycle training during my rehabilitation here either. During the endurance training I have always, let's say, performed the training on the treadmill. I have not cycled, I never cycle."*, Willow, 63yo, person with COPD
Incremental shuttle walk test (n=10)	

Measures maximum exercise capacity

"So, I know that they take longer to do both of them, but I think incremental shuttle walk test is a true measure of maximum exercise capacity. It's controlled, because of course it gets more difficult incrementally.", Sarah, 36yo, Physiotherapist

Good for patients with more capacity

"(...) In patients who can hardly walk I don't think the incremental shuttle would be great, I think the 6 minutes would be better, and I think the incremental would be greater in the others.", Diana, 54yo, Physiotherapist

Feasible in clinical practice

"I probably would say if this is a core outcome set then something that's feasible for most programmes that would be important, so that would be something like a 6-minute walk test or incremental shuttle walk test."

Good for exercise prescription

"And I like it for prescribing exercise as well, exercise prescription I think a shuttle is good for that, and the same with the endurance as well used in combination.", Sarah, 36yo, Physiotherapist

Not self-paced

"For the result to be more reliable [than the six-minute walk test] I think this one is great for you. (...) Because there is time between one beep and the other, so there is a certain cadence. I think that test is more complete, although it takes longer.", Cameron, 77yo, person with COPD

Might scare patients and cause dropouts

"So, I've used both the 6-minute walking distance and shuttle walk test, I think, I have very strong views about it because my patients, when they come to their initial assessment, they do that test and loads of them drop out, because it makes them so tired and so distressed and they think it's all going to be like that. So, I find that it causes a lot of dropouts. I think the shuttle is worse, I think that's the worst one, but when they come it's the first thing that they do, and it's not right, and at the very end, sometimes if they're not very well they don't achieve their potential, and they're psychologically crushed.", Emma, 57yo, Nurse

"I think the 6-minute walking pace [is better], not to the beep, the beep one gets quite fast and really pushes you out, I think." Int: Is it distressing? "Yes, yeah, yeah.", Grace, 71yo, person with COPD

Time consuming

"I know that they take longer to do both of them [ISWT and ESWT] (...)", Sarah, 36yo, Physiotherapist

"I think that test is more complete, although it takes longer.", Cameron, 77yo, person with COPD

Does not complement a cardiopulmonary exercise test

"(...) if you have a maximal exercise test, I think it would be stupid to combine that with a shuttle walk test because your measuring the same concept of exercise (...)", Connor, 40yo, Physiotherapist

It's necessary to also do the endurance shuttle walk test

"(...) the shuttle test my only reluctance is that it needs to be an incremental plus an endurance, I don't really think you could do just one, I think you need that endurance for full responsiveness.", Caleb, 40yo, Physiotherapist

	Not very good for patients with low capacity *"(...) In patients who can hardly walk I don't think the incremental shuttle would be great, I think the 6 minutes would be better, and I think the incremental would be greater in the others."*, Diana, 54yo, Physiotherapist
Endurance shuttle walk test (n=5)	
Not self-paced *"I think an endurance shuttle walk test that is based on an incremental shuttle walk test is more individualised and it's not self-paced, and this is why I think it's better."*, Aaron, 36yo, Physiotherapist Good for exercise prescription *"And I like it for prescribing exercise as well, exercise prescription I think a shuttle is good for that, and the same with the endurance as well used in combination."*, Sarah, 36yo, Physiotherapist	Difficult to implement *"(...) because these are tests that are pretty tough to perform, everything needs to be very much standardized, let's say preferably laboratory conditions, I think it's pretty challenging to do that in a good way, so maybe I would avoid to make that core."*, Connor, 40yo, Physiotherapist It's necessary to also do an incremental shuttle walk test *"(...) the shuttle test my only reluctance is that it needs to be an incremental plus an endurance, I don't really think you could do just one, I think you need that endurance for full responsiveness."*, Caleb, 40yo, Physiotherapist
Step tests (not specified) (n=3)	
Complements a walking test *"I liked it, it's different than walking, the effort is bigger, right? But I think they it is good, in fact the two complement each other in terms of the assessment of the patient's capacity, they complement each other [ISWT and step test]"*, Cameron, 77yo, person with COPD	Not feasible for most settings/countries *"(...) we got colleagues who have worked in other studies where they've been doing sort of step tests where you kind of need 2 people there to ensure safety, and all of that kind of adds to the costs and the complications of doing those measures. And I think, you know, people are doing pulmonary rehabilitation in lots of different settings and have a lot of diversity in access to resources and capacity to have that support."*, Lily, 28yo, Researcher Not meaningful to patients *"I don't know what that test measures, you know? I have difficulties [giving my opinion] because I don't know."*, Mary, 63yo, person with COPD
Dyspnoea	

Borg scale (n=4)	
It's possible to measure other aspects than dyspnoea intensity *"Although I have to specify, you can also use the Borg scale but ask for different things on the Borg scale. You can use a Borg scale to ask for the intensity of breathlessness, and you can also use a Borg scale to ask for the affective distress or unpleasantness of breathlessness. It just a different descriptor that you are using."*, Anthony, 46yo, Psychologist Particularly good to use during physical activity/exercise *"It depends a little bit on when your measuring dyspnoea. I think that subjective scales, such as the Borg scale for example, it's not optimal but it's not too bad to use this, especially when it comes to dyspnoea during activities."*, Aaron, 36yo, Physiotherapist The original is more precise than the modified *"That had more range, I thought that scale was great because it was bigger the range, I feel that when I say 12 or 13 is closer to the correct value, to the truth, whilst in a smaller scale is more difficult, right?"*, Cameron, 77yo, person with COPD	Very generic *"What I personally think is that there should not only be a general measure of dyspnoea, let's say on a Borg scale 'how breathless have you been last week', but that you also include something more on the affective side of breathlessness, so have a measure that asks, distinct, differentially, 'what was your intensity of breathlessness' on the one side, and on the other side, 'how affectively distressing was it, how unpleasant is the dyspnoea for you'."*, Anthony, 46yo, Psychologist It takes time to get familiarised *"Learning that takes some time. Maybe a week. When they come for the first time in the centre they need to experiment. 'If I do that I am 1, if I do this I am 3, 4, and when I did that I was 8! Oh!' and when they remember all these situations at the end they are able to know. But it's a pathway, you do not know that at the first time."*, Frank, 57yo, MD
Dyspnoea-12 questionnaire (D-12)(n=2)	
Comprehensive assessment of dyspnoea *"What I personally think is that should not only be a general measure of dyspnoea, but that you also include something more on the affective side of breathlessness, so have a measure that asks, differentially, what was your intensity of breathlessness on the one side, and on the other side, how affectively distressing was it, how unpleasant is the dyspnoea for you. (...) we have the D12 from the British colleagues, that have at*	

least sensory and affective differences and sometimes also the main qualities of breathlessness.", Anthony 46yo, Psychologist Short and easy to use *"If I was thinking about 'I'm going to improve dyspnoea' specifically, then I'll use something like a D-12 which again is easy, feasible to implement and takes very little time.",* Victoria, 49yo, Nurse	
Chronic respiratory disease questionnaire (CRQ) (n=2)	
Psychometrically robust *"It has a dimension, one dimension is dyspnoea with a 7-point Likert scale for the patient's 5 most important activities where they are evaluated, and that is very sensitive to change. So that could be an argument to recommend that measure for the evaluation of the effect of pulmonary rehab programme on dyspnoea intensity, perceptions of dyspnoea.",* Andrew, 59yo, Physiotherapist	
Modified medical research council dyspnoea questionnaire (mMRC) (n=6)	
Frequently used *"We know the MRC scale is a widely used one [measure of dyspnoea]",* Andrew, 59yo, Physiotherapist It's more functional *"We also use the MRC which I know isn't typical dyspnoea, is about function but it can give you some insight into people's breathlessness as well, so I think that's quite a useful one.",* Sarah, 36yo, Physiotherapist Psychometrically robust *"There's a pretty well accepted minimal important change established there, I think the characteristics in general, the clinimetrics are okay, so I think the mMRC is a possible instrument that is well accepted and*	Not very responsive to pulmonary rehabilitation *"(...) But we know that it is insensitive, relatively insensitive to pulmonary rehab. So I wouldn't recommend the MRC as an outcome measure.",* Andrew, 59yo, Physiotherapist Difficult for some patients to understand *"I think it's difficult sometimes to use it. We're trying to use it with patients but they have difficulty saying where they are 'are you a one, three, four, five?'",* Martha, 40yo, Occupational therapist

I see no reason to drop it and change it for something else let's say.", Connor, 40yo, Physiotherapist Short and easy to use *"We use the mMRC for dyspnoea. I like this one, it's pretty fast.",* David, 31yo, Physiotherapist	
Multidimensional dyspnoea profile (MDPI) (n=1)	
Comprehensive assessment of dyspnoea *"So, we have the MDP, the Multidimensional dyspnoea profile from Bentsen and colleagues in the US, that have at least sensory and affective differences and sometimes also the main qualities of breathlessness.",* Anthony, 46yo, Psychologist	
Pain	
Brief pain inventory (n=1)	
Comprehensive *"I think if somebody was describing quite a lot of pain, I might use the brief-pain inventory, I like the body diagram where they can indicate where the pain is and the different severities of pain.",* Sarah, 36yo, Physiotherapist	
Sleep	
Pittsburgh sleep quality index (n=1)	
Good sleep measure for pulmonary rehabilitation *"(...) if it was an outcome measure that you were looking for to implement in a pulmonary rehab programme in general, probably a sleep quality like the Pittsburgh.",* Victoria, 49yo, Nurse	
Fatigue	

Checklist of individual strength – fatigue scale (CIS-F)(n=1)	
Short and easy to use *"But in the other hand is frequently used in different kinds of pathologies and it's, I mean, it's an easy instrument to work, is short and is informative, so in that way, that could be a possible way [of measuring fatigue]"*, Connor, 40yo, Physiotherapist	There are not enough studies *"We typically use the CIS-fatigue – Checklist individual strength for fatigue, well, I don't have a lot of science to say this is the best one, no, I don't think we have that."*, Connor, 40yo, Physiotherapist
Functional assessment of chronic illness therapy fatigue scale (FACIT-F)(n=2)	
Comprehensive *"I think one of my, one of the questionnaires I like most is the FACIT fatigue scale, because it asks many aspects of fatigue. So we capture the whole fatigue picture, I think one question on how fatigued you are might not be very sensitive."*, Andrew, 59yo, Physiotherapist	
Disease-specific fears	
Breathlessness beliefs questionnaire (n=1)	
Available in English *"Another one we use here now and that it has, I think, an English version is the Breathlessness beliefs questionnaire, BBQ, and that has a scale more targeting fear of breathlessness and the other one fear of physical activities. And I think that has at least 2 major disease-specific fears that I see also in theoretical models of dyspnoea-fear-deconditioning-having more dyspnoea downward spiral, from that perspective."*, Anthony, 46yo, Psychologist	
COPD Angst Fragebogen (CAF) (n=1)	
Comprehensive *"It's named COPD Angst Fragebogen, so COPD anxiety questionnaire, and it has 5 different sub-components, fear of dyspnoea,*	Needs translation/cultural adaptation

fear of activity, fear of disease progression, fear of social exclusion and sleep related worries, which I think is comprehensive. And it's good.", Anthony, 46yo, Psychologist	*"A scale that I personally like is the CAF, the COPD anxiety questionnaire, but that is a German thing. It should be translated that's the question. So, we use it successfully in German samples but yeah",* Anthony, 46yo, Psychologist
Anxiety and distress	
Anxiety inventory for respiratory disease (AIR) (n=1)	
It distinguishes anxiety symptoms from respiratory ones and also measures panic *"... but the AIR I like because it removes all of those somatic items, so the items in theory can't be affected by the disease, they are simply assessing anxiety, and it also contains measures of panic, items related to panic as well which I think is really important, especially in people who have respiratory conditions, and obviously are short of breath and it induces panic.",* Sarah, 36yo, Physiotherapist	Not as convenient as other measures *"I don't think we use that [AIR] because it's not as convenient as HADS, because it measures anxiety and then it means we have to find another measure for depression.",* Sarah, 36yo, Physiotherapist
21-item Depression, anxiety and stress scale (DASS-21) (n=2)	
It also measures stress *"That is also I think a valuable option it has an addition stress scale, sub-scale, which I think also makes sense, so some people may perhaps report more stress relative to anxiety.",* Anthony, 46yo, Psychologist It's available for free *"So HADS has to have a commission to use it technically and the DASS is free",* Caleb, 40yo, Physiotherapist	
Generalised anxiety disorder-7 (GAD-7) (2)	
Good measure for primary care *"PhQ-9 and the GAD-7 that are sometimes combined as a method of psychological distress, and I feel like those are questionnaires that are*	

like in a general, in a primary care practice, they are very good instruments.", Tobias, 46yo, Psychologist It's available for free *"We wouldn't want to recommend a measure that everyone uses if it's going to cost a load amount of money, so, I think some people use things like the General anxiety questionnaire (...) so I guess it would be important that is something that is robust but freely available I guess."*, Lily, 28yo, Researcher	
Hospital anxiety and depression scale (HADS) (n=12)	
Doesn't have somatic items *"It has been used in many studies in COPD patients, and it has the advantage, I think, that disentangles a bit the psychological symptoms from those that can also be caused by the physiological condition that people have. So, some depression or anxiety questionnaires they ask physiological symptoms, which are also key symptoms of COPD for example, and then you kind of mix the psychological problems with the physiological problems, and that is something that you certainly want to avoid."*, Anthony, 46yo, Psychologist Psychometrically robust *"(...) but I find that I always come back to the HADS, because it seems the most reliable of them all."*, Emma, 57yo, Nurse Frequently used *"(...) but the most common used is the HADS, it is sensitive to change also with the pulmonary rehab as an intervention, so, that could be an argument. It has only 16 questions, so it is feasible for patients"*, Andrew, 59yo, Physiotherapist Also assesses depression	It should be discussed with a trained professional *"I think that for a good interpretation, it always needs to be discussed and preferably a psychologist or social worker should be included, or a trained nurse, but I think it's always good to discuss these results. And the conversations that I have pre or post-rehab, when I discuss the results and sometimes patients do not recognise when I say 'oh, it's rather high', so it's not always reliable, but it can help identifying problems in this area."*, Tobias, 46yo, Psychologist It's outdated *"(...) the Hospital Anxiety and Depression Scale is quite, is a very old-fashion tool."*, Emma, 57yo, Nurse It's not available for free *"The only thing that I'm a bit worried with that is that depending on the context you're using it, and it actually can be quite expensive, so, although we found it quite a useful measure, I would have to look again into what the potential cost would be, we wouldn't want to recommend a measure that everyone uses if it's going to cost a load amount of money."*, Lily, 28yo, Researcher

"I know most people are going to say the HADS, and is the one that we used the most, and the advantage of that is that it assesses both anxiety and depression.", Sarah, 36yo, Physiotherapist Short and easy to use *"(...) we use the Hospital Anxiety and Depression Scale, it's also relatively short, for most people easy to complete."*, Tobias, 46yo, Psychologist	It's not disease-specific *"So, we always use the HADS but I start to wonder if something like the AIR which was designed specifically for people with respiratory conditions is more suitable."*, Sarah, 36yo, Physiotherapist
Depression	
21-item Depression, anxiety and stress scale (DASS-21) (n=2)	
It also measures anxiety and stress *"That is also I think a valuable option it has an addition stress scale, sub-scale, which I think also makes sense, so some people may perhaps report more stress relative to anxiety."*, Anthony, 46yo, Psychologist It's available for free *"So HADS has to have a commission to use it technically and the DASS is free"*, Caleb, 40yo, Physiotherapist	
Patient health questionnaire-9 (PHQ-9) (n=3)	
It's available for free *"(...) and things like the PHQ-9, so I guess it would be important that is something that is robust but yeah, freely available I guess."*, Lily, 28yo, Researcher Good measure for primary care *"PhQ-9 and the GAD-7 that are sometimes combined as a method of psychological distress, and I feel like those are questionnaires that are*	

like in a general, in a primary care practice, they are very good instruments.", Tobias, 46yo, Psychologist	
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Doesn't have somatic items *"It has been used in many studies in COPD patients, and it has the advantage, I think, that disentangles a bit the psychological symptoms from those that can also be caused by the physiological condition that people have. So, some depression or anxiety questionnaires they ask physiological symptoms, which are also key symptoms of COPD for example, and then you kind of mix the psychological problems with the physiological problems, and that is something that you certainly want to avoid."*, Anthony, 46yo, Psychologist Psychometrically robust *"(...) but I find that I always come back to the HADS, because it seems the most reliable of them all."*, Emma, 57yo, Nurse Frequently used *"(...) but the most common used is the HADS, it is sensitive to change also with the pulmonary rehab as an intervention, so, that could be an argument. It has only 16 questions, so it is feasible for patients"*, Andrew, 59yo, Physiotherapist Also assesses anxiety *"I know most people are going to say the HADS, and is the one that we used the most, and the advantage of that is that it assesses both anxiety and depression."*, Sarah, 36yo, Physiotherapist Short and easy to use	It should be discussed with a trained professional *"I think that for a good interpretation, it always needs to be discussed and preferably a psychologist or social worker should be included, or a trained nurse, but I think it's always good to discuss these results. And the conversations that I have pre or post-rehab, when I discuss the results and sometimes patients do not recognise when I say 'oh, it's rather high', so it's not always reliable, but it can help identifying problems in this area."*, Tobias, 46yo, Psychologist *"I wonder how and what results they get from this, from all these questionnaires. I apparently just answered one question or maybe several questions wrong and then, well, it turned out that I was depressive. But I am not depressed at all. And that bothered me. Then I wonder what this diagnosis is based on, maybe questionnaires are easy to use, but I think it is better if the caregivers just have a conversation with the patients. I also discussed this afterwards with the psychologist. And perhaps the questionnaires are quick and easy, well, I don't think these can be used to diagnose or classify patients. It is also possible that depressed patients are not classified as depressed on a questionnaire and then they may not receive treatment."*, Hannah, 64yo, person with COPD It's outdated *"(...) the Hospital Anxiety and Depression Scale is quite, is a very old-fashion tool."*, Emma, 57yo, Nurse It's not available for free *"The only thing that I'm a bit worried with that is that depending on the context you're using it, and it actually can be quite expensive, so, although*

"(...) we use the Hospital Anxiety and Depression Scale, it's also relatively short, for most people easy to complete.", Tobias, 46yo, Psychologist	*we found it quite a useful measure, I would have to look again into what the potential cost would be, we wouldn't want to recommend a measure that everyone uses if it's going to cost a load amount of money."*, Lily, 28yo, Researcher It's not disease-specific *"So, we always use the HADS but I start to wonder if something like the AIR which was designed specifically for people with respiratory conditions is more suitable."*, Sarah, 36yo, Physiotherapist
Balance	
Berg balance scale (n=2)	
	Doesn't allow personalising treatment *"I like the Mini-BESTest as it gives you enough information about each of the subsystems of balance, so it allows you to tailor your training programme, to the subsystems that are most impaired. And I think that's why I prefer the BESTest to something like the Berg Balance scale as well.", Sarah, 36yo, Physiotherapist*
Balance evaluation systems test (BESTest) – full version (n=1)	
	Time consuming *"Yeah, so the BESTest takes about 45 min minimum to complete and we just don't have that time clinically.",* Sarah, 36yo, Physiotherapist
Mini balance evaluation systems test (Mini-BESTest) (n=1)	
It allows personalising treatment *"I like the mini-BEST as it gives you enough information about each of the subsystems of balance, so it allows you to tailor your training programme, to the subsystems that are most impaired.",* Sarah, 36yo, Physiotherapist	

Brief balance evaluation systems test (Brief-BESTest) (n=1)	
It allows personalising treatment *"For balance I think we should do the short-form, Brief-BESTest, because then we can really figure out which part of balance is impacted, so you can train it accordingly."*, Diana, 54yo, Physiotherapist	
Timed up and go (TUG) (n=1)	
Easy to use as a first measure to screen for potential impairment *"Haven't looked at them very well, but for balance, you could easily screen with the TUG, and if you need to, then go for the full measure of balance."*, Diana, 54yo, Physiotherapist It can also measure functional status *"For function and balance, in a way that TUG can get both of them, because there's such clarity in the literature, about risk of falling in the community and all of that, I think that TUG is a good measure."*, Diana, 54yo, Physiotherapist	
Functional status and activities of daily living	
Care dependency scale (n=1)	
Easy and comprehensive *"We use the care dependency scale, there are other instruments but I think that including the instrumental activities of daily living is important, so not only the activities of daily living. So, if you want to do an easier assessment of activities of daily living [than COPM], then, yeah, care dependency scale could be an option."*, Delilah, 41yo, MD	It has a ceiling effect *"We use the care dependency scale, but the disadvantage is that it has a ceiling effect."*, Delilah, 41yo, MD
Canadian occupational performance measure (COPM) (n=4)	

It allows personalising treatment *"Why we use it it's because it's personal. I think that's the most important thing (...) as a therapist it's the best way to measure the personal problematic activities because it's personal, and like using a questionnaire [with closed questions] it cannot be personal."*, Nicole, 34yo, Occupational therapist Particularly good to use in home setting *"Is a good tool, especially if you're living at home and you have an occupational therapist coming home too, and you do training on daily activities for like four weeks, and then you can measure after those four weeks, because you have been doing them where you are doing them. But if I have a patient that needs to be independent in getting in and out of bed and we train it here, the patients don't have the same bed at home, like we have here."*, Helen, 40yo, Occupational therapist	It requires a trained occupational therapist *"Our occupational therapist uses the Canadian occupational performance measure, which is I think very good, but it really needs a trained occupational therapist to use that."*, Delilah, 41yo, MD Difficult to use in research *"(...) and I work as a researcher as well and the COPM is like hell for a researcher, but as a therapist it's the best way to measure the personal problematic activities."*, Nicole, 34yo, Occupational therapist Time consuming *"But that's a really big tool. You have to list which activities and you have to grade how you do it today and what's your goal. And I know they may have been using it here before, but it's so difficult for us to measure."*, Helen, 40yo, Occupational therapist
Manchester respiratory activities of daily living questionnaire (n=1)	
Comprehensive *"I think one of the reasons we quite like it is that some of the activities of daily living measures we see in other works, sometimes are restricted to quite basic activities of daily living and then you get quite of a ceiling effect on that. So, we quite liked that this measure had quite a range of kind of more basic and more advanced activities of daily living, and it has got things to do with being outside of the home, like grocery shopping, that and things inside the home and basic stuff and a little bit of social stuff as well. So, it just has a quite nice range of things on there which is why we like it."*, Lily, 28yo, Researcher It's responsive to pulmonary rehabilitation *"I got a feeling that one of the reasons we looked at that as well is that I think that one has shown to be responsive to pulmonary rehabilitation."*, Lily, 28yo, Researcher	

Glittre ADL test (n=2)	
Comprehensive *"It's a very good integrative, global test, with testing balance, speed, endurance, small movements, precision, it's also very important to know that. It's really a picture of reality.",* Frank, 57yo, MD Meaningful to patients *"I think it's important to know your capacity, because sometimes on the day-to-day basis we don't know.",* Mary, 63yo, person with COPD	Causes high levels of fatigue *"I know that I felt really tired, at the end I was extremely tired.",* Mary, 63yo, person with COPD
Sit-to-stand test (not specified) (n=5)	
Good for small spaces/home setting *"But I think going to that kind of functional test, might be like a second-choice alternative in the home situation",* Connor, 40yo, Physiotherapist Meaningful to patients *"Sit-to-stand tests, I think that would be a good functional measure, it gives you a real indication of what matters to patients. So, that would be something under function that I think would be a good idea.",* Diana, 54yo, Physiotherapist Good for people with low capacity *"(...) when we have people with really a low capacity, geriatrics COPD patients, that segment, perhaps a stand to sit test is a suitable one (...)",* Andrew, 59yo, Physiotherapist Feasible for different settings/countries *"I'm overall very positive of using functional tests because if you can do a test that only needs a chair that's excellent. If you can do 5 repetitions or you can do 30 seconds or 1 minute, it's a chair, it's*	There are not enough studies *"It would be good if we for example had a functional test, let's say the sit-to-stand test. We could use that test to discriminate, for example if a person can't do a sit-to-stand, then perhaps the problem for that individual is more related to the strength or the power of the muscles and not the endurance. But if you have a patient who can do sit-to-stands, 5, 11 and then starts to get tired in the muscle, then perhaps it's getting more and more related to the endurance of the muscles, and if you have a person who can sit-to-stand forever and starts getting out of breath, then perhaps it's more a central limitation. But I do not think that we have the evidence, or the support today to say that we can use a functional test for this.",* Aaron, 36yo, Physiotherapist Needs to be standardised *"(...) but here I think it's really important to standardise the instructions.",* Aaron, 36yo, Physiotherapist

doable in home settings, in hospital settings, is doable in all different types of patients and you can get a good score. ", Aaron, 36yo, Physiotherapist	
1-minute sit-to-stand test (n=4)	
Easy to do and patient-friendly *"Yeah, I like this one a lot. It's easily done we just need a chair and now that we use it that commonly, most of the patients already know the test, and they know what to expect and they can really go towards their limits. So, I think this gives a good impression."*, David, 31yo, Physiotherapist Can be used to also assess muscle function *"This is a more recent view of mine, but moving more and more towards more functional muscle measurements like, let's say a 1-min sit-to-stand and thigs like that. Of course, it is not a pure muscle test, right? It's also a little bit of exercise capacity in there (...)"*, Connor, 40yo, Physiotherapist	Might scare patients *"(...) possibly the 1-minute sit-to-stand, but again, I think we might be frightening our patients when they first come (...)"*, Emma, 57yo, Nurse
30-seconds sit-to-stand test (n=1)	
Can be used to also assess muscle function *"Lower limb strength I think we should be assessing using something like a functional strength assessment like a 30-seconds sit-to-stand."*, Sarah, 36yo, Physiotherapist Particularly good for home setting/tele-rehabilitation *"(...) I know people can do it remotely with patients as well, so yes, that would be my preference."*, Sarah, 36yo, Physiotherapist Meaningful to patients	

"(...) so things like the 30-second sit-to-stand, patients seem to quite like it as well because they can see the connection between that and obviously getting up of the chair, and it's something that we've been able to do.", Sarah, 36yo, Physiotherapist	
Short physical performance battery (SPPB) (n=3)	
	It has a ceiling effect *"(...) If we can see that functionality is really limited SPPB is surely something that I would add as an extra measurement. But I would not add it as a core one, because it has such a large ceiling effect. I mean, we tried it in research with COPD patients and it's a bit useless as a general outcome if 80% of them score good to very good."*, Connor, 40yo, Physiotherapist Not feasible for all settings *"(...) but I think you need it to be quite time consuming and it involves, you need a chair for the sit-to-stand, you need 4 meters for the gait speed, so that does have its challenges in terms of sort of what settings you can do that in, for most people it's okay but it can be an issue.",* Lily, 28yo, Researcher
Londrina Activities of Daily living protocol (n=1)	
Easy to perform and patient-friendly *"It wasn't difficult to perform because I do those things at home. I like it, it makes me in a good mood".*, George, 68yo, person with COPD	
6-min pegboard and ring test (n=2)	
Meaningful to patients *"I realised, how much I got tired on the arms, it really gave me a notion of how tired I get on the arms, and I could relate. At home for example, I feel tired when blow drying my hair."*, Mary, 63yo, person with COPD	It might cause pain *"Oh, it hurts a lot, because you have to stay with your arms up and it needs to be fast."*, George, 68yo, person with COPD

Health-related quality of life and impact of the disease	
COPD assessment test (CAT) (n=10)	
Feasible for most settings *"Yes, so, for measuring quality of life in a pulmonary rehab programme I would go with the CAT. It's a health status measure and there are more specific and quality of life measures (...) I'm thinking about this from a feasibility perspective, so, if we want, if we want to be able to measure things then we need to make it so it is not, you know, too long and too much. And that's the reason I'd say CAT over anything else.",* Victoria, 49yo, Nurse It can be used to assess risk change in the ABCD assessment tool *"Yeah I think this one is very versatile because it also has the impact on the risk scale of the GOLD classification and so we can pretty clearly define if someone reduced this risk by taking part in pulmonary rehab.",* David, 31yo, Physiotherapist It can be used to assess individual symptoms *"As an occupational therapist, I can use the overall sum that it gets but I can also see how they're scoring the individual questions.",* Martha, 40yo, Occupational therapist	Not comprehensive enough *"But it also has its limitations, you cannot see every change, relevant change in a COPD assessment test."*, Delilah, 41yo, MD Difficult for some patients *"Whereas I think the CAT people actually need help to complete a lot of the time, I know it's quick to complete, but I think often we need to input a little bit.",* Sarah, 36yo, Physiotherapist Not good enough to assess the impact of dyspnoea on quality of life *"I think if I would like to look at dyspnoea that is not activity related then I don't think the CAT is enough.",* Aaron, 36yo, Physiotherapist Doesn't really assess quality of life *"I still can't call CAT a quality of life measure, I think it is a health status snapshot. And I found that some clinical sites here, they have shifted from a CRDQ to a CAT because they think it's quicker and therefore is easier to implement. And I find myself saying 'No, they are not quite the same'. ",* Caleb, 40yo, Physiotherapist Score depends on how the patient is feeling at that moment *"Sometimes these questionnaire things having a sliding scale it depends on the day, what you feel like. You think 'oh, well, yeah I was bad yesterday but I'm not too bad today', there's no sort of happy medium with them. You know, you can put 'I'm terrible at everything' and the next day 'Fine' you know? Well, not fine, but you know, better than.",* Grace, 71yo, person with COPD Not very personalised

	"I think in the CAT some points are not fitting. A questionnaire cannot be individualized, although this would be important, it is very time consuming, I understand.", Sandra, 56yo, person with COPD
Chronic respiratory disease questionnaire (n=5)	
Not too long and psychometrically robust *"So, I think the CRQ is quite good, it's not so time, you don't need so much time consumption and we know that is valid and reliable, and we have clinical important data. So, I prefer the CRQ than the SGRQ, when it comes to overall quality of life."*, Aaron, 36yo, Physiotherapist Frequently used *"I honestly, my experience with that [health-related quality of life questionnaires] is very limited in the way that I've been all my life, everybody in [country in Europe] has been working with the CRQ."*, Connor, 40yo, Physiotherapist It has personalised questions *"The reason I like the CRDQ is, I actually like the individualized nature of the first respiratory or dyspnoea questions. I actually feel that's more applicable to most patients, whereas the Saint George's has a very crude set of predefined areas, so I like the personalized approach of the CRDQ. (...) But I actually have no strong opinion on the questionnaires, because I think there are pros and cons to all of them."*, Caleb, 40yo, Physiotherapist It's respiratory-specific *"I think the obvious ones, disease-specific for sure, CRQ because I'm from [big country], you know, or the Saint George's, but I don't have a preference in one over the other."*, Diana, 54yo, Physiotherapist Comprehensive	

"I think I prefer the CRQ self-reported. I know it's a little bit longer [than CAT], but I think you get more information from that with the four domains, and of course it assesses symptoms as well, so dyspnoea.", Sarah, 36yo, Physiotherapist	
Saint George's respiratory questionnaire (n=9)	
Psychometrically robust and can be used in other diseases *"(...) the Saint George's respiratory questionnaire seems to provide good responses to COPD patients and also it has been proved to be quite good and reliable in other categories of diseases."*, Elliot, 58yo, MD Good for research *"(...) if I was doing a research study in a pulmonary rehab programme, mm I would want something like the SGRQ."*, Victoria, 49yo, Nurse It's respiratory-specific *"I think the obvious ones, disease-specific for sure, CRQ because I'm from [big country], you know, or the Saint George's, but I don't have a preference in one over the other."*, Diana, 54yo, Physiotherapist	It takes too much time and needs help from a healthcare professional *"SGRQ we only use it because we have a student to perform it, but it's too difficult to use it in the daily activity of the centre. We have to select a questionnaire with a self-administration mode, because the patient can do that, it's not some more work for the caregivers."*, Frank, 57yo, MD Too generic *"(...) whereas the Saint George's has a very crude set of predefined areas, so I like the personalized approach of the CRDQ"*, Caleb, 40yo, Physiotherapist It's an old measure *"the Saint George's Respiratory Questionnaire was, when it came out it was amazing, it was revolutionary, but now I think it's dated."*, Emma, 57yo, Nurse
Maugueri respiratory failure questionnaire (n=1)	
It's good for several respiratory diseases *"The Maugeri foundation which is an Italian questionnaire, I think this refers to older patients developing chronic respiratory failure, so this is not really specific for COPD, so it may be appliable to much more patients."*, Elliot, 58yo, MD	
12-Item short form survey (SF-12) (n=1)	
It measures well the construct of quality of life	

"I think a more important aspect is if quality of life measures are actually measuring quality of life and then which one to use. Obviously if you want to go to a core outcome set and standardize then you should agree on a specific one, but I do not have that much of a preference for like either the SF-12 or the EuroQoL.", Tobias, 46yo, Psychologist	
Chronic obstructive pulmonary disease-specific health-related quality of life questionnaire (VQ-11) (n=1)	
Quick and easy to use *"We have good results with VQ-11. Because it's a simple questionnaire, and we can assess easily before and after the intervention. (...) VQ-11 is the only one we can use in a routine basis."*, Frank, 57yo, MD	
EuroQol - 5 Dimension (EQ-5D) (n=2)	
Also assesses pain besides other symptoms *"I think that also has a pain, I think I'm right in remembering it has a pain domain as well, yeah, so it can be quite useful to assess pain as well."*, Sarah, 36yo, Physiotherapist It measures well the construct of quality of life *"If I would be designing my own rehab programme or I would be designing a core outcome set I would be really interested in having an instrument that reflects really well the construct of quality of life, whilst also being relatively short to administer and so in that sense, actually the EuroQoL measures they do fit that purpose really well."*, Tobias, 46yo, Psychologist It helps with cost-effectiveness analysis *"I think if I was going to use a second one I would use something like, a generic measure, like the EQ-5D, the 5 level one, because you can*	Not disease-specific *"There's a downside in that, is that you might miss, by using these very general questionnaires, you might miss some aspects of quality of life that are really specific to COPD, so they might not focus too much on physical activity."*, Tobias, 46yo, Psychologist

look at, well from a research perspective it helps with health-economic analysis.", Sarah, 36yo, Physiotherapist	
Muscle function	
Isokinetic system (n=4)	
Psychometrically robust *"I would take an isokinetic one for sure (...) because of the better validity.",* David, 31yo, Physiotherapist	Not feasible for most settings/countries *"Well, I would like to say Biodex or Cybex but people don't have that, it's expensive and it takes a lot of time, I mean if you want to measure quadriceps strength, only strength and one side, it would take at least 15 to 20 min. just to do that. So, just to prepare the whole setting and to prepare the patient… So, you can do a lot but it's very impractical. So, I believe in this for big screenings of sports teams and I believe in it for research purposes and to know more about the physiology, but as a core outcome that should be for everyone, yeah, no, it's not realistic, I think.",* Connor, 40yo, Physiotherapist
Strain gauge (n=2)	
Valid measure *"There's a paper from the Leuven team that looked at very simple measurement of isometric strength with a strain gauge, and they compared it with Biodex and it has excellent validity. So is just using a chair and a strain gauge and you can obtain the same validity. So, I would rather than go there.",* Connor, 40yo, Physiotherapist	Not commercially available *"But this has the disadvantage that this is not commercially available, so… It's not so straight-forward to build a chair like that, I mean, if you are in a giant reference hospital and they have technical services with lots of clever people who can build it for you, but we all don't have that luxury.",* Connor, 40yo, Physiotherapist
Hand-held dynamometry (n=5)	
Quick and easy to use *"I think it's easier to have a dynamometer in order to obtain a more, a more rapid measure. I think a dynamometer should be provided in a centre of pulmonary rehabilitation of chronic patients.",* Elliot, 58yo, MD	Only good for weak patients *"And then, microFET could be useful in very weak patients, but typically if patients get stronger, for me it's useless.",* Connor, 40yo, Physiotherapist It doesn't reflect endurance and it's important to measure it

	"We are used to measure strength, mvc. That's the common outcome measure that we often use in pulmonary rehab. But it reflects only strength and what we know from physiological studies, from biopsy studies, shows that we can expect more impairment of endurance than we can expect impairment in strength. And also for locomotor muscles, we can reason that endurance capacity is much more important than strength.", Andrew, 59yo, Physiotherapist
Maximum respiratory mouth pressures (n=1)	
Quick and easy to use *"It's relatively easy to measure it. So, that's the good news."*, Andrew, 59yo, Physiotherapist	It doesn't reflect endurance and it's important to measure it *"(...) And another, perhaps even greater concern is that it reflects strength, and for the respiratory muscles it is, perhaps, more important what the endurance capacity is than the strength, because these muscles have to perform 24h per day for 7 days per week, for 12 months per year, and perhaps muscle strength is not the best parameter to characterize the importance of the function, and perhaps that's also the reason the correlation between respiratory muscle function and for instance exercise capacity is not that high, perhaps we are not looking at the right outcome."*, Andrew, 59yo, Physiotherapist
Maximum repetitions (RM) (n=7)	
It's possible to measure strength and endurance *"So, for muscle strength I would rather do a 1-RM test and for endurance I would do multiple RM test."*, Aaron, 36yo, Physiotherapist Important to prescribe exercise *"(...) but of course, there are tests in lifting weights or measuring weights that can be also useful for the healthcare professional to obtain."*, Elliot, 58yo, MD Improves with PR serving as a motivator	Not feasible for all settings *"(...) perhaps in a home setting it would be really difficult to measure a 1-RM or multiple RM, and there perhaps a chair stand test would be very relevant to do, or a short physical battery test. But we shouldn't avoid doing things because it's a home setting, it should be okay because it's not less important in a home setting."*, Aaron, 36yo, Physiotherapist Not meaningful for daily life *"(...) but like the strength test is also, why is it important? Because if they are able to walk the stairs after rehabilitation, then that's important and not that*

"...and when you get the results and see you have improved, then you get very motivated to keep on exercising.", Theresa, 73yo, person with COPD	*they are able to press 15 kilos on the leg press."*, Nicole, 34yo, Occupational therapist Difficult to measure in some patients with disability *"I would say absolutely, but then I can see that there are people who really can't do that. There is, well, actually only one person on this team of 15 people and I don't think she could do that, but she's using her wheelchair."*, Harrison, 59yo, person with COPD
Physical activity	
Accelerometery (n=4)	
Frequently used *"Why accelerometry? Oh… I think it's the most commonly applied one"*, David, 31yo, Physiotherapist It's the optimal way to measure physical activity *"(...) activity monitors can be better, absolutely because they objectively measure what happens to the patients and not by a recall status of the patients that may differently answer to the question."*, Elliot, 58yo, MD	Not feasible for most settings *"We need to measure it objectively, but for us in [country in Europe] is not realistic that we can have an accelerometer in every primary care unit so we can send the patient home with an accelerometer and let them come back in a week. At this moment this is not feasible"*, Aaron, 36yo, Physiotherapist
Pedometers (n=5)	
It's an objective measure " *We need to measure it objectively* (…) *I would rather do it with a pedometer than do it with a questionnaire."*, Aaron, 36yo, Physiotherapist It's reliable *"So, a pedometer, I think it's reliable, that is evidence that is also in patients a reliable measure of physical activity, so these are good*	Not valid enough *"I think we have a problem with the pedometers that we can use, that they're not perhaps valid enough, especially in those who have a very low physical activity, they can't really detect those that are not really walking, they're just gliding almost when they walk. Then I think an accelerometer would be the best (...)."*, Aaron, 36yo, Physiotherapist Not comprehensive enough

arguments, I think to recommend a pedometer.", Andrew, 59yo, Physiotherapist Inexpensive "Pedometers for instance, they are cheap, do not cost that much, for instance in [European country] when I go to a nearby shop I can buy one for 5 euros. So, they are cheap, and quite, not perfectly reliable, but I think usable.", Andrew, 59yo, Physiotherapist	"There's also bad news, there's the other side of the coin, and that is that only measures steps per day, it measures volume, but it does not reflect the intensity of people walking, or the bout lengths that they are walking. And we know that health benefits for physical activity are not only determined by the volume, but are also determined by the intensity, and the number of bouts and the bouts length, so it gives a global idea of what people do, but that's it.", Andrew, 59yo, Physiotherapist Not patient-friendly *"(...) and patients might lose them, and patients find pedometers a new sense.",* Emma, 57yo, Nurse
Smartphones and wearables (n=5)	
They generate a lot of useful data *"When we enter this field, there are so many variables we can assess, when we use a fitbit device for example, we can assess heart rate throughout the day, during training (...)",* David, 31yo, Physiotherapist More valid than a questionnaire *"Because I do think that this would provide more valid data than to use a questionnaire, because the questionnaires are, the validity of the questionnaires is not good enough",* Aaron, 36yo, Physiotherapist Easy to wear *"It's [wrist band/watch]very good because you do not need the thoracic band when you are running, so it's easy and it's incredibly interesting.",* Frank, 57yo, MD They will become more psychometrically robust in the future "In a few years we will provide every patient with a Polar or a Garmin that can easily, and even validly measure these kinds of things even	Not psychometrically robust enough *"Hopefully in the future the phones will be so good that we can use the phones, but to my knowledge the error in the phones is still too large",* Aaron, 36yo, Physiotherapist The data generated is difficult to analyse *"But of course, if you get data from devices you have to analyse the numbers. And it's difficult."* Frank, 57yo, MD Might be difficult to use for some patients *"(...) the patients we know in Europe, I think people are not so easy living with IT devices.",* Frank, 57yo, MD

longer than one week, right? So, I think the times are changing and I mean, with all the wearables that are arising and the quality there is improving, it's a matter of time. (...) if we talk about of core outcome set for programmes all over the world, as much as possible, so not only the ones performing research on it, I think we will have to focus on commercially available wearables, right? Things there are built in the iPhone, I mean, if I look at my steps that I'm having on my iPhone, is not that bad, the assessment is not that bad, and of course is not state of the art and it might not be an actigraph, but technology is improving throughout the years so I think just screening physical activity throughout wearables there are owned by the consumers themselves will get more and more normal practice.", Connor, 40yo, Physiotherapist Useful to motivate patients *"I don't use a pedometer, I use a mobile app, and in average I do 8000 steps. (...) I think now I am more concerned, and I try to walk more".*, Mary, 63yo, person with COPD.	
PROactive instruments (n=1)	
Psychometrically robust *"I think that demonstrated to be accurate and sensitive and valid."*, Emma, 57yo, Nurse	
International physical activity questionnaire (IPAQ) (n=1)	
	Subjective *"(...) from a questionnaire perspective, I would use like an IPAQ, the international physical activity questionnaire, my preference is if you're measuring physical activity though to measure it objectively."*, Victoria, 49yo, Nurse

Acute exacerbations of COPD and healthcare utilisation	
GOLD ABCD assessment tool (n=1)	
Was developed by experts *"I do think that what we have in the GOLD statement, because the people who have wrote the GOLD statement are related to exacerbations, I think this is a good starting point. To look at the severity based on that."*, Aaron 36yo, Physiotherapist	
Number of exacerbations in the previous year (n=2)	
It's important to have a long-term view *"I think what needs to be measured for exacerbations is knowledge of what was perhaps at a minimum, the previous 12 months of exacerbations before entering rehab, and I think it needs to be realistically the number of exacerbations in the 12 months after, I think the time point is relevant, to say at least one year"*, Caleb, 40yo, Physiotherapist	Not robust enough *"When you ask patients for instance, 'how many exacerbations did you have last year?' then they mention other figure than you get when you look for instance at the use of medications from pharmaceutical databases. So, it's depending on how reliable you want to have that outcome. (...) But for the clinical routine, clinical practice, I think we have to rely on interviews of patients. "*, Aaron, 36yo, Physiotherapist
Number of exacerbations during PR (n=1)	
Recall is not too bad *"Well I think the number of exacerbations and the severity and the treatment. (...) Given that's self-reported and within an 8-week period you'd expect that wouldn't be too bad."*, Victoria, 49yo, Nurse	
Number of hospitalisations (respiratory and non-respiratory related) (n=1)	
Pulmonary rehabilitation can improve it *"So, if you went to the effort of looking for hospitalisations, I think you know, including both [respiratory and non-respiratory related] would be important, because we know that pulmonary rehab like does have effects on other comorbidities."*, Victoria, 49yo, Nurse	

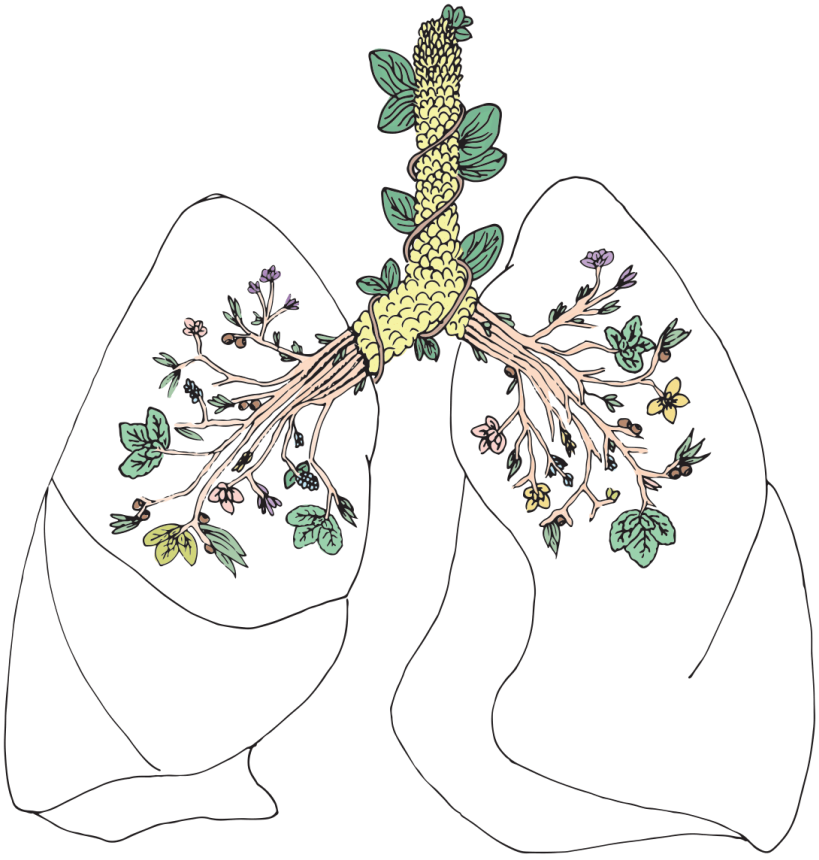
Frailty	
Fried's phenotype (n=1)	
It's responsive to pulmonary rehabilitation *"(...) it comes back to the reason of earlier on, that in my opinion the Fried does give the responsiveness element to sort of show that we can use rehab to improve frailty status."*, Caleb, 40yo, Physiotherapist	Not comprehensive enough *"(...) it is not giving the true full picture of frailty, it is only representing one aspect of the frailty."*, Caleb, 40yo, Physiotherapist
Frailty index-Comprehensive geriatric assessment (FI-CGA) (n=1)	
	Not responsive to pulmonary rehabilitation *"Rockwood based accumulated deficit model (...) is all about comorbidities, comorbidities don't usually go away, you sort of have them and they are persistent, they might be better managed, but you still have them, so you are less likely to find a change or a difference if you use those models."*, Caleb, 40yo, Physiotherapist
Handgrip dynamometry (n=1)	
Quick and easy to use "I do think one measure of frailty which could be either timed up and go or handgrip strength would be good. (..) because they're so quick and easy, it's over, the handgrip is literally ((does the gesture of handgrip)), you know?", Emma, 57yo, Nurse Correlates with other strength measures *"(...) but I believe, or from what I've read, the timed up and go and the handgrip strength, correlates with quadriceps strength."*, Emma, 57yo, Nurse	
Timed up and go (TUG) (n=1)	

Quick and easy to use "I do think one measure of frailty which could be either timed up and go or handgrip strength would be good. (..) because they're so quick and easy, it's over, the handgrip is literally ((does the gesture of handgrip)), you know?", Emma, 57yo, Nurse Correlates with other strength measures *"(...) but I believe, or from what I've read, the timed up and go and the handgrip strength, correlates with quadriceps strength."*, Emma, 57yo, Nurse	
Self-efficacy	
COPD self-efficacy scale (n=2)	
It's familiar *"COPD self-efficacy scale. But to be honest I don't have a preferred measure. I think you should look at the evidence and see which one has more validity and reliability but should measure self-efficacy for sure."*, Diana, 54yo, Physiotherapist	It might be outdated *"I think there's a COPD self-efficacy scale, now there might be something more up to date, but I would like to, in pulmonary rehab, measure that."*, Emma, 57yo, Nurse
Pulmonary rehabilitation adapted index of self-efficacy (PRAISE) (n=1)	
	Might not be responsive to pulmonary rehabilitation *"(...) it doesn't always change with pulmonary rehab and that's either because of the measure, or it's because we don't really focus on behaviour change very much with pulmonary rehab."*, Sarah, 36yo, Physiotherapist
Motivation	
Patient activation measure (PAM) (n=1)	
Overall good measure	Time-consuming

"(...) from research, reading it, it sounded good. (...) So, I think if someone has got time, I think it's a good measure. ", Emma, 57yo, Nurse	*"But I think it's a lot of, it needs a lot of discussion with the patient, potentially is quite time-consuming, so, possibly."*, Emma, 57yo, Nurse
Cognitive function	
Montreal cognitive assessment (MoCA) (n=1)	
It's the measure we know most about for COPD *"So, just on my knowledge, I know the MoCA , I haven't used it myself, but I know that and so perhaps I would still use that today based on what we know, but this is an area that I think we need to develop something that is better or perhaps something they are using in other populations and test it also in COPD."*, Aaron, 36yo, Physiotherapist	Not comprehensive enough *"When I talk to my colleagues who are cognitive scientists and they look at the type of measures that we use in COPD, they say that 'okay these are not bad, but they measure one aspect of cognitive, they measure this of cognitive but cognitive function is much wider'."*, Aaron, 36yo, Physiotherapist
Body composition	
Bioelectrical impedance (n=2)	
Quick to use *"It's very quick. So, we have to look for those practical, the practicality of the apparatuses also. So, I would say, for that reason I would say bioimpedance."*, Norah, 51yo, Dietitian	Some equipment is not very accurate *"But we don't use it when they leave because it's not accurate, but it's like, ultimately that's of course what we want to see a difference in and affect the muscle mass. But so, we use weight instead."*, Taylor, 35yo, Dietitian
Dual-energy x-ray absorptiometry (DEXA) (n=3)	
Psychometrically robust *"DEXA is the gold method for measuring body composition"*, Norah, 51yo, Dietitian Important to detect comorbidities *"The DEXA (...) If I have a decreased bone density, osteoporosis… that is not assessed in other settings. But it is important to know."*, Kevin, 63yo, person with COPD	Not feasible for most settings/countries *"It's quite expensive, and it's also time consuming."*, Taylor, 35yo, Dietitian

Energy expenditure for nutritional status	
Indirect calorimetry (n=1)	
Psychometrically robust *"It's the gold standard, there are different types of indirect calorimetry. "*, Norah, 51yo, Dietitian	Most are not mobile *"I would rather have one that is more mobile so we can use it when they are resting and when they do the activity. (...) That's why I would like to have mobile energy expenditure [instruments], so I can take it to the home also."*, Norah, 51yo, Dietitian
Social status	
De Jong Gierveld Loneliness Scale (n=1)	
It's familiar *"The loneliness scale from the Jong one, but there also 1 or 2 other validated loneliness scales. I'm also not very often using social support scales, loneliness we personally measure it with the loneliness scale, but I have no super big preference there."*, Anthony, 46yo, Psychologist	

Dark shade represents the outcome and lightest shade the outcome measure associated with the number of times reported.



Chapter 7

A core outcome set for pulmonary rehabilitation of people with COPD: results from a modified Delphi survey

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Submitted

ABSTRACT

Background: There is high heterogeneity of outcomes and measures reported in pulmonary rehabilitation (PR) trials of people with chronic obstructive pulmonary disease (COPD). This hinders study comparability and benchmarking of PR. We have developed a core outcome set (COS) to overcome these challenges.

Methods: This study was informed by a systematic review and two qualitative studies and had patient involvement since its inception. A 2-round Delphi survey was available in seven languages. Outcomes (n=63) scored 7-9 (crucial) by ≥70% of the participants and 1-3 (not that important) by ≤15% of participants from both groups in the Likert scale were automatically included in the COS, whilst outcomes that were considered crucial by only one of the groups were further discussed and voted in a consensus meeting.

Results: A total of 299 people (n=229 healthcare professionals/researchers/policy makers; n=70 people with COPD and informal caregivers) participated in the survey (83% retention), which covered 29 countries/five continents. After the second round, 6 outcomes were included and 3 were added in the consensus meeting. The final COS contains dyspnoea, exercise capacity, fatigue, health-related quality of life, health behaviours/lifestyle, knowledge about the disease, lower limb muscle function, personal goals, and problematic activities of daily living.

Conclusion: A COS for PR of people with COPD is now available and can be used by different stakeholders to improve consistency and comparability of studies, benchmark PR and improve the quality of care provided. Future research should establish the core measures and investigate the uptake of this COS.

Introduction

Pulmonary rehabilitation (PR) is recognised as an essential pillar of the management of symptomatic patients with chronic obstructive pulmonary disease (COPD)[1,2]. Generally, PR programmes are safe and have a positive impact on patients' daily symptoms, exercise capacity, and quality of life[2]. Nevertheless, a systematic review identified high heterogeneity in the measurement of outcomes in PR trials[3]. This hinders the comparison of programmes, effective evidence synthesis (i.e., meta-analysis)[4] and limits benchmarking of PR[5].

Due to the widely recognized need to tackle this heterogeneity and to establish metrics demonstrating the quality of PR, some outcome indicators have been proposed[1,5-11]. Such initiatives have, however, been exclusively based on expert opinions, with no robust methodology such as the development of a core outcome set (COS) followed. A COS is defined as an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care[4].

A COS for PR has the potential to generate significant clinical and research impacts. A COS can aid the assessment of the quality of PR programmes in clinical practice, which may lead to improvements in the quality of care provided. Secondly, by establishing a common set of outcomes to be measured, a COS can also facilitate the comparison and synthesis of study results, which could inform future research and clinical practice.

Hence, this study aimed to define a COS that should be consistently measured and reported in PR of people with COPD.

Methods

This study consisted of a two-round Delphi survey followed by a consensus meeting. The study is part of a COS registered in the Core Outcome Measures in Effectiveness Trials (COMET) initiative database (https://www.comet-

initiative.org/Studies/Details/1151). The COS was developed considering the Core Outcome Set-STAndards for development (COS-STAD recommendations)[12] and the COMET handbook[13], and is reported according to the Core Outcome Set-STAndards for Reporting (COS-STAR Statement)[14].

Ethical approval was obtained by the Ethics Committee of the Research Unit of Health Sciences of the School of Nursing of Coimbra (UICISA) (P466-10/2017) and the Ethics Committee of University of Aveiro (20-CED/2022). Compliance with the General Data Protection Regulation (GDPR) was ensured through the approval of the study by the GDPR office of the Faculty of Health, Medicine and Life Sciences at Maastricht University. All participants provided informed consent.

This study had patient and public involvement (PPI)[13,15] since its inception, through the inclusion of a patient representative in the design and development of the study. The patient representative ensured that the process was patient-friendly, e.g., duration, language suited for patients, and that the study had sufficient patient input[16].

Participants and inclusion/exclusion criteria

Two panels of experts were constituted: people with COPD and informal caregivers, and healthcare professionals, researchers and policy makers.

People from different countries and backgrounds were recruited, to ensure diverse contributions and international applicability[17]. Although there is no consensus on the most suitable sample size for Delphi surveys, a minimum of 10-18 participants per stakeholder group has been suggested[18]. We aimed to engage 120 participants on the survey, 60 from each stakeholder group.

Patients and informal carers were recruited through the research team's network, and patient associations (48 were contacted). Healthcare professionals, researchers and policy makers were recruited via the teams' network, and professional societies/associations (21 were contacted). The study was also disseminated on social

media and among those previously involved in a qualitative study[19] to maximise the recruitment.

The inclusion and exclusion criteria were explicitly stated by email and provided with the social media dissemination material. Patients were included if they were adults, diagnosed with COPD and had participated or were participating in a PR programme. Informal carers were included if they were adults, had an informal relationship with a person with COPD (e.g., family, friend, neighbour) and had provided support (e.g., physical, practical, psychosocial, financial) to a person with COPD while they were included in a PR programme. Healthcare professionals, researchers and policy makers were included if they had been involved in the design, implementation, assessment of PR or data resulting from it. Participants were excluded if they had an impairment in communication (reading and/or understanding).

Information sources

The initial list of outcomes was developed by combining the outcomes retrieved from a systematic review[3] and those obtained by interviews with patients, informal carers, and healthcare professionals, researchers and policy makers in two other studies[19,20]. Due to the large number of outcomes (n=163 from systematic review and 8 from qualitative studies), some outcomes with similar health meanings (e.g., walking distance and cycling time) were collapsed into broader outcomes (e.g., exercise capacity). This approach was chosen as Delphi studies with higher number of items and larger panels are associated with lower response rates[21]. The final list of the first round of the survey was composed of 57 outcomes with descriptors that were discussed and agreed by the research team (Please see **Appendix A**).

The survey

The Delphi survey was available electronically and in paper for local (Portuguese) participants who wanted to participate but could not access the online

survey (e.g., digital skills). The survey was developed using Qualtrics (Qualtrics XM, Provo, Utah, USA).

To maximize the possibility of developing a global COS, the survey was translated from English into Portuguese, Dutch, Spanish, Italian, French and German, using forward translation with 1 proficient speaker of English and each other language[22].

The Delphi survey was pilot tested with a patient representative and a healthcare professional, to ensure its length was feasible and that it was easy to understand.

The initial part of the survey was composed of a brief explanation of the research, a video developed by the COMET initiative to explain the development of a COS[23], advantages, and disadvantages of taking part in the study, a plain language summary[24] and the informed consent. A document with a plain language description and a representative image (when possible) for each outcome, that were reviewed by two healthcare professionals/researchers and a patient representative[13], was also provided (**Appendix B**).

Participants were asked to provide information regarding their sex, age, occupation, country, and stakeholder group. Informal caregivers were also asked to disclose the type of relationship with the patient (e.g., family member).

The list of outcomes was alphabetically ordered to avoid bias[25]. Participants scored each outcome in a 9-point Likert scale in which the outcomes scored from one to three were "not that important", four to six were "important but not critical" and seven to nine were "critical" to measure[26]. An option of "unable to score" was also provided, as some participants might have never experienced a particular outcome[16]. At the end of the first round of the survey participants were able to suggest outcomes to be scored on the following round to ensure all outcomes valuable for these stakeholders were considered [27].

The second round of the survey used the same scoring system and contained all outcomes of the previous round and the additional ones suggested by participants (**Appendix A**). Feedback of the previous round with the score distribution of each stakeholder group for each outcome was provided (**Appendix C**), as confrontation with the opinions of other participants could increase consensus[27]. Three rounds of gentle reminders were sent by e-mail, asking participants to complete the second round of the survey to minimise high attrition rates [27].

After the second round, outcomes that were scored between seven and nine by ≥70% of the participants and between one to three by ≤15% participants from both groups were automatically included in the final COS, outcomes that only one of the groups considered essential were further discussed in the consensus meeting, and the remaining outcomes were excluded from the COS[17].

All analysis were performed using R (v. 4.1.2, R Foundation for Statistical Computing, Vienna, Austria) and Excel (Microsoft, Redmond, Washington, USA).

Consensus meeting

The consensus meeting consisted of a group discussion, followed by voting of uncertain outcomes by the Steering Committee (authors)[13].

Prior to the consensus meeting, handouts were sent to the participants as suggested by the COMET initiative [28], consisting of i) an introduction of what is a core outcome set, information about what happened in the project before, ii) a plan for the day and iii) the list of outcomes that were agreed previously; the list of outcomes that were excluded; and the list of outcomes that needed a decision during the meeting with a plain language definition and an image.

The meeting was then conducted online, through Zoom (California, USA). A nominal group technique was used to ensure all participants thoughts were considered[29]. The session started with an introductory phase where there was a slide

set prepared by the moderator (S.S-M) to explain the results of the Delphi survey and to structure the meeting.

Outcomes from the Delphi survey that were automatically included were first reviewed, to finalize the recommendations and make possible adjustments. Then, for inconclusive outcomes, a silent generation of ideas was performed. Participants were asked to think and write which of those outcomes (if any) should be in the final COS and why, without consulting other people[29]. Then, participants were invited to share their ideas to the group, one at a time[29]. A discussion was then followed with pros and cons of including each outcome[29]. Finally, electronic voting consisted of asking participants at the same time whether each outcome mentioned in the previous phase was crucial to assess the effectiveness of PR or not. They were asked to keep in mind that a maximum of 9 outcomes would be considered, to ensure the applicability of the COS[17]. Consensus was reached if fewer than 30% ($n \leq 1$) of the voters disagreed[30].

Results

The Delphi survey was composed of two rounds[13]. The first round occurred from 17/05/2022 to 08/07/2022 and the second from 21/09/2022 to 31/10/2022. The consensus meeting took place on the 12th of January 2023 and lasted 63 minutes.

A total of 299 participants from 29 countries completed the first round of the survey, of whom 198 were healthcare professionals, 103 were researchers, 68 were people with COPD, 10 were policy makers, and three were informal caregivers. Participants were mostly females (n=176, 58.9%) with an average age of 49 (±14) years old. Of all healthcare professionals, most respondents were physiotherapists (n=98, 49.2%) or medical doctors (n=49, 24.6%). A retention rate of 82.9% was achieved in the second round, with 27 countries involved. Characteristics of the sample are displayed in **Table 1** and a map of the distribution of responses can be observed in **Figure 1**. The consensus meeting integrated the members of the steering committee (three healthcare professionals/researchers and one patient representative).

Table 1. Characteristics of participants who completed the first (n=299) and second round of the survey (n=248).

	First round						Second round					
Characteristics	Total (n=299)	People with COPD (n=68)	Informal caregivers (n=3)	HCP (n=198)	Researchers (n=103)	Policy makers (n=10)	Total (n=248)	People with COPD (n=64)	Informal caregivers (n=1)	HCP (n=163)	Researchers (n=86)	Policy makers (n=8)
Age, years	48.7±14.3	66.6±7.9	42.7±9.0	43.9±10.7	42.7±11.5	53.0±7.1	49.8±14.8	67.5±7.3	32	44.6±11.2	41.7±11.0	51.8±10.4
Sex, men, n (%)												
Men	120 (40.1)	36 (52.2)	0 (0.0)	71 (35.9)	42 (40.8)	5 (50.0)	104 (41.9)	36 (56.3)	0 (0)	60 (36.8)	36 (41.9)	2 (25.0)
Relationship with person with COPD, n (%)												
Grandson/Granddaughter	N.A	N.A	1 (33.3)	N.A	N.A	N.A	N.A	N.A	0 (0)	N.A	N.A	N.A
Son/Daughter	N.A	N.A	1 (33.3)	N.A	N.A	N.A	N.A	N.A	0 (0)	N.A	N.A	N.A
Other member of the family	N.A	N.A	1 (33.3)	N.A	N.A	N.A	N.A	N.A	1 (100)	N.A	N.A	N.A
Country, n (%)												
Argentina	2 (0.7)	1 (1.5)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)	2 (1.2)	1 (1.2)	0 (0.0)
Australia	26 (8.7)	1 (1.5)	0 (0.0)	22 (11.1)	10 (9.7)	1 (10.0)	20 (8.1)	1 (1. 6)	0 (0.0)	17 (10.4)	9 (10.5)	3 (37.5)

Austria	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Belgium	4 (1.3)	1 (1.5)	0 (0.0)	2 (1.0)	1 (1.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)	1 (0.6)	1 (1.2)	0 (0.0)
Brazil	6 (2.0)	0 (0.0)	0 (0.0)	5 (2.5)	6 (5.8)	0 (0.0)	4 (1.6)	0 (0.0)	0 (0.0)	3 (1.8)	4 (4.7)	0 (0.0)
Canada	15 (5.0)	3 (4.4)	0 (0.0)	11 (5.6)	3 (2.9)	3 (30.0)	10 (4.0)	1 (1.6)	0 (0.0)	8 (4.9)	2 (2.3)	1 (12.5)
Chile	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Colombia	5 (1.7)	1 (0.0)	0 (0.0)	4 (2.0)	0 (0.0)	0 (0.0)	6 (2.4)	1 (1.6)	0 (0.0)	5 (3.1)	1 (1.2)	0 (0.0)
Croatia	2 (0.7)	0 (0.0)	0 (0.0)	2 (1.0)	1 (1.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)
Cuba	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.5)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Denmark	4 (1.3)	0 (0.0)	0 (0.0)	3 (1.5)	3 (2.9)	0 (0.0)	6 (2.4)	0 (0.0)	0 (0.0)	5 (3.1)	5 (5.8)	0 (0.0)
France	8 (2.7)	0 (0.0)	0 (0.0)	7 (3.5)	5 (4.9)	0 (0.0)	8 (3.2)	0 (0.0)	0 (0.0)	7 (4.3)	6 (7.0)	0 (0.0)
Germany	4 (1.3)	2 (2.9)	0 (0.0)	1 (0.5)	2 (1.9)	2 (20.0)	3 (1.2)	1 (1.6)	0 (0.0)	2 (1.2)	2 (2.3)	1 (12.5)
Hungary	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
India	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.5)	1 (1.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Italy	10 (3.3)	0 (0.0)	0 (0.0)	9 (4.6)	5 (4.9)	0 (0.0)	10 (4.0)	0 (0.0)	0 (0.0)	10 (6.1)	3 (3.5)	0 (0.0)
Japan	2 (0.7)	0 (0.0)	0 (0.0)	2 (1.0)	1 (1.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)	2 (1.2)	1 (1.2)	0 (0.0)
Netherlands	60 (20.1)	39 (57.4)	1 (33.3)	17 (8.6)	10 (9.7)	0 (0.0)	61 (24.6)	49 (76.6)	0 (0.0)	10 (6.1)	8 (9.3)	0 (0.0)
Norway	2 (0.7)	1 (1.5)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	2 (0.8)	1 (1.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Philippines	6 (2.0)	1 (1.5)	0 (0.0)	5 (2.5)	0 (0.0)	0 (0.0)	4 (1.6)	0 (0.0)	0 (0.0)	4 (2.5)	0 (0.0)	1 (12.5)
Poland	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.5)	1 (1.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.6)	1 (1.2)	0 (0.0)
Portugal	55 (18.4)	11 (16.2)	2 (66.7)	38 (19.2)	11 (10.7)	0 (0.0)	46 (18.5)	9 (14.1)	1 (100)	34 (20.9)	10 (11.6)	0 (0.0)
Spain	25 (8.4)	6 (8.8)	0 (0.0)	17 (8.6)	11 (10.7)	1 (10.0)	15 (6.0)	0 (0.0)	0 (0.0)	14 (8.6)	9 (10.5)	0 (0.0)

Sweden	8 (2.7)	0 (0.0)	0 (0.0)	6 (3.0)	7 (6.8)	1 (10.0)	9 (3.6)	0 (0.0)	0 (0.0)	6 (3.7)	5 (5.8)	1 (12.5)
Switzerland	8 (2.7)	0 (0.0)	0 (0.0)	7 (3.5)	4 (3.9)	1 (10.0)	3 (1.2)	0 (0.0)	0 (0.0)	4 (2.5)	2 (2.3)	0 (0.0)
Turkey	7 (2.3)	0 (0.0)	0 (0.0)	5 (2.5)	5 (4.9)	0 (0.0)	5 (2.0)	0 (0.0)	0 (0.0)	4 (2.5)	4 (4.7)	0 (0.0)
United Kingdom	26 (8.7)	1 (1.5)	0 (0.0)	22 (11.1)	10 (9.7)	0 (0.0)	17 (6.9)	1 (1.6)	0 (0.0)	12 (7.4)	8 (9.3)	0 (0.0)
Ukraine	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
United States of America	6 (2.0)	0 (0.0)	0 (0.0)	5 (2.5)	4 (3.9)	0 (0.0)	6 (2.4)	0 (0.0)	0 (0.0)	5 (3.1)	3 (3.5)	1 (12.5)
Occupation, n (%)												
Retired	N.A.	42 (61.8)	0 (0.0)	N.A.	N.A.	N.A.	N.A.	41 (64.1)	0 (0.0)	N.A.	N.A.	N.A.
Disabled	N.A.	14 (20.6)	1 (33.3)	N.A.	N.A.	N.A.	N.A.	17 (26.6)	0 (0.0)	N.A.	N.A.	N.A.
Employed	N.A.	11 (16.2)	1 (33.3)	N.A.	N.A.	N.A.	N.A.	5 (7.8)	1 (100)	N.A.	N.A.	N.A.
Unemployed	N.A.	1 (1.5)	1 (33.3)	N.A.	N.A.	N.A.	N.A.	1 (1.6)	0 (0.0)	N.A.	N.A.	N.A.
Physiotherapist	N.A.	N.A.	N.A.	100 (50.5)	N.A.	N.A.	N.A.	N.A.	N.A.	89 (54.6)	N.A.	N.A.
Medical Doctor	N.A.	N.A.	N.A.	49 (24.7)	N.A.	N.A.	N.A.	N.A.	N.A.	40 (24.5)	N.A.	N.A.
Nurse	N.A.	N.A.	N.A.	31 (15.7)	N.A.	N.A.	N.A.	N.A.	N.A.	20 (12.3)	N.A.	N.A.

Respiratory therapist	N.A.	N.A.	N.A.	5 (2.5)	N.A.	N.A.	N.A.	N.A.	N.A.	5 (3.1)	N.A.	N.A.
Occupational therapist	N.A.	N.A.	N.A.	4 (0.2)	N.A.	N.A.	N.A.	N.A.	N.A.	2 (1.2)	N.A.	N.A.
Exercise physiologist	N.A.	N.A.	N.A.	2 (1.0)	N.A.	N.A.	N.A.	N.A.	N.A.	2 (1.2)	N.A.	N.A.
Movement therapist	N.A.	N.A.	N.A.	2 (1.0)	N.A.	N.A.	N.A.	N.A.	N.A.	1 (0.6)	N.A.	N.A.
Psychologist	N.A.	N.A.	N.A.	1 (0.5)	N.A.	N.A.	N.A.	N.A.	N.A.	1 (0.6)	N.A.	N.A.
Medical technician	N.A.	N.A.	N.A.	2 (1.0)	N.A.	N.A.	N.A.	N.A.	N.A.	2 (1.2)	N.A.	N.A.
Paramedic	N.A.	N.A.	N.A.	1 (0.5)	N.A.	N.A.	N.A.	N.A.	N.A.	0 (0.0)	N.A.	N.A.
Pharmacy technician	N.A.	N.A.	N.A.	1 (0.5)	N.A.	N.A.	N.A.	N.A.	N.A.	1 (0.6)	N.A.	N.A.

HCP: healthcare professionals; N.A.: Not applicable.

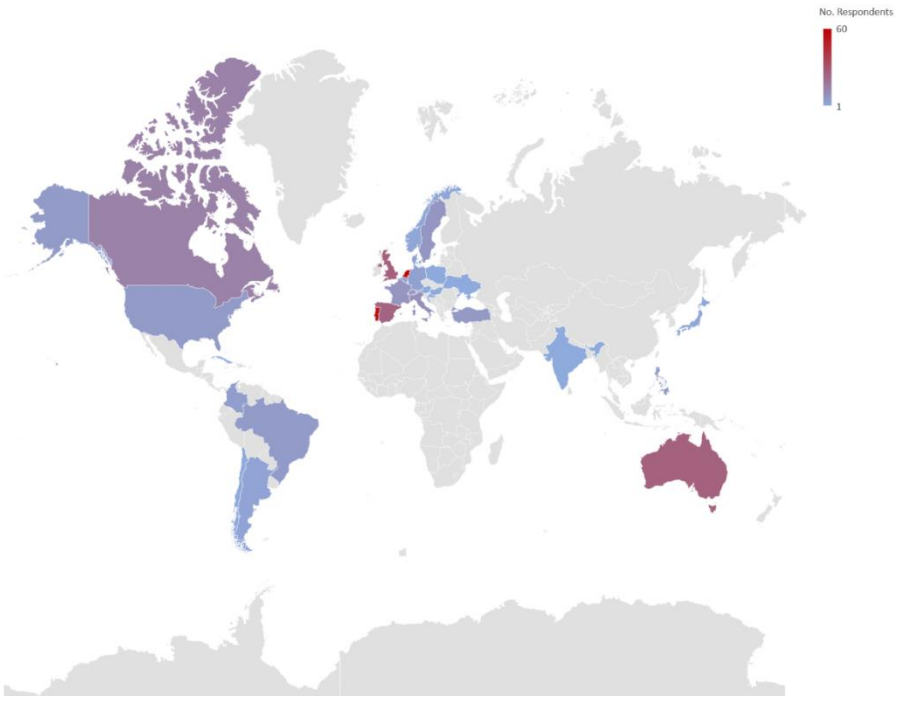

Figure 1. Distribution of responses to the first round of the Delphi survey (n=299), across the 29 countries that participated. Colour scheme at the top right corner indicates the density of responses.

Opinions were consistent between rounds with a change in voting for four outcomes (energy expenditure, fatigue, general well-being, and muscle function). After the first round, five outcomes were crucial for both stakeholder groups (dyspnoea, exercise capacity, general well-being, health-related quality of life (HRQoL) and impact of the disease), 14 outcomes were inconclusive (only one of the stakeholder groups had at least 70% of people voting as crucial) and the remaining (n=38) would be excluded if the Delphi survey ended. Six additional outcomes were suggested by participants. A total of 63 outcomes were voted in the second round (**Appendix A**). After the last round of the survey, six outcomes were included in the COS (dyspnoea, exercise capacity, fatigue, HRQoL, impact of the disease and muscle

function), 43 were excluded and 14 were further discussed in the consensus meeting (**Table 2**).

The process of outcome inclusion and exclusion can be observed in **Table 2.** Outcomes were grouped using the COMET initiative taxonomy[31].

Table 2. List of outcomes with percentage of voting by both stakeholder groups, across Delphi rounds and in the consensus meeting.

Outcomes considered for the Delphi survey	First round		Second round	
	People with COPD and informal caregivers (n=70)	HCPs, researchers, policy makers (n=229)	People with COPD and informal caregivers (n=65)	HCPs, researchers, policy makers (n=183)
Death				
Mortality	53.5%	64.3%	49.2%	67.2%
Physiological/clinical				
Acute exacerbations of COPD	54.9%	80.4%	58.5%	86.3%
Anxiety symptoms	46.5%	63.9%	38.5%	55.7%
Arterial blood gases	36.6%	25.2%	29.2%	15.8%
Balance	50.7%	41.7%	41.5%	27.9%
Biomarkers (e.g., LDL, C-reactive protein)	28.2%	19.1%	20.0%	4.9%
Body mass index	38.0%	28.7%	30.8%	15.8%
Body water	31.0%	14.8%	13.8%	7.7%
Cognitive function	62.0%	45.2%	50.8%	41.0%
Comorbidities	45.1%	52.6%	30.8%	44.3%
Coping strategies	63.4%	73.5%	56.9	82.5%
Cough	62.0%	42.2%	52.3%	31.7%
Depression	53.5%	66.5%	49.2%	69.4%
Dietary intake	43.7%	44.3%	33.8%	32.8%
Disease-specific fears	38.0%	60.9%	36.9%	53.6%
Distress	46.5%	57.4%	46.2%	52.5%
Dyspnoea	84.5%	95.7%	83.1%	96.2%
Energy expenditure	67.6%	53.9%	78.5%	53.0%
Exercise capacity	76.1%	86.1%	84.6%	92.9%
Falls	35.2%	58.7%	29.2%	53.0%
Fat free mass	25.4%	32.6%	20.0%	19.7%
Fat mass	32.4%	21.3%	23.1%	11.5%
Fatigue	69.0%	77.0%	70.8%	81.4%
Flexibility	49.3%	18.7%	60.0%	13.1%

Frailty	54.9%	55.2%	52.3%	55.2%
General well-being	70.4%	72.2%	69.2%	81.4%
Heart rate recovery	N.A.	N.A.	60.0%	35.0%
Loss of appetite	28.2%	34.3%	24.6%	41.0%
Lung function	85.9%	43.9%	80.0%	21.9%
Muscle function	60.6%	72.2%	76.9%	76.0%
Pain	52.1%	57.4%	41.5%	45.4%
Physical well-being	N.A.	N.A.	58.5%	66.7%
Posttraumatic stress disorder symptoms	40.8%	31.3%	32.3%	16.4%
Psychological well-being	N.A.	N.A.	55.4%	61.2%
Respiratory muscle function	78.9%	47.4%	73.8%	32.8%
Sleep	56.3%	54.3%	67.7%	51.4%
Sputum	45.1%	42.2%	35.4%	25.7%
Swallowing function	45.1%	33.5%	40.0%	23.5%
Vital signs	50.7%	47.8%	44.6%	29.0%
Weight change	47.9%	25.7%	29.2%	17.5%
Life impact				
Achieving personal goals	54.9%	77.8%	41.5%	82.5%
Activities of daily living	63.4%	89.1%	67.7%	89.1%
Care dependency	59.2%	53.0%	53.8%	55.7%
Health behaviours/lifestyle	67.6%	74.3%	56.9%	80.9%
Health-related quality of life	81.7%	88.3%	75.4%	94.5%
Impact of the disease	76.1%	81.7%	76.9%	80.9%
Knowledge about the disease	70.4%	69.1%	58.5%	78.7%
Loneliness	45.1%	45.2%	21.5%	29.5%
Mood	50.7%	53.9%	41.5%	44.3%
Motivation to exercise/be physically active	67.6%	83.5%	66.2%	87.4%
Participation in society	N.A.	N.A.	47.7%	49.2%
Patient concerns	N.A.	N.A.	50.8%	60.1%

Physical (in)activity	62.0%	82.2%	60.0%	88.5%
Satisfaction with sex life	36.6%	23.5%	26.2%	13.7%
Sedentary behaviour	N.A.	N.A.	24.6%	69.4%
Self-efficacy	46.5%	59.1%	41.5%	69.4%
Self-esteem	59.2%	49.1%	52.3%	38.8%
Self-management	62.0%	76.1%	60.0%	83.1%
Smoking cessation	54.9%	82.2%	60.0%	86.9%
Social support	50.7%	58.3%	63.1%	51.9%
Resource use				
Change in medication	56.3%	32.6%	49.2%	21.3%
Healthcare utilisation	62.0%	59.1%	66.2%	63.9%
Adverse events				
Adverse events (generic)	49.3%	55.7%	49.2%	47.5%

HCP: Healthcare professionals; N.A.: Not applicable

Represents outcome included with ≥70% of participants voting as crucial
Represents outcome excluded due to <70% of participants of either group voting as crucial
Represents inconclusive outcomes (only one of the panels had ≥70% of participants voting as crucial) that were further discussed in the consensus meeting.

During the meeting we decided to rephrase the outcome “impact of the disease” into “problematic activities of daily living” and consequently remove “activities of daily living” from the uncertain outcomes to be voted. This decision was reached due to the similar inherent meaning of the two outcomes (i.e., how/which daily activities of patients are affected), and as it was consensual that symptoms and HRQoL (outcomes already included in the COS) included the measurement of the impact of the disease. Seven of the 13 outcomes that needed a decision were mentioned as important during the nominal group technique and were, therefore, voted: smoking cessation (25% voted to include), lung function (25% voted to include), knowledge about the disease (100% voted to include), coping strategies (25% voted to include), personal goals (100% voted to include), self-management (25% voted to include) and health behaviours/lifestyle (75% voted to include).

The meeting resulted in a recommendation to measure nine outcomes before and immediately after PR programmes. The decision to measure the core outcomes only on a short-term was based on the high heterogeneity of paths patients follow after PR (e.g., some patients stop exercising, some engage in physical activity/exercise programmes), which could confound the assessment of PR effectiveness. The final COS is, therefore, composed of the outcomes: dyspnoea, exercise capacity, fatigue, health behaviours/lifestyle, HRQoL, knowledge about the disease, lower limb muscle function, personal goals, and problematic activities of daily living (**Figure 2**).

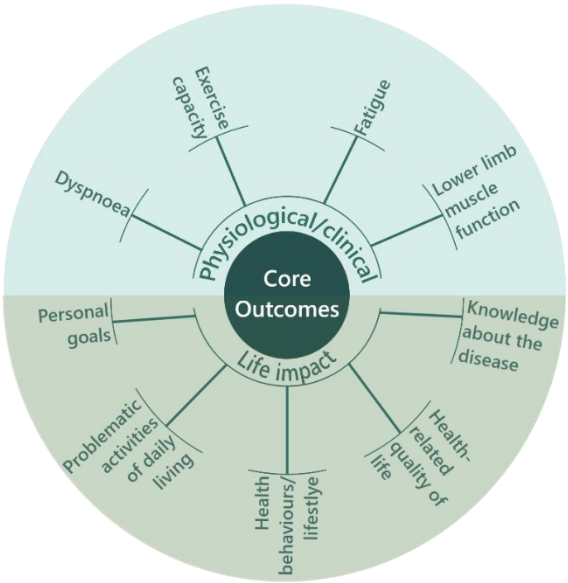

Figure 2. Core outcomes included in the core outcome set (COS) using the domains (physiological/clinal outcomes, life impact outcomes) of the Core Outcome Measures in Effectiveness trials (COMET) initiative's taxonomy.

Outcome definitions

Definitions for each outcome were determined based on the literature and by consensus of the Steering Committee during the meeting. These definitions can be used in the future to help choose the measurement instrument for each construct.

Dyspnoea

Dyspnoea has been described as a "subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity."[32].

Exercise capacity

Exercise capacity, and specifically functional exercise capacity can be defined as "one's maximal potential to realize a functional activity in a standardized environment (e.g., walking distance during the 6-minute-walk test)."[33].

Fatigue

Fatigue can be defined as "a subjective, unpleasant symptom which incorporates total body feelings ranging from tiredness to exhaustion creating an unrelenting overall condition which interferes with individuals' ability to function to their normal capacity"[34].

Health-related behaviours/lifestyle

Health-related behaviours can be defined as "actions taken by individuals that affect health or mortality. These actions may be intentional or unintentional, and can promote or detract from the health of the actor or others."[35]. There are multiple behaviours that are related to lifestyle choices which impact patients health, such as smoking, physical activity and sleep[35].

HRQoL

HRQoL refers to the "aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment"[36] or "a component of the broader concept of quality of life that is defined as satisfaction with health"[2].

Knowledge about the disease

The definition of health literacy used by the World Health Organization was adapted for this outcome i.e., the ability of individuals to gain access to, understand and use information about the disease in ways which promote and maintain good health[37,38].

Lower limb muscle function

Muscle dysfunction is defined as "the loss of at least one of the two main muscle properties: strength and endurance"[39,40]. Although muscle endurance and other properties might be important to assess[41], it was consensual that lower limb muscle strength should be the core outcome assessed, as it is the most studied muscle characteristic in COPD, has a clear prognostic value, can be improved with PR and is easily measured[39,42].

Personal goals

Personal goals were defined as goals that patients aim to achieve with PR and are set by themselves.

Problematic activities of daily living

Activities of daily living (ADL) are meaningful tasks of everyday life that can be basic (e.g., eating, dressing, bathing) or instrumental i.e., associated with independent living (e.g., transportation, shopping, managing money, housework)[43,44].

Discussion

This study developed a COS for PR of patients with COPD. The COS is composed of nine outcomes - dyspnoea, exercise capacity, fatigue, health behaviours/lifestyle, HRQoL, knowledge about the disease, lower limb muscle function, personal goals, and problematic activities of daily living; that are relevant for various stakeholders.

The proposed set of outcomes is of utmost importance for enhancing both clinical practice and research. From a clinical standpoint, the COS can be an integrated step of an iterative process of improving the quality of PR, such as the Plan-Do-Check/study-Act cycle (PDC)[45]. Using this four-stage cyclic method, after results are ascertained with the COS, programmes can plan changes, perform them, check whether results were different with the new changes (using the COS) and act towards new steps of improvement if needed. Additionally, the COS can enable comparison

of results between patients and centres in clinical practice, promote transparency to payers, and can be used as a structured minimal assessment guide. Finally, by demonstrating the benefits of PR in important outcomes, the COS may help to attract funding and influence policy changes.

In terms of research, this COS has various benefits. Firstly, it can increase consistency across trials, leading to a decrease in outcome reporting bias, research waste, and an improvement in the ability to conduct meta-analyses. Secondly, this COS can serve as a vehicle for knowledge translation by enabling comparison of outcomes between COPD and other diseases.

Mental health issues (including symptoms of anxiety and depression) occur frequently in patients with COPD[46], and PR reduces these symptoms[47]. Therefore, the exclusion of anxiety and depression during the Delphi process was somewhat unexpected. This finding is however consistent with other outcome measurement recommendations for COPD (PR or physiotherapy-related treatments of COPD, stable and acute states of COPD with no interventions) which did not include mental health outcomes [11,48-50]. Nevertheless, a COS is a minimum of measurements that should be performed. Additionally measuring the effects of PR on mental health is still encouraged, particularly for patients who exhibit these symptoms at baseline.

Most outcomes recommended in this COS are not COPD or respiratory-specific (e.g., functional exercise capacity, fatigue, health behaviours/lifestyle, HRQoL, personal goals, and problematic activities of daily living). In fact, some of these outcomes have also been identified as critical in other COS initiatives such as the International Consortium for Health Outcomes Measurement (ICHOM) sets [51-53], and other rehabilitation-related COS developed for musculoskeletal, cardiac, or neurorehabilitation, and rehabilitation after clinical illness [54-58]. This overlap in outcomes across different conditions and rehabilitation services may facilitate the sharing of resources, comparison of disease trajectories and programmes, enrich knowledge, and enable better translation of research findings to other settings.

Whilst this COS provides some key outcome indicators that should be reported, other key indicators for structure and process should also be defined in the future for internal and external quality control purposes[1,5,59]. Structure indicators are related to the infrastructures and resources of PR programmes, such as equipment and personnel available, while process indicators reveal the path of the patient within the service delivered and the elements of care provided (e.g., time on waiting list, length and components of programmes)[5,59].

This study has some strengths and limitations. The development of this COS followed a robust methodology recommended by the COMET initiative[13], and is a result of several studies: a systematic review of 267 studies[3], two qualitative studies with 29 patients with COPD, 11 informal carers and 30 healthcare professionals, researchers and policy makers[19,20], an international Delphi survey completed by 248 participants (patients and healthcare professionals, researchers and policy makers) covering 29 countries, and a consensus meeting with three clinicians/researchers and a patient representative. Thus, we believe this COS is valid for different stakeholders and has international applicability. Nonetheless, we did not characterise participants in great detail and participants' characteristics and beliefs probably contributed to their choices. Therefore, it is possible that some outcomes were not chosen (e.g., anxiety) due to the participants characteristics (e.g., having no symptoms of anxiety).

Additionally, a large proportion of countries from Africa and Asia were not covered with this COS, limiting its applicability in these regions.

This COS is a comprehensive set of outcomes that includes multiple and differential domains, previously acknowledged as needed, due to the complexity of the disease and the multicomponent nature of PR[19]. Nevertheless, the COS should be updated as necessary with rising of new evidence (e.g., every five years)[13].

Future steps include defining "how" to measure (i.e., instruments to use) the proposed outcomes, as otherwise some heterogeneity might persist. This step can be addressed with a systematic review of measurement properties to identify the

instruments with the best properties for each core outcome (already registered in PROSPERO, ID: CRD42022313344), and a new consensus study, if several instruments are equally robust and other aspects such as their feasibility in clinical practice, applicability across settings and charges with licensing, need to be considered[19,60].

Future work could also focus on implementing strategies aiming at enhancing the COS use as uptake in most areas has been low[61]. Finally, clinical training on how to measure these outcomes, after the instruments are defined, might be needed as a well-qualified multidisciplinary team is desirable.

Conclusion

This study developed a COS for PR of people with COPD. The COS includes dyspnoea, exercise capacity, fatigue, health behaviours/lifestyle, HRQoL, knowledge about the disease, lower limb muscle function, personal goals, and problematic activities of daily living. It can now be used by different stakeholders to improve consistency and comparability of studies, benchmark PR and improve the quality of care. Future research should establish the core measures and investigate the COS uptake.

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Supplementary materials

Appendix A. List of outcomes scored in Delphi survey.

Table A.1. Outcomes scored in round 1 (n=57) and round 2 (n=63) of the Delphi survey.

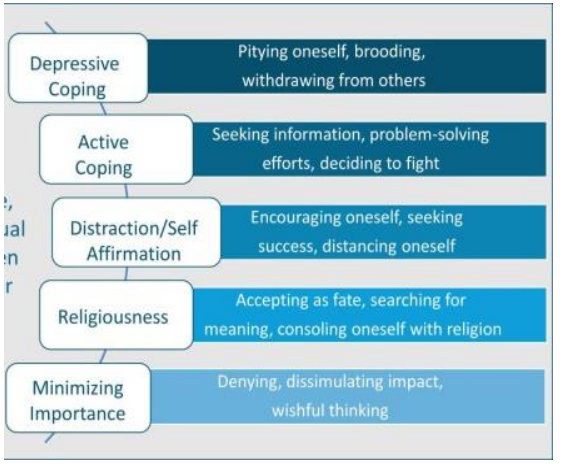
Outcomes of round #1	Outcomes of round #2
Achieving personal goals	Outcomes of round #1
Activities of daily living	Heart rate recovery
Anxiety symptoms	Participation in society
Biomarkers	Patient concerns
Balance	Physical well-being
Acute exacerbations of COPD	Psychological well-being
Adverse events	Sedentary behaviour
Arterial blood gases	
Body mass index	
Body water	
Care dependency	
Change in medication	
Cognitive function	
Comorbidities	
Coping strategies	
Cough	
Depression	
Dietary intake	
Disease-specific fears	
Distress	
Dyspnoea	
Energy expenditure	
Exercise capacity	
Falls	
Fat free mass	
Fat mass	
Fatigue	
Flexibility	
Frailty	
General well-being	

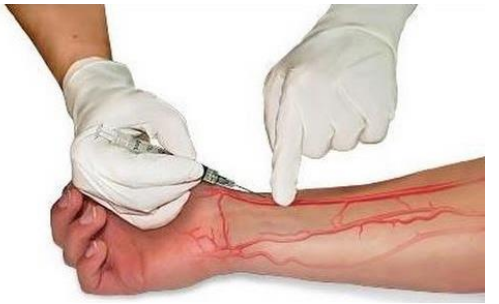
Healthcare utilisation	
Health behaviours/lifestyle	
Health-related quality of life	
Impact of the disease	
Knowledge about disease	
Loneliness	
Loss of appetite	
Lung function	
Mood	
Mortality	
Motivation to exercise/ be physically active	
Muscle function	
Pain	
Physical (in)activity	
Posttraumatic stress disorder symptoms	
Respiratory muscle function	
Satisfaction with sex life	
Self-efficacy	
Self-esteem	
Self-management	
Sleep	
Smoking cessation	
Social support	
Sputum	
Swallowing function	
Vital signs	
Weight change	

Appendix B. Outcome descriptions

Table B.2. Outcome descriptions with examples and pictures (when possible).

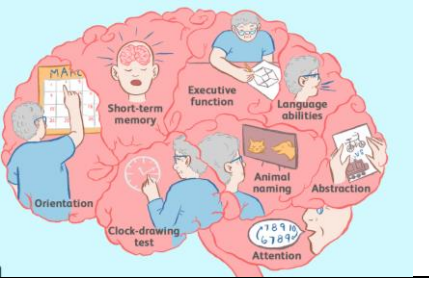
Outcome	Description/Examples	Reference	Picture
Personal goals	Goals set by patients to be achieved with pulmonary rehabilitation		
Activities of daily living	"The tasks of everyday life. These activities include eating, dressing, getting into or out of a bed or chair, taking a bath or shower, and using the toilet. Instrumental activities of daily living are activities related to independent living and include preparing meals, managing money, shopping, doing housework, and using a telephone. Also called ADL."	NIH National Cancer Institute	

Acute exacerbations of COPD	"An exacerbation of COPD is defined as an acute worsening of respiratory symptoms that results in additional therapy"	GOLD 2022	
Adjustment to illness/coping styles or strategies	"The method a person uses to deal with stressful situations (disease). These may help a person face a situation, take action, and be flexible and persistent in solving problems."	NIH National Cancer Institute	
Adverse events	An adverse event can be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the	Adapted from the European Medicines Agency	

	use of the intervention, whether or not considered related to the intervention.		
Anxiety	"an emotion characterized by apprehension and somatic symptoms of tension in which an individual anticipates impending danger, catastrophe, or misfortune. The body often mobilizes itself to meet the perceived threat: Muscles become tense, breathing is faster, and the heart beats more rapidly."	APA dictionary of Psychology	
Arterial blood gases	"Blood gases are a measurement of how much oxygen and carbon dioxide are in your blood. They also determine the acidity (pH) of your blood." Carbon dioxide is exhaled. It is common for patients with COPD to have hypercapnia, which means that there is carbon dioxide retention, e.g., it is not being completely exhaled.	NIH Medline Plus	

Balance	"Balance refers to an individual's ability to maintain their line of gravity within their base of support. It can also be described as the ability to maintain equilibrium, where equilibrium can be defined as any condition in which all acting forces are cancelled by each other resulting in a stable balanced system."	Physiopedia	
Biomarkers	Measurable and quantifiable biological parameters. These are important to determine a disease (e.g., (e.g., hypercholesterolemia - high cholesterol) and can be collected through samples such as blood, urine, sputum.	MeSH term	 Urine sample  Saliva sample  Blood sample

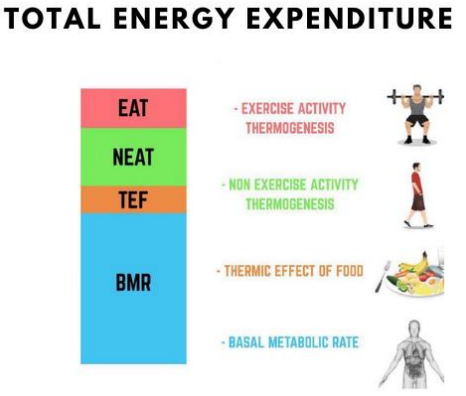
Body mass index	"Body Mass Index (BMI) is a person's weight in kilograms divided by the square of height in meters. A high BMI can indicate high body fatness. BMI screens for weight categories that may lead to health problems, but it does not diagnose the body fatness or health of an individual."	Centers for Diasease Control and Prevention (CDC)	
Body water	Percentage or ratios of water in the body		

Care dependency	"Care dependency can be defined as a subjective, secondary need for support in the domain of care to compensate a self-care deficit."	Boggatz T et al. The meaning of care dependency as shared by care givers and care recipients: a concept analysis. J Adv Nurs. 2007 Dec;60(5):561-9.	
Cognitive function	"Cognitive function is a broad term that refers to mental processes involved in the acquisition of knowledge, manipulation of information, and reasoning. Cognitive functions include the domains of perception, memory, learning, attention, decision making, and language abilities."	Encyclopedia of Quality of Life and Well-being Research	

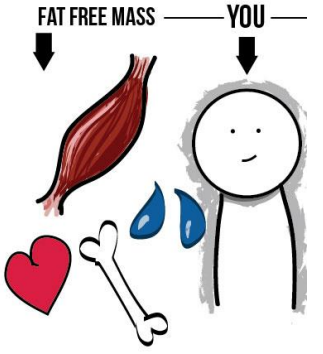
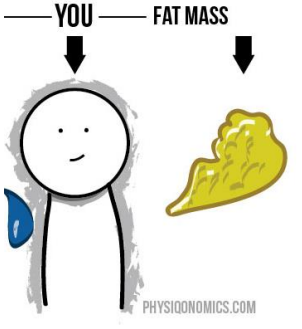
Comorbidities	A comorbidity is "a disease or medical condition that is simultaneously present with another or others in a patient." For example: A person with COPD who has diabetes. For the purpose of this study, COPD is considered the main disease and diabetes is the comorbidity.	Oxford dictionary	
Cough	"A cough is your body's natural reflex to help clear your airways of irritants and prevent infection." It can be acute (e.g., result of a common cold) or chronic (persistent over time).	NIH National Heart, Lung and Blood Institute	

Depression	"A negative affective state, ranging from unhappiness and discontent to an extreme feeling of sadness, pessimism, and despondency, that interferes with daily life."	APA dictionary of Psychology	
Dietary intake	"Dietary intake refers to the daily eating patterns of an individual, including specific foods and calories consumed and relative quantities."	Encyclopedia	

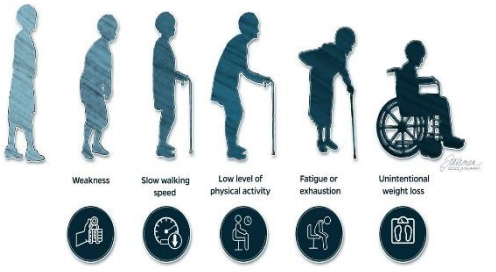
Disease-specific fears	Fears that are related to COPD. For example, fear of dyspnoea, fear of disease progression, and fear of physical activity/exercise	Reijnders T et al. The impact of disease-specific fears on outcome measures of pulmonary rehabilitation in patients with COPD. Respir Med. 2019 Jan;146:87-95.	
Distress	"The negative stress response, often involving negative affect and physiological reactivity: a type of stress that results from being overwhelmed by demands, losses, or perceived threats. It has a detrimental effect by generating physical and psychological maladaptation and posing serious health risks for individuals. This generally is the intended meaning of the word stress. "	APA dictionary of Psychology	

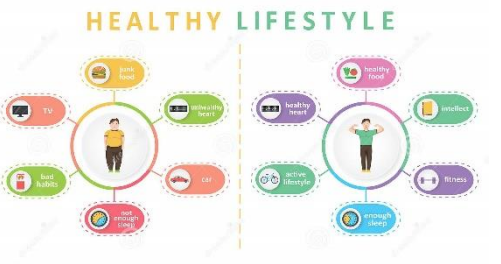
Dyspnoea	"An experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity". Also known as breathlessness.	American Thoracic Society. Dyspnea. Mechanisms, assessment and management: a consensus statement. Am J Respir Crit Care Med. 1999; 159: 321–340	
Energy expenditure	"The total energy cost of maintaining constant conditions in the body plus the energy cost of physical activities."	Encyclopedia of Human Nutrition	

Exercise capacity	Exercise capacity is the maximum amount of physical effort that a patient can sustain.	Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition, Chapter 8	
Falls	"A fall is defined as an event which results in a person coming to rest inadvertently on the ground or floor or other lower level."	WHO	

Fat free mass	Is the body mass other than fat mass. "it comprises tissues such as skeletal muscle, heart, brain, liver, kidneys, and the GI tract organs."	Book "Eating Disorders and Obesity in Children and Adolescents", Chapter 3	
Fat mass	Proportion of human body that is strictly composed by fat		

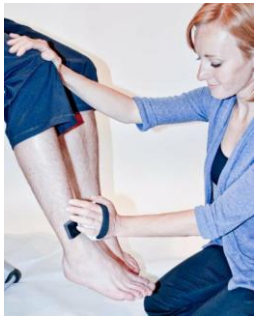
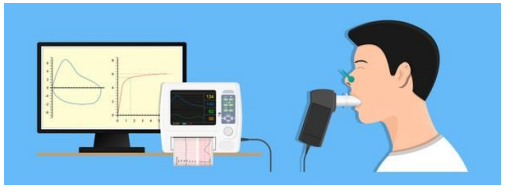
Fatigue	"Fatigue is a feeling of weariness, tiredness, or lack of energy."	NIH Medline Plus	
Flexibility	"Flexibility has been defined as the range of motion of muscle and connective tissues at a joint or group of joints."	Book "Fitness Measures and Health Outcomes in Youth.", Chapter 7	

Frailty	A deterioration of several body systems due to ageing that results in a state of vulnerability, progressing to higher levels of weakness and worse ability to do daily living activities.	Adapted from Xue Q. L. (2011). The frailty syndrome: definition and natural history. Clinics in geriatric medicine, 27(1), 1–15.	
General well-being	"a state of happiness and contentment, with low levels of distress, overall good physical and mental health and outlook, or good quality of life."	APA dictionary of Psychology	

Healthcare utilization	"Health Care Utilization is the quantification or description of the use of services by persons for the purpose of preventing and curing health problems, promoting maintenance of health and well-being, or obtaining information about one's health status and prognosis."	Encyclopedia of Behavioral Medicine	
Health behaviour/lifestyle	"Health-related behaviors, are actions taken by individuals that affect health or mortality. These actions may be intentional or unintentional, and can promote or detract from the health of the actor or others." Examples: smoking, substance use, physical activity, adherence to prescribed treatments.	Short, S. E., & Mollborn, S. (2015). Social Determinants and Health Behaviors: Conceptual Frames and Empirical Advances. Current opinion in psychology, 5, 78–84.	
Health-related quality of life	"Those aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment"	Karimi, M., Brazier, J. Health, Health-Related Quality of Life, and Quality of Life: What is the Difference?. PharmacoEconomics 34, 645–649 (2016).	

Heart rate recovery	Heart rate recovery is a measurement of the heart's ability to return to its normal, resting pace after finishing a workout		
Impact of disease	Impact of symptoms of COPD on daily living activities		
nowledge about the disease	Awareness, understanding, or information about the disease that has been obtained by experience or study, and that is either in a person's mind or possessed by people generally.	Adapted from Cambridge dictionary	

Loneliness	"Affective and cognitive discomfort or uneasiness from being or perceiving oneself to be alone or otherwise solitary."	APA dictionary of Psychology	
Loss of appetite	Reduced desire to eat		

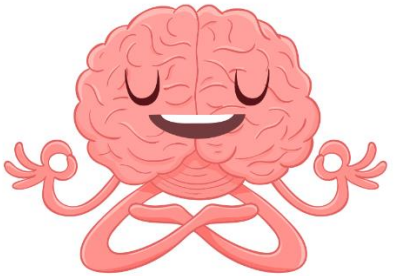
Lower limb muscle function	How the muscles of the legs work. Examples: Muscle strength, endurance, power		 
Lung function	"A term used to describe how well the lungs work in helping a person breathe. Also called pulmonary function" Examples are: forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), etc.	NIH National Cancer Institute	

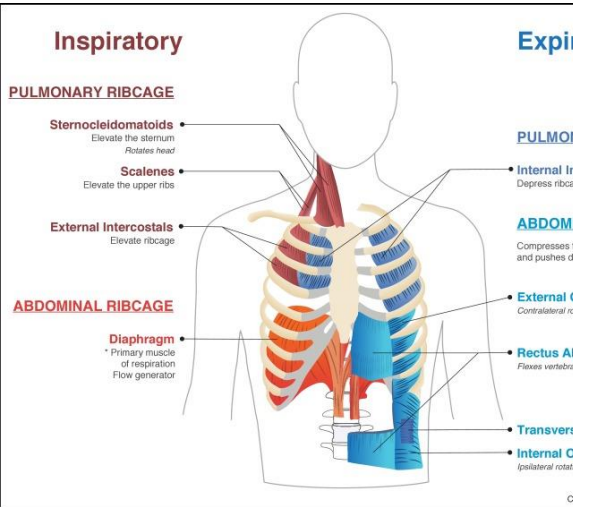
Medication change	Change in medication, such as short-acting bronchodilators (inhalers). This does not necessarily mean to remove the use of inhalers, or to change the inhaler care or techniques.	Cambridge dictionary	
Mood	"The way you feel at a particular time" Examples: happy, sad, pleased, annoyed	Cambridge dictionary	
Mortality	"A term also used for death rate, or the number of deaths in a certain group of people in a certain period of time. "	NIH National Cancer Institute	

Motivation to exercise/be physically active	The impetus to engage in exercise or physical activity, that operates in humans at a conscious or unconscious level. Motives can be personal, social, or secondary motives, such as affiliation, competition, and individual interests and goals.	Adapted from APA dictionary of Psychology	
Pain	"An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."	International Association for the Study of Pain	

Participation in society	A person's involvement in activities that provide interaction with others in society or the community.	Levasseur, Richard, Gauvin, & Ramond, 2010, p. 2148	
Patient concerns	A complaint or grievance raised by a patient about health or care rendered to him or her.		

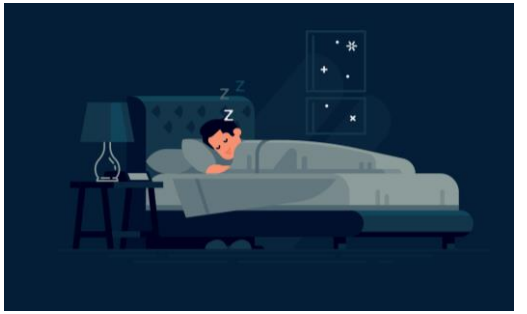
Physical (in)activity	"Any bodily movement produced by skeletal muscles that requires energy expenditure." Physical inactivity is the failure to achieve the amount of physical activity recommended.	WHO	
Physical well-being	Self-rated physical health and vitality coupled with perceived absence of physical discomfort	Reker, Gary T.; Wong, Paul T. P. (1984). Psychological and Physical Well-Being in the Elderly: The Perceived Well-Being Scale (PWB). Canadian Journal on Aging / La Revue canadienne du vieillissement, 3(1), 23–32. doi:10.1017/s0714980800006437	

Psychological well-being	A state of happiness and contentment, with low levels of distress, overall good mental health and outlook on life	Adapted from the APA dictionary of Psychology	
PTSD symptoms	Symptoms due to post-traumatic stress disorder, such as flashbacks, bad dreams, avoiding places, frightening thoughts, angry outbursts, etc. These symptoms can be caused by: exposure to traumatic events at work, serious health problems, war, serious accidents, physical or sexual assault, abuse (childhood or domestic), etc.	NHS	

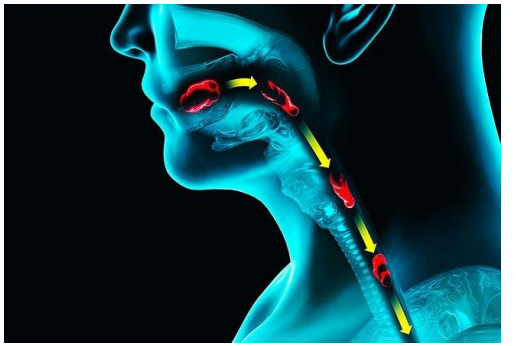
Respiratory muscle function	How the respiratory muscles (trunk) work. Examples: strength and endurance		
Satisfaction with sex life	A person's sexual activity and relationships considered as a whole.	Oxford dictionary	

Sedentary behaviour	Sedentary behaviour is any waking behaviour characterized by low energy expenditure, while in a sitting, reclining or lying posture.	Network SBR. Letter to the Editor: Standardized use of the terms" sedentary" and" sedentary behaviours". Appl Physiol Nutr Metab. 2012;37(3):540–542. doi: 10.1139/h2012-024.	
Self-efficacy	A person's conviction/belief of being able to do a specific task or achieve certain desired results. Example: perception of being, or not, capable to be physically active or to engage in an exercise programme.	Adapted from APA dictionary of Psychology	

Self-esteem	"the degree to which the qualities and characteristics contained in one's self-concept are perceived to be positive. It reflects a person's physical self-image, view of his or her accomplishments and capabilities, and values and perceived success in living up to them, as well as the ways in which others view and respond to that person."	APA dictionary of Psychology	
Self-management	"An individual's control of his or her behavior, particularly regarding the pursuit of a specific objective (e.g., weight loss)."	APA dictionary of Psychology	

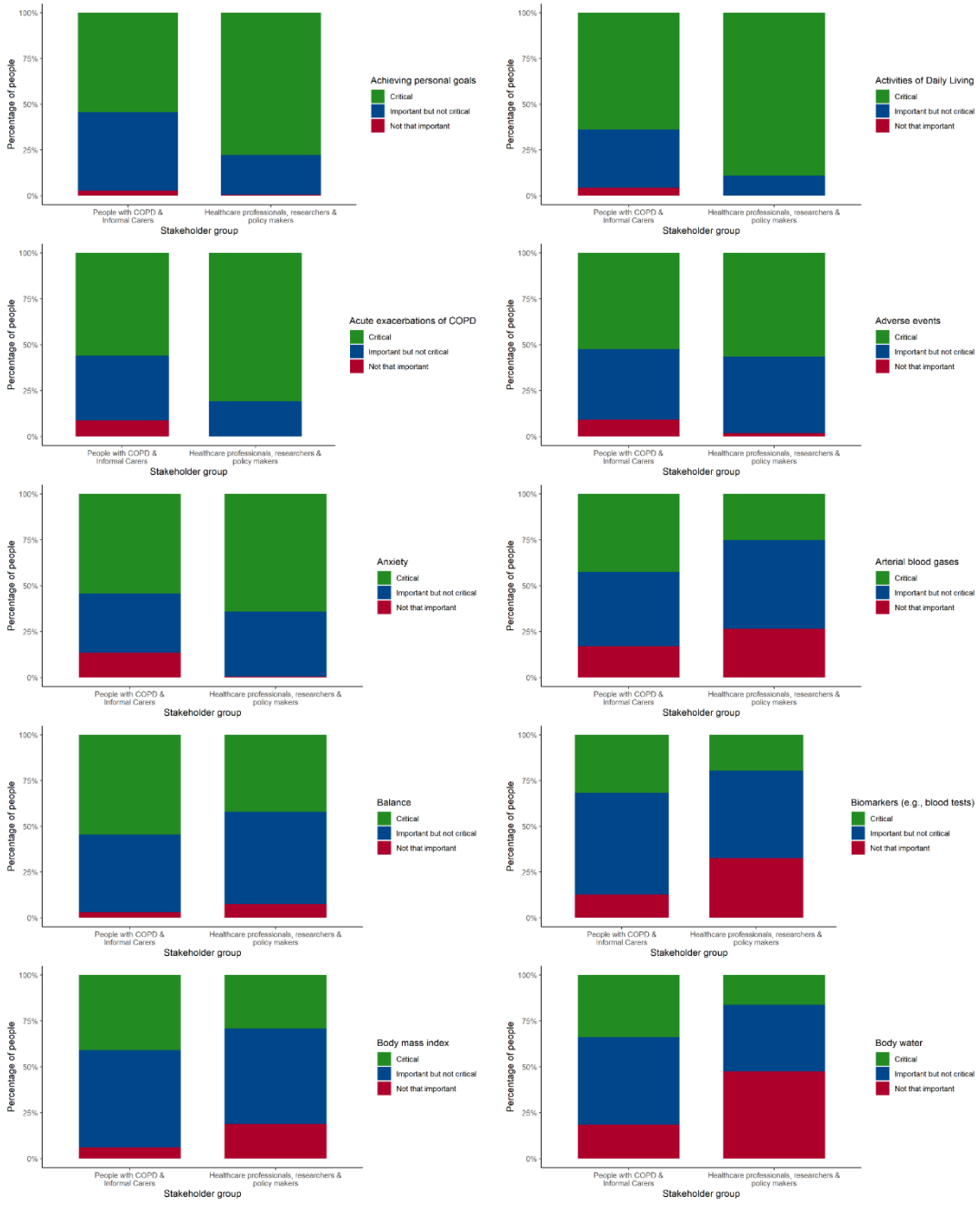
Sleep	“The resting state in which the body is not active, and the mind is unconscious”	Cambridge dictionary	
Social status/support	"The provision of assistance or comfort to others, typically to help them cope with biological, psychological, and social stressors. Support may arise from any interpersonal relationship in an individual’s social network, involving family members, friends, neighbors, religious institutions, colleagues, caregivers, or support groups. It may take the form of practical help (e.g., doing chores, offering advice), tangible support that involves giving money or other direct material assistance, and emotional support that allows the individual to feel valued, accepted, and understood."	APA dictionary of Psychology	

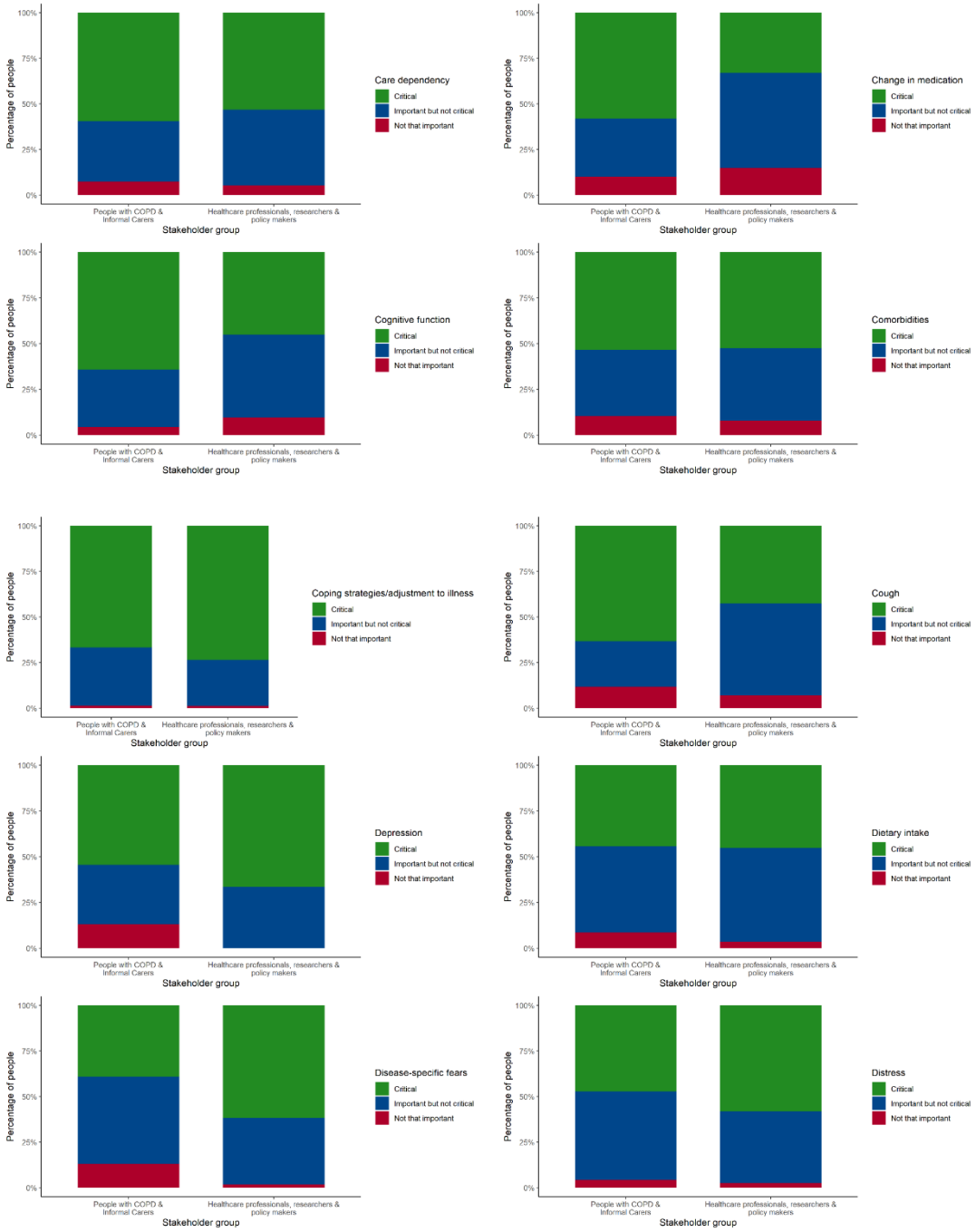
Smoking cessation	To quit smoking.		
Sputum	"Material coughed up from the lungs and expectorated via the mouth." Also known as mucus or phlegm	MeSH term	

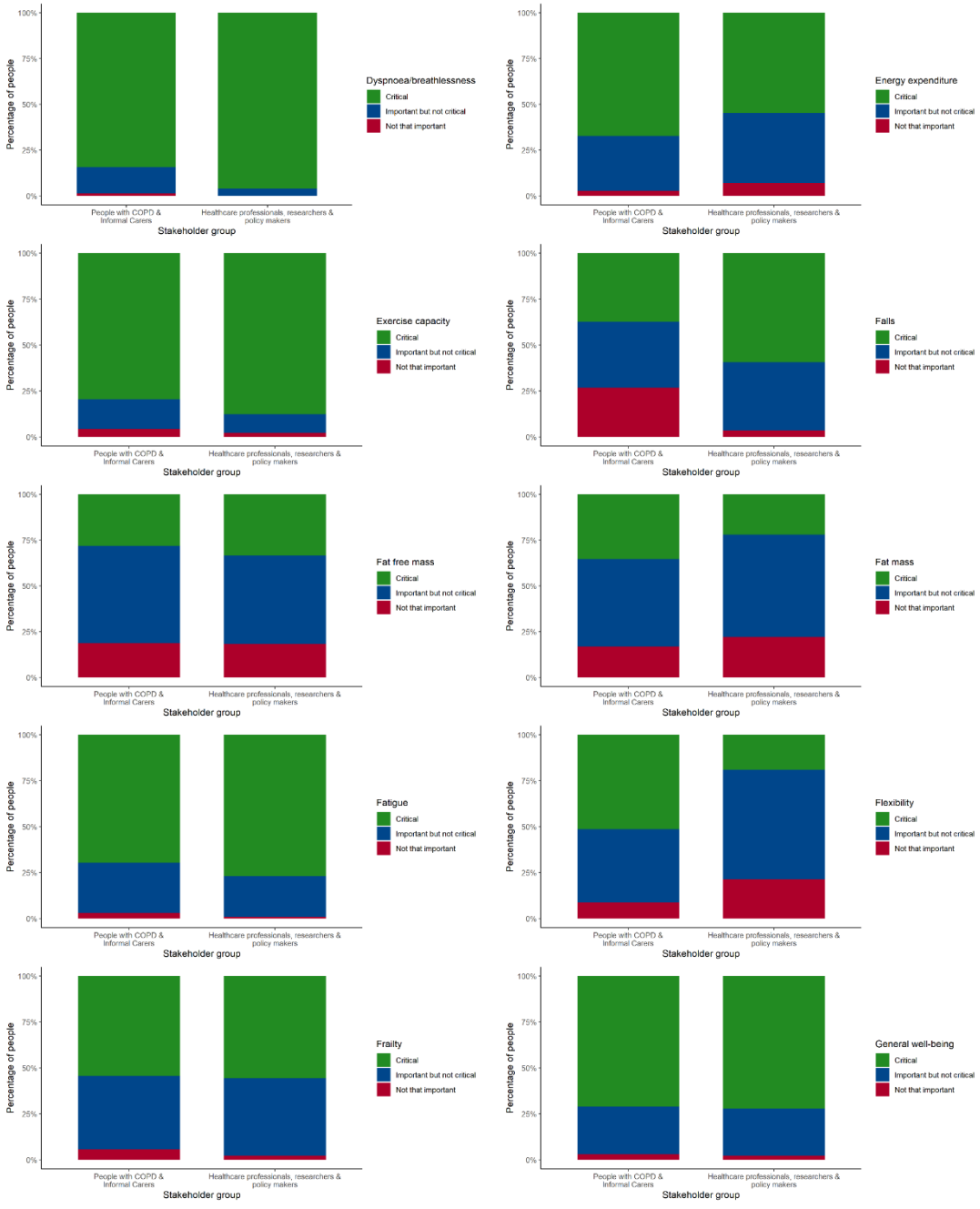
Swallowing function	Ability to pass food from the mouth to the stomach.	
Vital signs	Essential body functions Examples: temperature, heart rate, respiratory rate, blood pressure	

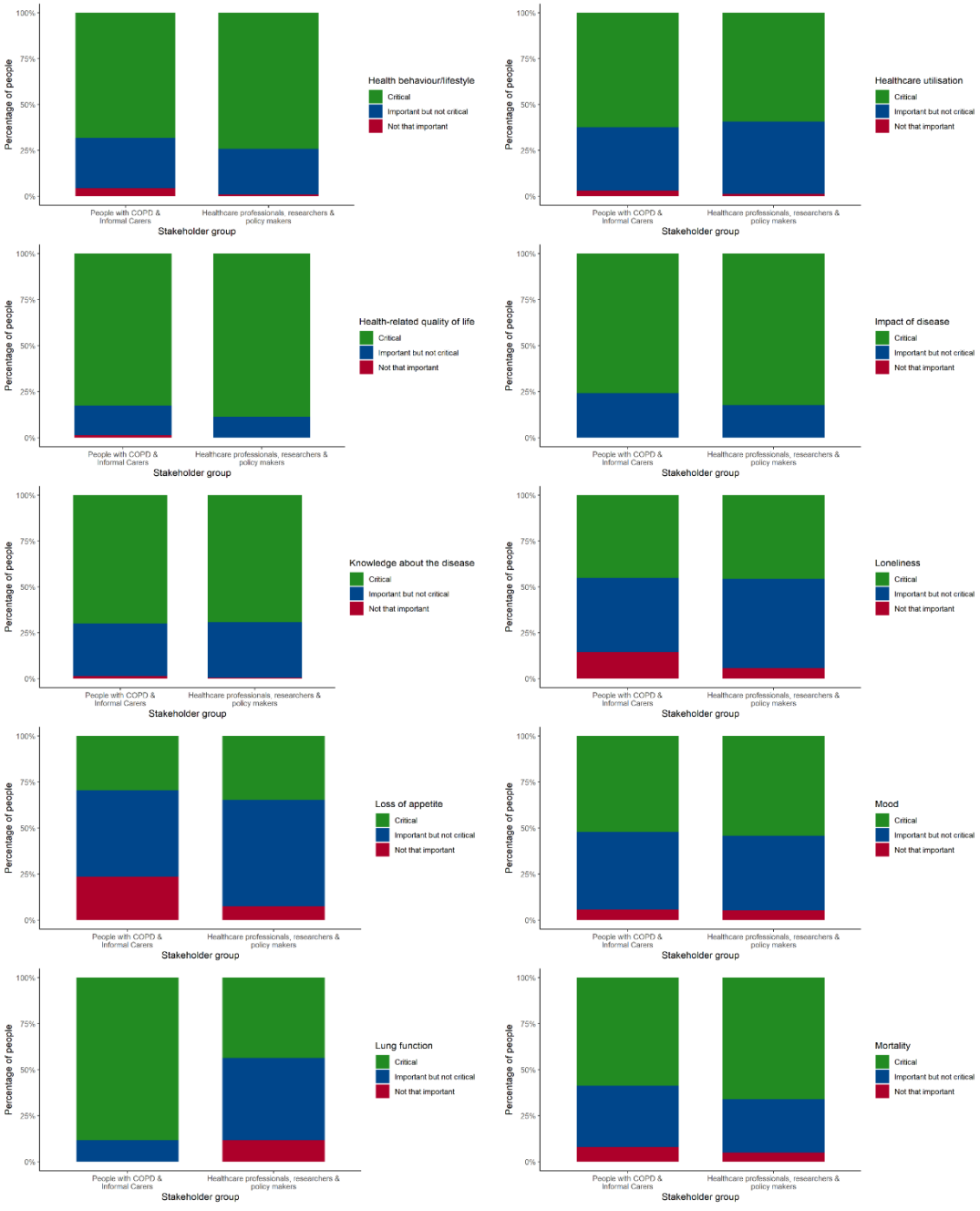
Weight change	Change in the weight of a person with COPD after pulmonary rehabilitation compared to before	

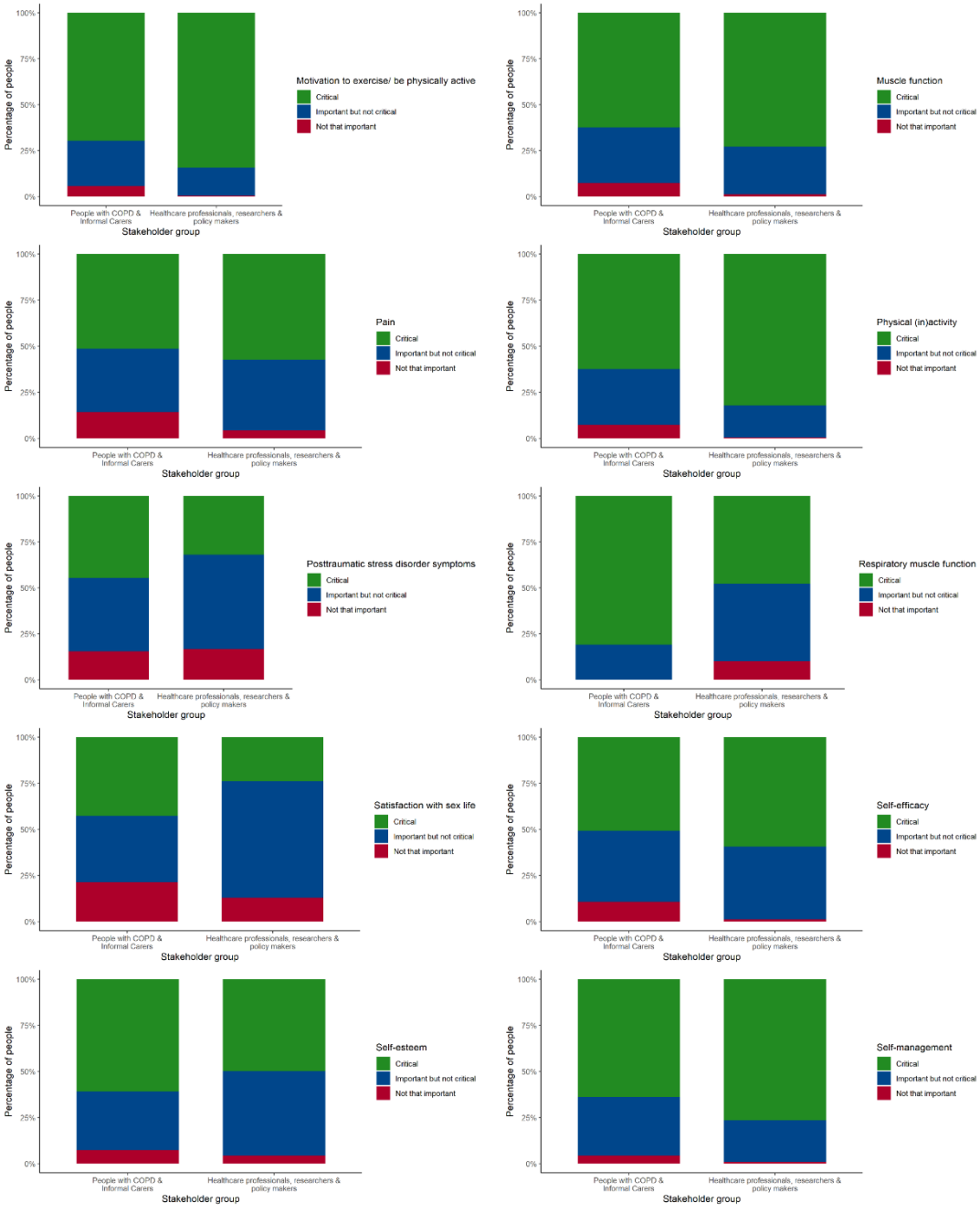
Appendix C. Feedback of the first round of Delphi survey provided to participants

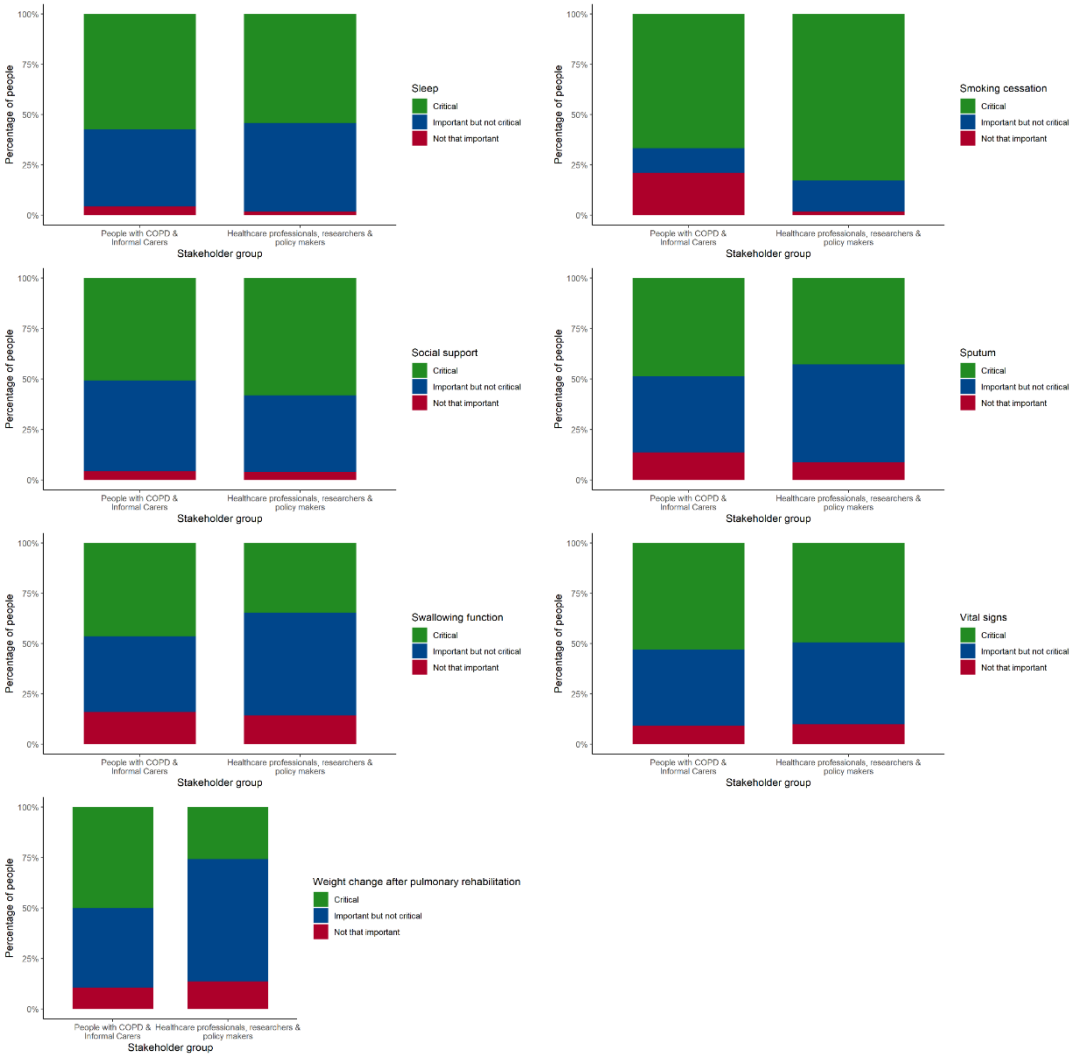


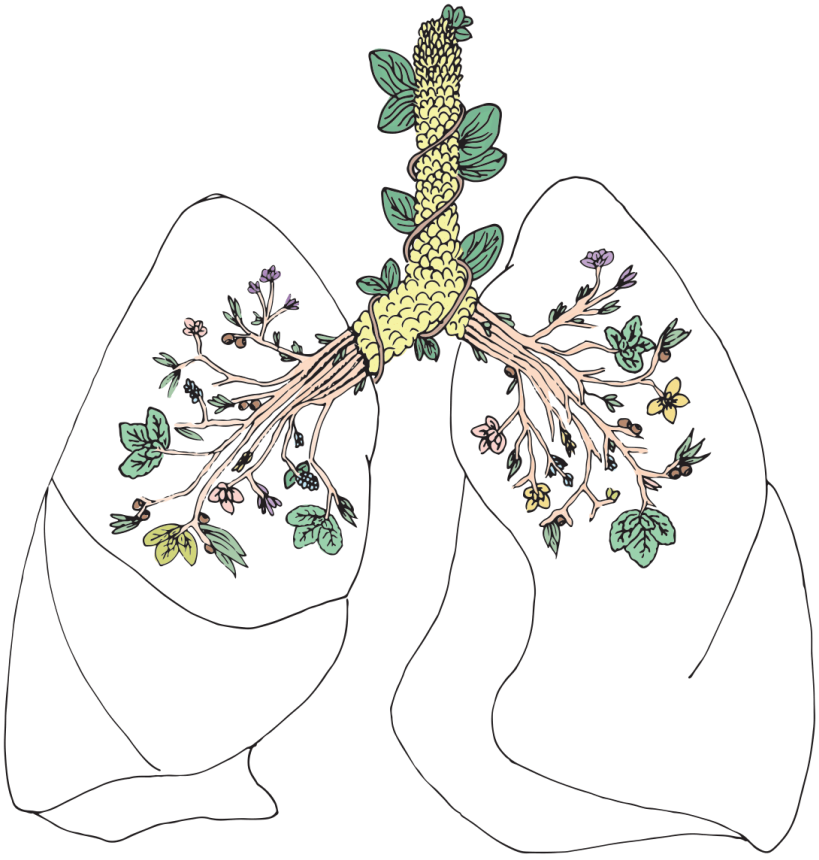

Percentage of people
100%
75%
50%
25%
0%
People with COPD & Informal Carers
Healthcare professionals, researchers & policy makers
Stakeholder group
Care dependency
Change in medication
Cognitive function
Comorbidities
Coping strategies/adjustment to illness
Cough
Depression
Dietary intake
Disease-specific fears
Distress
Critical
Important but not critical
Not that important


Dyspnoea/breathlessness
Energy expenditure
Exercise capacity
Falls
Fat free mass
Fat mass
Fatigue
Flexibility
Frailty
General well-being
Critical
Important but not critical
Not that important
Percentage of people
100%
75%
50%
25%
0%
People with COPD & Informal Carers
Healthcare professionals, researchers & policy makers
Stakeholder group


Health behaviour/lifestyle
Healthcare utilisation
Health-related quality of life
Impact of disease
Knowledge about the disease
Loneliness
Loss of appetite
Mood
Lung function
Mortality
Critical
Important but not critical
Not that important
Percentage of people
100%
75%
50%
25%
0%
People with COPD & Informal Carers
Healthcare professionals, researchers & policy makers
Stakeholder group


Motivation to exercise/ be physically active
Muscle function
Pain
Physical (in)activity
Posttraumatic stress disorder symptoms
Respiratory muscle function
Satisfaction with sex life
Self-efficacy
Self-esteem
Self-management
Critical
Important but not critical
Not that important
Percentage of people
100%
75%
50%
25%
0%
People with COPD & Informal Carers
Healthcare professionals, researchers & policy makers
Stakeholder group


Sleep
Smoking cessation
Social support
Sputum
Swallowing function
Vital signs
Weight change after pulmonary rehabilitation
Critical
Important but not critical
Not that important
Percentage of people
100%
75%
50%
25%
0%
People with COPD & Informal Carers
Healthcare professionals, researchers & policy makers
Stakeholder group



Chapter 8
Summary and general discussion

Summary and general discussion

The primary objective of this thesis was to create a COS for PR of patients with COPD. The aim was to design a set that could be utilized in both research and clinical settings, to address the limitations in synthesizing evidence and the difficulty in benchmarking PR outcomes due to the diversity of measurement methods. Indirectly, this thesis also sought to shed light on the PR-relevant treatable traits of individuals with COPD and their influence on the varying responses to this intervention. The ultimate goal of this secondary objective was to enhance our understanding of some of the factors that impact the effectiveness of PR in this population.

Results of this thesis suggest that there are nine core outcomes of PR that can be operationalized through a set of internationally and multistakeholder-applicable measurements. Findings further suggest that i) simple and practical measurement tools can be useful for screening for treatable traits, and are preferred by various stakeholders as they can be applied in different PR settings, such as inpatient, outpatient, community, and home-base; ii) it is important to carefully consider the choice of measurement to assess the effectiveness of PR; and iii) there is a need for further investigation into the treatable trait strategy within PR, as it may have the potential to differentiate responders from non-responders ahead of time, thereby optimizing patient selection and personalizing treatment.

Chapter 2 of this thesis confirmed the substantial variability in outcome measurement in PR trials, with 163 outcomes and 217 distinct measures employed across studies. This finding reinforced the necessity of a COS in this area to improve comparability between studies and benchmarking of PR. Furthermore, the chapter provided an initial list of outcomes to be used in a future consensus study, and also a comprehensive overview of the structure and content of PR interventions since 2000, which enriched our understanding of the PR landscape.

In **Chapter 3** we demonstrated that a cut-off of 19.5 repetitions in a simple office-based test, i.e., the 1-minute sit-to-stand test can accurately differentiate individuals with COPD with a functional impairment from those without this treatable trait. This test can, therefore, be used as an initial screening tool prior to more in-depth assessments of functional status, such as the 6-minute walk test, and may be a valuable marker of the presence or absence of this PR-relevant treatable trait.

Findings of **Chapter 4** confirmed the existence of varying responses to PR in a less studied but highly relevant outcome (i.e., functional status), with a significant proportion of people with COPD (43-45.5%) not experiencing a clinically meaningful improvement in their functional status following PR. Additionally, this study emphasized the importance of cautiously selecting the appropriate measurement instrument for each outcome, as this impacts the interpretation of patients as responders or non-responders to the intervention.

Chapter 5 revealed that individuals with COPD possessing treatable traits at baseline, defined using internationally accepted criteria, are four to 20 times more likely to achieve a favourable outcome from PR compared to those without treatable traits (i.e., closer to normal functioning). Henceforth, this study implies the potential benefits of incorporating a treatable trait strategy in PR. By adopting this strategy, PR could be made more efficient through improved patient selection, based on a patient's likelihood of responding to the intervention, and by better personalizing and optimizing it to accommodate patients' needs (i.e., only selecting the PR components needed for each patient, such as different educational topics, types of exercise training, psychotherapy or nutritional counselling). Nevertheless, this approach needs further investigation.

Chapter 6 provides important insights into outcome measurement in PR. In conjunction with the results from **Chapter 2**, this study also resulted in a comprehensive list of outcomes to be included in a consensus-driven definition of the core outcomes of PR. This qualitative investigation shed light on the importance of

assessing outcomes that are meaningful to patients and of showing that PR is beneficial for people with COPD. Additionally, it highlighted the need to have comprehensive assessments that are consistent across PR settings, psychometrically sound but practical measurements tools, and the usefulness of a COS to promote benchmarking of PR and advance the field. Nevertheless, it acknowledged the potential challenges of COS implementation such as resistance to change clinical practice and its use as a maximal instead of a minimum set of measurements.

Lastly, **Chapter 7** gathered previous research and particularly findings from **Chapter 2 and 6** and presented the COS for PR of people with COPD. This 2-round Delphi study followed by a consensus meeting identified nine crucial outcomes of PR: dyspnoea, exercise capacity, fatigue, health-related quality of life, health behaviours/lifestyle, knowledge about the disease, lower limb muscle function, personal goals, and problematic activities of daily living. These outcomes should now be consistently measured and reported as a minimum in all PR trials and programmes, to demonstrate the effectiveness of the intervention for people with COPD and the quality of programmes.

Based on the novel findings of this thesis, the following topics will be discussed in more detail. Firstly, treatable traits of people with COPD and implications of this strategy for PR will be discussed considering the results of **Chapter 3, Chapter 4 and Chapter 5**. Then, findings in the literature about other COS and their uptake will be confronted with the results of this thesis, mainly presented in **Chapter 2, Chapter 6** and **Chapter 7**.

The treatable trait strategy and its importance for PR

The treatable traits strategy is a precision medicine model that aims to personalize the management of patients with chronic respiratory conditions by identifying and targeting specific problems or traits[1]. This approach involves assessing patients for a set of clinically relevant, identifiable, and measurable traits

and creating a personalized treatment plan based on the identified problems[2]. This strategy has shown promising results in treating disease complexity in asthma, when compared to conventional treatment (regular interventions provided in a specialised asthma clinic)[3].

In 2016, a comprehensive list of pulmonary (e.g., airflow limitation, chronic bronchitis), extra-pulmonary (e.g., deconditioning, obesity) and behavioural/lifestyle treatable traits (e.g., smoking, exacerbation management) were proposed for measurement in patients with airway disease[1,2]. However, not all of these traits are relevant for PR (cannot be addressed) and additional important extra-pulmonary and behavioural traits, such as muscle dysfunction, functional impairment, balance limitations, and low levels of physical activity, may need to be considered.

In **Chapter 3**, we determined a specific cut-off point for the 1-minute sit-to-stand test, which could serve as a useful treatable trait for assessing functional status. This cut-off value can be utilized to efficiently identify patients who would benefit from PR and allow for meaningful referral criteria to be established. The cut-off value of 19.5 repetitions showed not only high sensitivity but also high specificity, which is crucial for accurately confirming the presence of a trait[2]. Furthermore, this chapter addressed an important research opportunity within the treatable trait strategy field by identifying a new feasible marker, that can be used across multiple settings[2]. Similarly, other cut-offs for PR-relevant traits have been previously established, such as severe dyspnoea (≥2 points on the mMRC)[4], reduced muscle strength (1RM/weight ≤31%)[5] symptoms of anxiety and depression (≥8 points on the Hospital Anxiety and Depression Scale)[6], poor HRQoL (≥46 points on the Saint George's respiratory questionnaire)[7], high symptom burden (≥18 points on the COPD assessment test)[7] poor balance (≤16 points on the Brief- Balance Evaluation System Test)[8], low physical activity levels (<5000 steps per day)[9,10]. In combination with the proposed treatable trait of this thesis, these identified traits could potentially form a comprehensive set of traits in the future, to be evaluated prior to initiating PR.

Nonetheless, the suitability and validity of these traits for PR should be further assessed with multiple stakeholders.

Chapter 4 of this thesis showed that people who responded better to PR were those with lower performance at baseline in functional tests, and that the use of different measures within the same outcome domain might result in different interpretations of the patient's response. Thus, this emphasized the importance of conducting a meticulous selection of appropriate measures for the identification of treatable traits at baseline, as it might significantly impact the subsequent evaluation of the intervention's effectiveness in targeting these traits. Other studies have also found better responses to PR in people who were more symptomatic and had more limitations at baseline[11-13]. Mounting on this evidence, **Chapter 5** showed that having treatable traits at baseline increases the likelihood of responding to PR up to 20 times, compared to not exhibiting the treatable traits at baseline.

Results of the aforementioned chapters and responder analyses in existing literature suggest that the enrolment process for PR might be more efficient by first identifying patients who are more likely to benefit from the intervention. Additionally, employing a treatable trait strategy may optimize the intervention by selectively focusing on necessary components tailored to each patient's treatable traits, thereby conserving valuable time and resources for both clinicians and patients.

Recently, a systematic review of the literature found that PR was insufficiently addressing the treatable traits of people with COPD[14]. However, the search of this review was only based on a list of treatable traits that was not designed for PR studies[1], hence, the true potential of a treatable trait strategy within PR remains to be explored.

Therefore, a treatable trait strategy might be a new avenue to pursue within PR, but before the widespread use of this approach, it is important to identify PR-relevant treatable traits with valid criteria (i.e., cut-offs), create an algorithm to decide

which component of PR is activated for which treatable trait, and compare it to a conventional strategy, in terms of cost-effectiveness.

Core outcome sets and their impact

A large number of COS (n=370) with about 15 being focussed on the lungs and airways category, have been published since 1981, due to their potential to decrease research waste and promote evidence-synthesis[15]. Of the latest 33 studies developing COS, only 18% met the minimum standards set by the COMET initiative[15]. This finding highlights the importance of applying the proposed rigorous methodology and reporting according to the guidelines[16,17], as followed in this thesis.

Our COS was informed by a systematic review (**Chapter 2**), two qualitative studies (**Chapter 6**) and [18], a Delphi survey and a consensus meeting (**Chapter 7**), which had patient input since their inception. The first systematic review of published COS in other fields revealed that the most frequent method of consensus used was a semi-structured group discussion, workshops or meetings[19], which are less robust than a multipaneled Delphi survey. Furthermore, only 33% conducted a literature or systematic review, 15% a Delphi survey, 8% a nominal group technique, and only 18% had public involvement[19]. Moreover, a median of 4 countries were involved in the development of those COS, which contrasts with the 29 countries covered by the COS presented in this thesis[19]. **Chapter 7** also included lower and middle income countries[20] - Argentina, Brazil, Colombia, India, Philippines, Turkey, and Ukraine, which has been a recognised priority in COS development[15].

Few studies have been conducted to assess the uptake of COS in randomized controlled trials (RCTs) and systematics reviews, which limits our understanding of the needs to optimize application of this COS[21]. Nevertheless, available research indicates COS uptake rates to vary greatly with some COS never used in RCTs whilst others (e.g., rheumatoid arthritis) have been fully utilized in 82% of RCTs in the respective field[21]. Of note, the COS that had the highest uptake recommended the

measurement of 8 outcomes (similar to the hereby proposed) and has been developed almost three decades ago[22]. A review of COS uptake in Cochrane systematic reviews, further showed that only 5% of those reviews used the COS to define the outcomes to be searched, while 35% could have considered COS[23]. Despite the poor uptake, an increasing number of organisations are recommending COS and there seems to exist a good overlap between outcomes recommended in COS, in regulatory documents, and in health technology assessments[24]. Similar outcomes have also been recommended across rehabilitation of different health conditions[25-29], which suggest the potential of sharing resources among rehabilitation services.

Several barriers for COS uptake have been suggested, such as lack of awareness of existing COS, lack of consensus on "how to measure" or lack of validated measures, lack of patient and other important stakeholder involvement, lack of clarity on the definition of outcomes/domains, patient burden, costs associated with measurements and lack of standardised recommendations across regulatory agencies[21,30]. In light of the aforementioned obstacles, the forthcoming stages of the proposed COS expounded in this thesis must focus on identification of measurement instruments that not only demonstrate robust psychometric properties but also exhibit feasibility for both clinicians and patients. Moreover, dissemination of the research findings to regulatory bodies and professional organizations responsible for developing clinical guidelines in the field of respiratory medicine, such as the European Respiratory Society and the American Thoracic Society, is imperative.

Methodological considerations

The present thesis established a COS for PR in individuals with COPD, with the ultimate objective of enhancing the uniformity of clinical trial assessments and establishing a common benchmark for PR outcomes across diverse settings. However, the primary focus was confined to defining the specific outcomes to be measured (i.e., "what to measure"), and some degree of heterogeneity will continue to persist as

researchers and clinicians retain the ability to select disparate measurement instruments. Therefore, establishing the measurement instruments i.e., "how to measure" for each outcome of the COS, is an important further step.

Following the recommendations of the COMET and the COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) initiatives, this can be achieved through a systematic review of the measurements properties of instruments used for each outcome (when none is available)[31]. However, a new consensus-based study, such as a consensus meeting might be needed, in case of instruments with equally robust measurement properties, and to ensure that other aspects such as feasibility of measures (costs, burden), or their behaviour in responder analysis (as seen in **Chapter 4**), are considered[31]. A systematic review of the literature is already registered in the international prospective register of systematic reviews (PROSPERO, ID CRD42022313344) and will be conducted in the future to complete all stages of the COS.

Conclusions and future directions

A COS for PR of people with COPD can now be used in both research and clinical practice, and by multiple stakeholders, such as trialists, systematic reviewers, funders, programme payers, clinicians, and patients.

Future research should explore the suitability of a treatable trait approach within PR and validate our treatable trait candidate (**Chapter 3**), and ascertain the uptake of this COS.

To promote the adoption of the COS proposed in this thesis, it is recommended that a systematic review be undertaken to identify trials that employ this COS, with regular updates every 2 years[24]. Additionally, to gain a comprehensive understanding of any impediments or catalysts for the uptake of the COS, soliciting feedback from the relevant stakeholders is crucial[24]. These insights can then be

utilized to develop and implement novel strategies aimed at enhancing the adoption and utilization of the COS in PR.

Lastly, it is important to start a comprehensive dissemination strategy of this COS, through several channels, such as trialists, patient organizations, relevant Cochrane review groups (airways and rehabilitation), clinical guideline developers, research funders, journal editors, clinical professional bodies (of each country), regulators, research ethics committees and trial registries, health technology assessment bodies (NICE), conferences, and social media[24].

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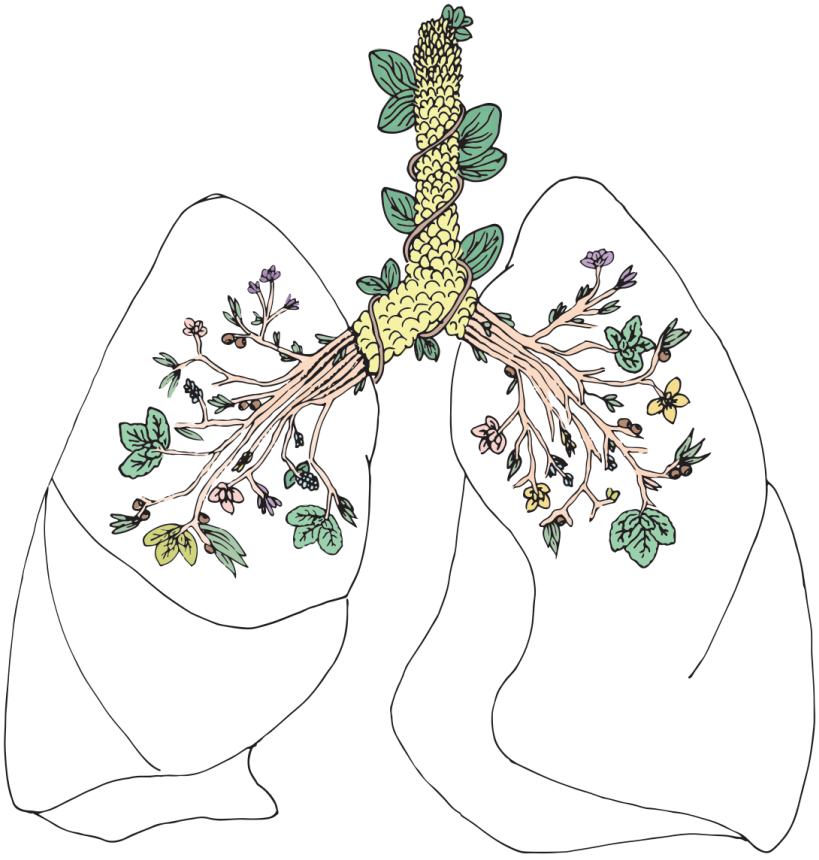


Impact section

Impact section

This thesis provided various findings that can have a significant impact beyond the research field. This section reflects on the scientific and social impacts of this thesis considering four paradigms: 1) Research – What is the main aim of the thesis and the main results and conclusions; 2) Relevance – What is the (potential) contribution of the findings of the thesis to the scientific and social sectors?; 3) Target groups – To whom and why are the scientific results relevant/favourable; and 4) Activities – How can the target groups be involved in and informed of the findings, so the knowledge can be used in the future?

Research and relevance

The main aim of this thesis was to develop a COS. We found that nine outcomes are crucial to be measured from the perspectives of different stakeholders and should therefore be used hereafter in PR trials and clinical practice. This thesis also contributed to the knowledge in the field of treatable traits, by identifying a robust marker of functional impairment and showing that a treatable trait strategy should be further explored, since patients who exhibit treatable traits at baseline are those who respond better.

A COS for PR in patients with COPD might result in direct clinical and research benefits (**Figure 1**). Clinically, including outcomes relevant to different stakeholders might improve the quality of patient's assessments, it may enhance the understanding of patients' responses, enable benchmarking and replicability of best practices (by comparing the same outcomes between different programmes/populations), and by showing the results to patients, centres, and payers we can improve transparency and ensure trust among all parties. A COS may also help healthcare professionals to implement PR programmes, with a quick assessment guide.

Considering the research field, the developed COS might generate consistency among trials, whilst lessening the risk of outcome reporting bias, thus enabling the comparison of different studies across distinct settings. Moreover, the standardisation of outcomes achieved through a COS, may help to change policies regarding PR, by consistently showing the benefits of the intervention and therefore attracting funding to improve its access. Using the COS in research studies may also enable benchmarking PR (detecting the best model). Additionally, by enhancing our understanding of responders and non-responders to PR and of treatable traits, a COS might indirectly help to prioritise patients to this scarce intervention and promote its personalisation. Finally, the core outcomes can be compared across different diseases, to better understand the effectiveness of rehabilitation services for different groups of patients, and therefore translate knowledge from the best practices to those in need.

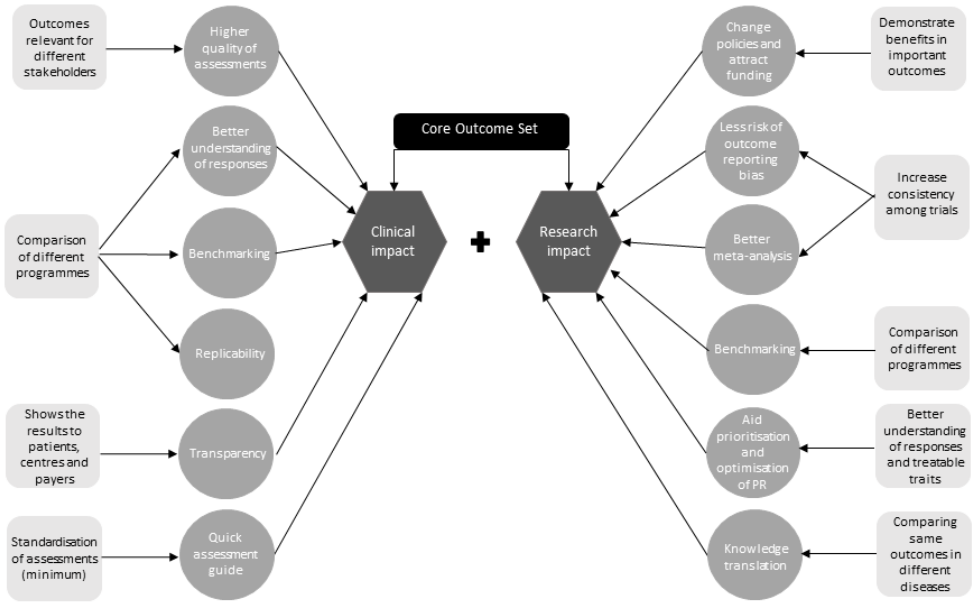


Figure 1. Potential impact of the core outcome set for pulmonary rehabilitation of people with chronic obstructive pulmonary disease (COPD). TT: treatable traits; PR: pulmonary rehabilitation.

Target groups

Results of this thesis are of interest to a wide community of patients, researchers, clinicians, regulators, and other professionals involved in outcome measurement and confirm the beneficial effects of PR for patients with COPD.

Patients and patient organisations should be aware of this COS, so they can identify centres with the best practices, know their progress with PR and what is expected. Additionally, it may enable peer comparison in a positive competitive way and easy transfer of data from centre to centre when patients are referred to other PR programmes. Furthermore, patients and patient organisations might encourage PR practices to adopt this COS.

For clinicians, this COS might improve their efficiency in assessment and health record registration, by having a structured set of assessments to perform and

results to register. In fact, in the future it could be of value to have the COS embedded in electronic health registry systems, to improve the level of information on patients' records, facilitate data collection, transfer between centres and analysis of big data for multiple centres, e.g., within a country.

Researchers planning studies with PR as an intervention should now consider the full use of this COS to assess the effectiveness of their interventions and use one of the core outcomes as a primary endpoint in their analysis, so their results can be later combined in meta-analysis.

This thesis will greatly benefit systematic reviewers. If this COS has high uptake by trialists, systematic reviewers will be able to perform bigger data pools and meta-analysis, and therefore increase the strength of certainty about the evidence in the field.

Professional bodies and guideline developers/policy makers will also benefit from the work of this thesis, as it can serve as a robust base to drive recommendations on outcome measurement in PR and therefore foster higher quality in PR programmes worldwide.

Research funders might also benefit from this work, as they can encourage the use of more robust designs in studies during the application process and therefore fund studies who are using the COS which might have a lesser risk of outcome reporting bias. Similarly, trial registries and journals could incorporate in the submission form a question related to the use of a COS and therefore promote outcome reporting transparency.

Finally, this COS might also be of value to health technology assessment and audit agencies. For health technology assessment, the COS can be used to test different devices using the same outcomes (especially important for tele-rehabilitation) which can enable determining their access and pricing. For audit agencies, this COS can be part of an iterative process of quality improvement of PR,

using the core outcomes to ascertain effectiveness of different centres and assign best practices, in conjunction with other indicators, such as process and structure measures.

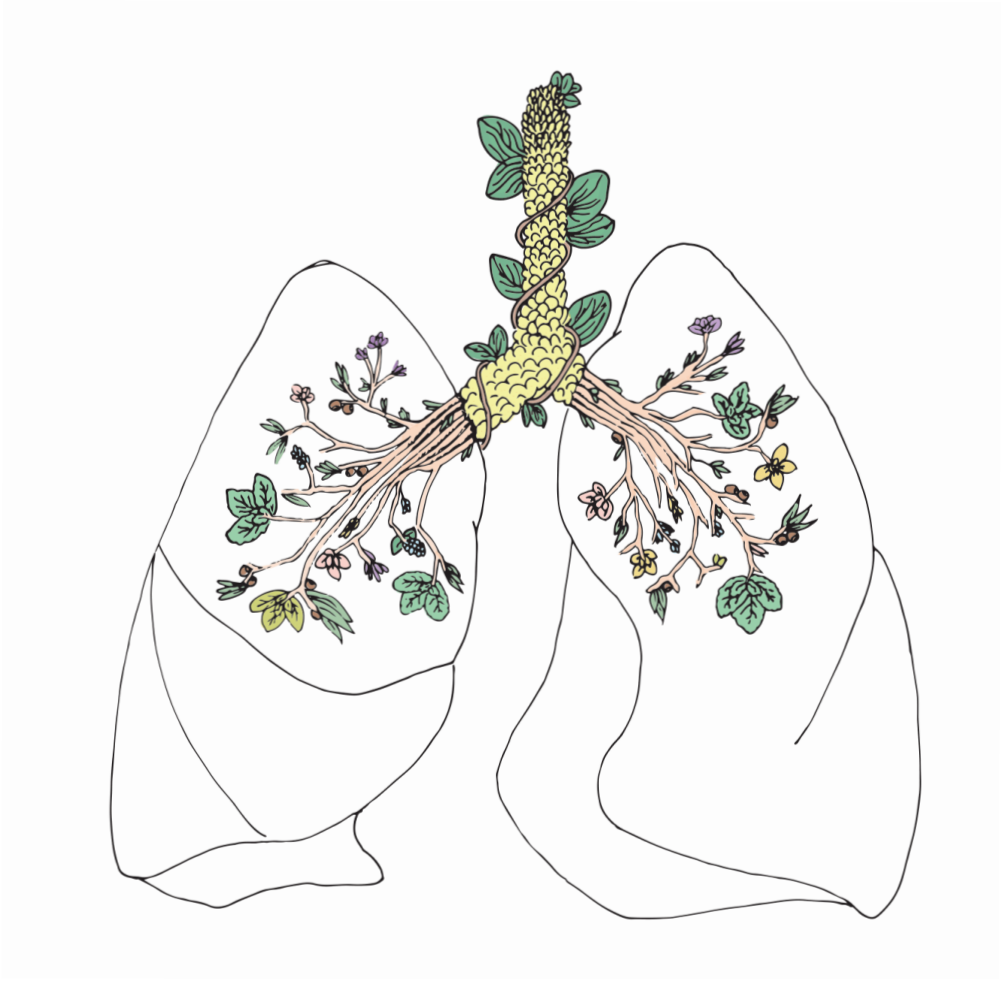
Activities performed and planned

Many activities have been conducted to ensure the dissemination of results of this thesis. Firstly, results have been published in international peer-reviewed journals and have been presented in international and national scientific meetings.

Studies have also gain interest in social media and have been shared by different professional groups, such as the PR assembly of the American Thoracic Society, and the Group 1.02 "Rehabilitation and Chronic Care" of the European Respiratory Society.

Additionally, results have been shared with multiple stakeholders (patients, clinicians) and professional bodies throughout the COS process and have gained positive feedback and further attention from the general public. Results were also reported in a Portuguese news outlet *My Pneumologia.*

Nonetheless, many activities still need to take place in the future. The final results of this thesis (**Chapter 7**) will be disseminated in national and international congresses, with all stakeholders involved in the studies (**Chapter 6 and 7**), professional associations (local and international), patient organisations, research funders and health technology assessment and audit bodies. Finally, after the "how to measure" phase is established, support to healthcare professionals will be provided through training courses and online material on how to use the core measurement instruments.



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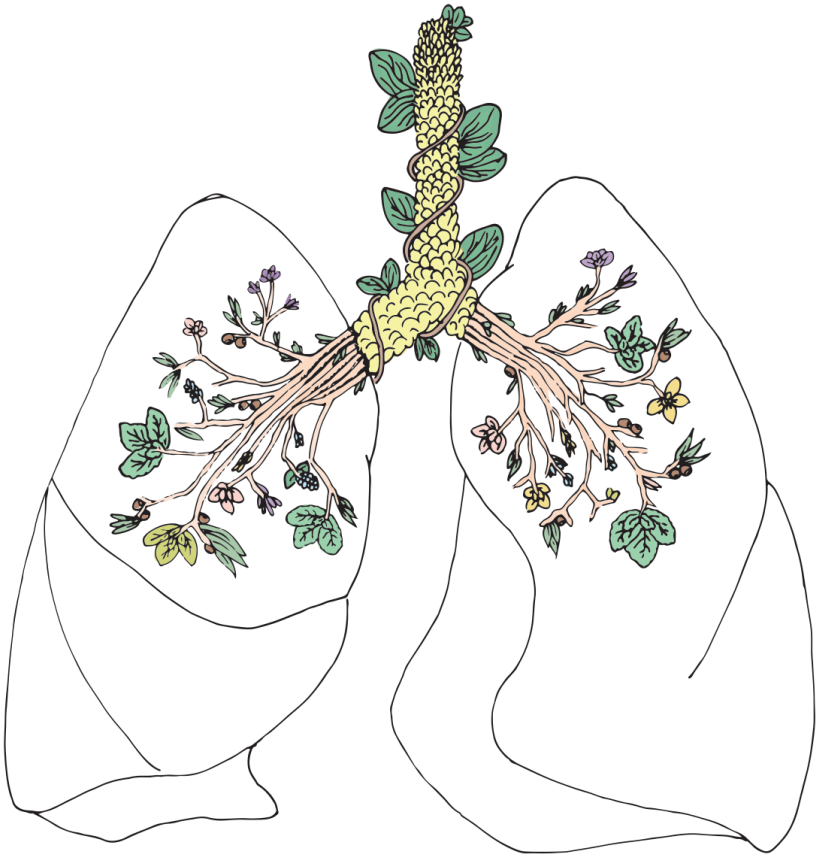
Lastly, I would like to acknowledge all institutions, patient and professional associations, who have helped with the dissemination of my research studies.

As a wise patient once said

I do this for you, for me, and for science

Carlos Anjos



About the author and scientific publications

About the author

Sara was born on April 20, 1992, in Aveiro, Portugal. After finishing high school in the Portuguese School of Dili (East Timor) she studied Nursing for one year in the University of Aveiro. Soon after she entered the course she realised Physiotherapy was a more suitable degree for her profile and therefore started the Degree in Physiotherapy in the same University in 2012. During her degree in Physiotherapy she had contact with the respiratory field namely through lectures, clinical placements and a final research project, which raised her curiosity and interest in research and respiratory physiotherapy. She then became a research fellow at the respiratory research and rehabilitation laboratory (Lab3R) of the School of Health Sciences of the University of Aveiro (ESSUA), and pursued a post-graduation course in adult respiratory physiotherapy that was followed by a Master's degree in Physiotherapy in the same University. In 2018 she was awarded a grant by the European Lung Foundation for the best abstract in patient-centred research that resulted from her master's dissertation and was also awarded a merit scholarship from the Ministry of Science, Technology and Higher Education (MCTES) of Portugal due to excellence in master's degree. After completing her primary degree and before entering her PhD journey, Sara was involved in six funded research projects, both as research fellow and a research team member.

In 2019 Sara started her PhD in a joint collaboration between the Maastricht University and University of Aveiro, and in the same year she was an invited lecturer for the curricular unit of "Intervention in Physiotherapy III" for third year Physiotherapy students. Her research focused on developing a core outcome set, i.e., minimum set of outcomes that should always be measured and reported, for pulmonary rehabilitation of people with COPD, with the ultimate aim of making

evidence synthesis in the field more efficient and improve the quality of care provided to patients. During her PhD she received the 2021 Ciro+ Short-Term Research Training Fellowship, that enabled her to spend three months at Ciro, Horn, The Netherlands, where she contacted with a different pulmonary rehabilitation setting (tertiary care), international researchers and a high-resource outcome assessment scheme. Throughout this period Sara followed several courses, such as the course "Clinimetrics" from EpidM of Amsterdam UMC and the "Clinical Investigator European Certification, Level 2 Certificate: Principal Investigator" from PharmaTrain, as well as several webinars, such as the "Cochrane training webinar on Qualitative Evidence Synthesis - Selecting studies and assessing methodological limitations" and the "ERS Webinar - Panel discussion on ERS Statement – A core outcome set for clinical trials evaluating the management of COPD exacerbations". During this period, she also presented the results of her research on several national and international scientific meetings.

Sara is currently employed as an advisor to the Office of Studies and Planning of the Portuguese Order of Physiotherapists, where she is responsible for the conduction of nation-wide research related to the profile of the physiotherapist and researcher in physiotherapy, development of guides and reports related to assessments and records in physiotherapy and cost-effectiveness studies of Portuguese physiotherapy practices.

Scientific publications

Book chapter

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Submitted articles

Souto-Miranda, Saraiva I, Spruit MA, Marques A. A Core Outcome Set for Pulmonary Rehabilitation of patients with COPD: results of a modified Delphi survey

Machado A, Dias C, Rebelo P, **Souto-Miranda S**, Mendes MA, Ferreira D, Martins V, Simão P, Burtin C, Marques A. Functional status in people with COPD and its relationship with disease severity – a cross-sectional study with matched controls

Conference contributions

International

Souto-Miranda S, Rocha V, Mendes MA, Simão P, Martins V, Marques A "Presence of extra-pulmonary treatable traits in people with COPD increases the likelihood of responding to pulmonary rehabilitation" (2022), Pulmonology, 28 Supl Congr 3:25, https://www.journalpulmonology.org/en-pdf-X2531043722034180

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