

Multimorbidity, frailty and COPD: are the challenges for pulmonary rehabilitation in the name?

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Abstract

The overwhelming majority of people with chronic obstructive pulmonary disease (COPD) have at least one co-existing medical condition often conceptualized as ‘comorbidities’. These co-existing conditions vary in severity and impact; it is likely that for some patients, COPD is not their most important or severe condition. The concepts of multimorbidity and frailty may be useful to understand the broader needs of people with COPD undergoing pulmonary rehabilitation. Multimorbidity describes the co-existence of two or more chronic conditions, without reference to a primary condition. Best care for people with multimorbidity has been described as a shift from providing disease-focused to patient-centred care. Pulmonary rehabilitation is well placed to deliver such care as it focuses on optimizing function, encourages integration across care settings, values input from multidisciplinary teams and measures patient-important outcomes. When designing optimal pulmonary rehabilitation services for people with multimorbidity, the concept of frailty may be useful. Frailty focuses on impairments, rather than medical conditions including impairments in mobility, strength, balance, cognition, nutrition, endurance, mood and physical activity. Emerging data suggest that frailty may be modifiable with pulmonary rehabilitation. The challenge for pulmonary rehabilitation clinicians is to broaden our perspective on the role and outcomes of pulmonary rehabilitation for people with multimorbidity.

Introduction

It is uncommon to meet an individual with chronic obstructive pulmonary disease (COPD) who does not have at least one other chronic health condition. Amongst Medicare beneficiaries in the United States, 18% of individuals with COPD have one to two co-existing conditions, 30% have three to four co-existing conditions and 49% have five or more¹. Amongst those referred for pulmonary rehabilitation, the proportion of patients with at least one co-existing condition varies from 51% to 96%². Co-existing conditions have important implications for outcomes in COPD. People with co-existing diabetes, hypertension or cardiovascular disease have increased risk of hospitalization and all-cause mortality compared to those with COPD alone, with greater risks in those with more severe lung disease³. Similarly, depression and anxiety are associated with a greater risk of readmission to hospital and mortality following a COPD exacerbation^{4,5}.

In recent years several studies have addressed the impact of co-existing medical conditions on the outcomes of pulmonary rehabilitation for people with COPD, with some showing a positive impact and others a negative one. For example, for people with COPD and cardiometabolic disease, pulmonary rehabilitation outcomes have been reported as better by Walsh and colleagues⁶ but worse by other groups^{7,8}. Similarly, mood disturbance may either increase⁹ or decrease⁸ the likelihood of clinically significant gains with rehabilitation. There are also varying conclusions regarding the impact of obesity on pulmonary rehabilitation outcomes^{10,11}. This variability may arise in part from the complexity of participants in modern pulmonary rehabilitation programs, who have co-existing conditions of varying severity and impact. All these studies have assumed that as participants in pulmonary rehabilitation, COPD is the primary and most important of the co-existing conditions; it is possible that for some patients their other health conditions are more important or more severe. In some instances pulmonary rehabilitation

may not have met the broader needs of individual participants with significant co-existing health challenges.

Frailty is a concept that relates to comorbidity. Unlike comorbidity that focuses on medical conditions, frailty focuses on the impairments regardless of the conditions. Markers of frailty could include impairments in mobility, strength, balance, cognition, nutrition, endurance, mood and physical activity ¹²⁻¹⁴. Individuals with COPD and other chronic conditions often have impairments affecting numerous systems and are therefore more likely to meet the criteria for frailty.

Given that it is common for pulmonary rehabilitation candidates to have multiple chronic conditions, it is increasingly likely that many of their important clinical problems will not be directly related to respiratory disease. People with COPD have expressed their preference for individualized models of care that target the clinical problems they perceive to be most important ¹⁵. In this paper we will discuss how we could broaden our perspective on the role and outcomes of pulmonary rehabilitation, with particular reference to the concepts of multimorbidity and frailty.

Multimorbidity vs comorbidity - does the label matter?

Traditionally, co-existing conditions have been described using the term ‘comorbidity’, defined as the presence of one or more additional disorders co-occurring with a primary disorder, which in this case is COPD. However such a definition pre-supposes that one condition is ‘primary’ and remains so over time. More recently, the term multimorbidity has been used to describe co-existence of two or more chronic conditions in the same individual, without reference to a

primary condition ¹⁶. The concept of multimorbidity acknowledges that chronic conditions may overlap; may vary in severity; and may change in importance or burden over time. A conceptual framework comparing comorbidity and multimorbidity in a typical patient who might present to pulmonary rehabilitation is presented in Figure 1. For this individual at this particular time, COPD is not the dominant problem and there is interaction between co-existing chronic conditions; this is better reflected by a multimorbidity model. Multimorbidity is now the most common chronic condition experienced by adults, affecting almost three in four individuals aged 65 years and older ¹⁶. It is heavily influenced by health inequalities, occurring 10-15 years earlier in those who live in more deprived areas compared to those who live in the most affluent areas ¹⁷. Individuals with multimorbidity are at greater risk of adverse outcomes and treatment complications than their individual conditions would confer; are more likely to receive ineffective care; have higher health care costs; and have worse survival ^{18, 19}.

Delivery of health care to people with multimorbidity is challenging and not well supported by clinical practice guidelines. This was well illustrated in 2005 in a paper which detailed the application of the most recent clinical guidelines to a hypothetical 79-year-old woman with osteoporosis, osteoarthritis, type 2 diabetes mellitus, hypertension and COPD ²⁰. The five relevant disease-specific clinical practice guidelines recommended 12 separate medications, taken in 19 doses on five occasions throughout the day, as well as 14 non-pharmacological activities, some of which were contradictory (for example weightbearing exercise for osteoporosis vs non-weightbearing exercise for type 2 diabetes with peripheral neuropathy). Such a treatment regimen is unlikely to be safe, effective or efficient, and its burden is unlikely to promote adherence. Only two of the five clinical practice guidelines directly addressed multimorbidity. More recently, qualitative studies have described dispiriting experiences of care

for people with multimorbidity. Patients and carers report poor communication with and between health care providers; a lack of care coordination; long wait times for services; difficulty making decisions about health care; being unsure how to prioritise; and feeling alone (21). Family physicians described poor communication and lack of care coordination across services; concerns regarding the ability of patients to adhere to complex treatment regimens; difficulty quantifying the harms and benefits of guideline-directed care; concerns regarding adverse events when following multiple guidelines; unrealistic expectations of patients and families; and insufficient time or reimbursement to deal with the complexities of multimorbidity in everyday practice ^{21, 22}.

Whilst important efforts are underway to make evidence-based care more accessible to people with multimorbidity ²³, current guidelines do not meet the challenges of multimorbidity and as a result, pulmonary rehabilitation clinicians still face significant challenges. A review of seven recent guidelines relevant to rehabilitation for people with chronic disease ²⁴⁻³⁰ reveals that three guidelines do not mention co-existing conditions, whilst another three guidelines make only passing mention of minor program adaptations such as commencing exercise training at low workloads and progressing slowly, or being as physically active as possible. The most extensive discussion is in the American Thoracic Society / European Respiratory Society pulmonary rehabilitation statement ²⁴ which suggests additions to existing assessments to improve safety and efficacy (eg use of cardiopulmonary exercise test and electrocardiograms, assessment of anxiety and depression); use of specialized equipment, particularly for bariatric patients; and modifications to exercise prescription for those who cannot tolerate the usual training protocols, including consideration of interval training and inspiratory muscle training. Broadening of education for pulmonary rehabilitation providers is suggested, to ensure recognition of relevant

signs and symptoms across a broad range of chronic conditions. The authors conclude that further research is needed, to better understand pulmonary rehabilitation outcomes in this group. This recommendation reflects the paucity of clinical trial data in pulmonary rehabilitation for patients with multimorbidity. Analysis of studies included in a recent Cochrane review of pulmonary rehabilitation for COPD ³¹ reveals that out of 65 randomized controlled trials, 51% excluded people with cardiac disease and 48% excluded those with musculoskeletal disease (Figure 2), conditions that are present in 43% and 42% of people with COPD respectively ²³. It will remain difficult for clinical guideline developers and clinicians to adequately address multimorbidity whilst there is insufficient research to guide their decisions.

Why pulmonary rehabilitation is well placed to improve outcomes for people with multimorbidity

Providing best care for people with multimorbidity has been described as a shift from disease-focused interventions to patient-focused care:

‘To align with the clinical reality of multimorbidity, care should evolve from a disease orientation to a patient goal orientation, focused on maximizing the health goals of individual patients with unique sets of risks, conditions, and priorities’ ¹⁶(page 2494).

This involves identifying patient and family goals and preferences for care; identifying disease-related and other modifiable barriers to goal achievement, including social and environmental circumstances; understanding and communicating the likely effect of treatments on goal attainment; and facilitating shared decision making.

In practical terms, best care for people with multimorbidity has the following features:

- Focussed on optimizing function
- Measures patient-centred outcomes
- Avoids inappropriate, excessive and non-beneficial care
- Ensures integration and coordination across disease conditions
- Ensures integration between clinicians and settings of care
- Has coordinated input from multidisciplinary health care teams, assembled to meet each patient's needs ^{16, 18}.

These features will be familiar to health professionals in pulmonary rehabilitation. Pulmonary rehabilitation programs have always had a strong focus on improving function, and measurement of patient-important outcomes is considered essential to best practice care ^{24, 32}. Pulmonary rehabilitation programme coordinators frequently assume a role in care coordination, ensuring that members of the multidisciplinary team are appropriately involved to meet the needs of individual patients. Recently, pulmonary rehabilitation has been acknowledged as a core component of integrated care for people with COPD^{24, 33}. However to date, these activities have occurred within a respiratory disease framework. To ensure that we are well equipped to provide patient-centred care to the growing number of individuals with multimorbidity, broader thinking may be required.

A key shift in thinking might be around how we describe, assess and measure outcomes for patients undergoing pulmonary rehabilitation. For patients with COPD, severity of disease is frequently described in terms of forced expiratory volume in one second (FEV₁) or GOLD stage; assessments and outcome tools are frequently disease specific (eg Chronic Respiratory Disease questionnaire, St George's Respiratory Questionnaire) or may not adequately describe the range

of functional impairments experienced by people with multimorbidity (eg 6-minute walk test or incremental shuttle walk test). New measurement tools that accurately describe the range of impacts on physical, psychological and social function in people with multimorbidity are needed, to guide patient-centred care. An ideal measurement tool for patients with multimorbidity would be applicable regardless of underlying diagnoses; sensitive to changes with pulmonary rehabilitation; relevant across other settings of care; capture patient-important outcomes; and facilitate shared decision making about best care for the individual ¹⁸. The concept of frailty and its associated measurement tools has the potential to provide such a comprehensive assessment for patients with multimorbidity in pulmonary rehabilitation.

What is frailty?

A consensus on the definition of frailty does not currently exist. In the geriatric literature, physical frailty is based on a definition provided by “the interventions on frailty working group” including mobility, strength, balance, motor processing, cognition, nutrition, endurance and physical activity ¹². Until recently, frailty had not been considered in individuals with COPD, now two main models appear to exist. Fried’s five markers of frailty focus on the physiological components of frailty including; gait speed, weight loss, exhaustion, grip strength and physical activity ¹³. Gobbens et al’s definition of frailty is dynamic and multi-dimensional, describing frailty as a decline in one or more domains of human function. Specifically, Gobbens et al noted that frailty also includes psychological and social elements in addition to physical factors ¹⁴. Frailty is not dependent on the underlying diagnosis; is common in people with respiratory disorders, especially those with co-existing medical conditions; and describes key elements of function, many of which are addressed by pulmonary rehabilitation. As a result, measures of

frailty may be useful to describe, assess and measure outcomes in pulmonary rehabilitation programs for individuals with comorbidities.,

Frailty in COPD

On average, 11% of community-dwelling older persons are classified as frail ³⁴. Although frailty is associated with aging, individuals with COPD have a twofold increase in prevalence of frailty compared to their 'healthy' elderly counterparts ³⁵. In individuals with COPD living in the community, the prevalence of frailty has been reported to be 58% ³⁶. As those enrolled in PR often present with co-existing chronic conditions, the prevalence of frailty may even be higher. In a recent study, over 60% of patients attending a PR program were reported to exhibit some level of frailty ³⁷. Indeed, a key component of frailty is suggested to be a reduction in exercise capacity and those referred to PR nearly always complain of reduced exercise tolerance.

There are likely a number of factors contributing to the increased prevalence of frailty in individuals with COPD. The high prevalence of multimorbidity is a key factor - co-existing conditions including diabetes, peripheral vascular disease, heart failure and osteoarthritis are also associated with an increased prevalence of frailty ^{14, 38-41}. Loss of muscle mass is an important contributor to frailty ¹³ and peripheral muscle weakness is common in those with COPD as a likely consequence of systemic inflammation or the use of corticosteroids ^{13, 42, 43}. The debilitating nature of COPD also affects an individuals' ability to remain physically active ⁴⁴ and reductions in physical activity levels have been associated with an increase in frailty prevalence ⁴⁵. Both peripheral muscle strength and physical activity are further impacted following an acute exacerbation ⁴⁶⁻⁴⁸. Acute exacerbations, defined as an increase in symptoms, become increasingly

common as the disease progresses and as such, they are likely to contribute to the process of frailty. Self-reported shortness of breath has been shown to be the greatest predictor of frailty³⁶ and frailty is associated with a reduction in peak oxygen consumption⁴⁹.

Consequences of frailty

Individuals who are recognized as frail have a marked reduction in activities of daily living, increased healthcare utilization³⁶ and are at a greater risk of mortality⁵⁰. In fact, frailty increases the risk of long-term (12 years) mortality by 80% in individuals with COPD compared to 34% in those without COPD⁵⁰. In addition, findings from a recent qualitative study describe the frustration and fear felt by older, frail people at the prospect of losing their independence, highlighting the impact of frailty on psychological wellbeing⁵¹.

Assessment of frailty

Multi-component assessment:

It is now readily acknowledged that the assessment of frailty needs to include multiple components. Three multi-component assessments have been applied in COPD including Frieds' definition of frailty^{37,52}, the Frailty Staging System⁵⁰ and the Tilburg Frailty Indicator⁵³.

Frieds' five markers of frailty: Frieds' model focuses on the physical aspect of frailty. The model includes five criteria displayed in Table 1. Individuals who meet two of these five criteria are defined as pre-frail and those who meet three are classified as frail. According to Fried and colleagues, those classified as pre-frail are at an elevated risk for falls, disability, death and hospitalization but three items had greater predictive power for these adverse outcomes¹³.

The Frailty Staging System: An alternative measure of frailty is the Frailty Staging System (FSS)⁵⁴ consisting of domains of function: visual function, hearing function, arm and leg function, urinary continence, nutritional status, mental state, depression, activities of daily living (ADL), home environment and social support. Individuals are classified as frail or not frail in each domain, a score of one is given when the function is lost. This tool was designed to be a pragmatic assessment of frailty that could be easily applied within the clinical setting and it was designed to be flexible in-terms of the targets to be assessed and the manner in which assessment is conducted. Galizia et al⁵⁰ applied seven domains of the FSS in individuals with COPD which are displayed in Table 2). These authors further classified the severity of frailty into mild, moderate and severe. Those who were classified as frail in one domain were considered to be mild, those who were classified as frail in 2 or 3 domains were classified as moderate and people who had a loss of function in 4 or more domains were considered severe. The risk or mortality was highest in those who were classified as severely frail⁵⁰.

The Tilburg Frailty Indicator: The Tilburg Frailty Indicator developed by Gobbens et al (2010) includes physical, psychological and social domains^{14,53}. Physical frailty is assessed via eight questions, four questions ask about psychological wellbeing and three questions are assigned to the social domain. Individuals can answer yes, sometimes or no and the maximum score able to be obtained is 15. A score of five or greater is indicative of frailty.

Park et al³⁶ used this framework to assess frailty in individuals with self-reported COPD. Data was taken from the NHANES survey and as not all the criteria included in the Tilburg Frailty Indicator were available (e.g. balance, endurance, mood, coping), frailty was assessed using nine

criteria across the three domains (Table 3). Frailty assessed using these nine criteria provided a total frailty score, which was found to demonstrate internal consistency (.66). A cut off point of 2 was used to define frailty. Those individuals with COPD identified as being frail had greater disabilities³⁶.

Single –item assessment of frailty

The application of a multi-component model of frailty can be considered cumbersome, especially in a busy clinical setting and there has been an increasing focus on identifying single-item assessments that may be used as surrogate markers of frailty. To date, the most frequent factors used in the assessment of frailty in older adults include; gait speed, physical function and cognition⁵⁵. In individuals with COPD the value of gait speed and physical activity as indicators of frailty have been considered.

Gait Speed: Gait speed, defined as the time it takes to walk a short distance, takes very little time and space to assess. It is a component of Fried's five factors of frailty and has been associated with a number of important health outcomes in elderly individuals including; hospitalizations⁵⁶, falls⁵⁷, falls⁵⁸ and mortality⁵⁹.

Usual gait speed over four metres (4MGS) provides a global assessment of functional capacity in community dwelling adults. The test involves walking a 4-metre course at 'usual' walking speed, from a standing start. The test is performed twice without resting between repetitions and the faster time is used to calculate the 4MGS in metres/second⁶⁰. A gait speed less than 0.8metres/second is considered 'slow' and has been associated with adverse health outcomes⁵⁹. The 4MGS has good convergent validity with the 6MWT ($r=0.77-0.82$)⁶¹. Importantly, 4MGS

has been shown to be an indicator of future readmissions in individuals with COPD following an acute exacerbation⁶². The 4MGS is responsive to improvements with pulmonary rehabilitation, with the largest effects seen in patients with the slowest gait speed (effect size 1.0) and evidence of a ceiling effect in those with well preserved gait speed (effect size 0.2)⁶³.

To date, the only measure of gait speed to be directly compared with a multi-component assessment of frailty in individuals with COPD is 100-foot walk time. One hundred-foot walk time has been applied in a population undergoing pulmonary rehabilitation and was found to be a good indicator of physical frailty assessed using Fried's five factors⁵². The test was shown to be responsive to pulmonary rehabilitation at six weeks with a mean increase of 8.4m per minute observed, although no additional improvement was detected at week 12⁵².

Physical activity: A low level of physical activity, assessed using the Minnesota leisure time activity questionnaire, is one of Fried's five markers for frailty. Recently Valenza et al have modified the Fried criterion and re-classified low physical activity in individuals with COPD as <150min/week⁴⁵. Physical activity levels less than this threshold were identified using the Baecke physical activity questionnaire, which includes items about household activities, sport, and leisure time activities with values less than nine considered to be sedentary. A total physical activity score of 3.54 and 3.88 respectively for individuals following an acute exacerbation and for those with stable COPD was reported to be predictive of frailty⁴⁵.

Recently, objectively measured physical activity has been included as part of a multi-component assessment of frailty, however a deficit in this domain alone was not indicative of clinical frailty

³⁶. A multi-component assessment of frailty, including low levels of physical activity defined as less than 85.35 counts per min assessed using the Actigraph (ActiGraph Model 7164 accelerometer, LLC; Ft. Walton Beach, FL), has had some success in predicting greater healthcare utilization ³⁶.

How does frailty impact on pulmonary rehabilitation?

Pulmonary rehabilitation targets many of the components of frailty, including slowness, weakness, fatigue and physical inactivity. To date there has been little exploration of the utility of frailty measures in pulmonary rehabilitation, or whether rehabilitation can alter frailty. One study from the United Kingdom examined 816 individuals with COPD who were assessed for outpatient pulmonary rehabilitation and found that 26% met Fried's criteria for frailty ⁶⁴. Those with frailty had twice the odds of program non-completion compared to their non-frail counterparts (adjusted odds ratio 2.2, 95% confidence interval 1.39 to 3.46). However individuals with frailty who completed pulmonary rehabilitation (defined as undertaking 50% of planned sessions) had better outcomes than non-frail individuals for exercise performance, subjectively measured physical activity, symptoms and health status. More than 60% of program completers who were assessed as frail at baseline were no longer frail at the end of pulmonary rehabilitation. A reduction in frailty following rehabilitation was also seen in a smaller study (n=41), however results were less consistent, perhaps because of the smaller sample size ⁵².

It is not yet known whether reductions in frailty following pulmonary rehabilitation can be sustained over time, or whether these reductions impact on health outcomes such as hospital admission and mortality. It is notable that only 55% of frail individuals were able to complete an outpatient program; this signals a clear need for new ways to support individuals with complex

needs to attain the benefits of pulmonary rehabilitation.

How can pulmonary rehabilitation meet the needs of individuals with multimorbidity in the future?

A patient-focused approach to multimorbidity in pulmonary rehabilitation might have the following features:

Broad inclusion criteria: admission to a pulmonary rehabilitation program should be based on symptoms, function limitation and consideration of frailty. Diagnosis provides useful information, but should be a secondary criterion when considering eligibility. Co-existing health conditions should not exclude individuals from pulmonary rehabilitation, except where there are concerns regarding the safety of exercise. Referrals and history taking in pulmonary rehabilitation should acknowledge the impact of multimorbidity on patient symptoms, function and presence of frailty.

Goal focused: Patient and family goals and preferences for care must be central to program design and outcome assessment. Effective goal setting is critical to rehabilitation practice and is not a new concept in pulmonary rehabilitation ⁶⁵, but is even more critical if there is to be an explicit focus on patient-centred care.

Modular approach to rehabilitation content: pulmonary rehabilitation includes exercise training education and behavior change ²⁴; beyond this the ideal program content is not known. In the context of multimorbidity, the content of a patient-centred pulmonary rehabilitation program will vary. Pulmonary rehabilitation practitioners need to feel comfortable providing rehabilitation for impairments in other systems beyond respiratory, targeting the components of frailty. This is likely to require a sound understanding of rehabilitation for heart failure, cancer and

musculoskeletal disorders, as well as appropriate structures to provide psychological and social support. Membership of the multi-disciplinary team should be determined by the needs of the individual patient, rather than ideology or tradition. For instance, the diabetes educator or pain specialist may be a key team member in some cases. Financial and other incentives should be considered to ensure that delivery of pulmonary rehabilitation directly addresses patient goals and measures whether these goals are achieved.

Broader training for pulmonary rehabilitation practitioners: As suggested in the ATS/ERS pulmonary rehabilitation statement ²⁴, broader training will be required for health professionals delivering pulmonary rehabilitation. This will ensure that important symptoms of co-existing conditions are recognized and can be adequately addressed. Pulmonary rehabilitation practitioners need an in-depth understanding of the role and nature of rehabilitation across a range of chronic diseases, as well as sophisticated skills in adapting the exercise component to address individual patient needs and goals. Training in goal setting will be essential for all new pulmonary rehabilitation practitioners.

Outcome assessment aligned with individual goals and preferences: Whilst respiratory-specific outcomes are excellent for capturing respiratory symptoms such as dyspnea and cough, other important domains such as fatigue may not be adequately covered. Concepts such as frailty may be useful to understand and measure the impacts of multiple health conditions upon individuals, regardless of underlying diagnoses. The Multiple Chronic Conditions Measurement Framework ¹⁸ proposes an individualized measurement framework for people with multimorbidity. As well as measures of health and wellbeing, other important process measures for the care of people with multimorbidity can be included such as the degree of care coordination, the extent of shared-decision making and the cost of care.

Ensure pulmonary rehabilitation research reflects patient populations: Whilst research that includes patients with more diverse characteristics is bigger, messier and more complex, it better reflects the patients who are admitted to pulmonary rehabilitation programs. Both researchers and funders should explicitly consider multimorbidity when new trials are proposed. Patients who are frail (eg with slow gait speeds) should not be excluded from pulmonary rehabilitation trials.

Clinical practice guidelines: Recently, important efforts have been made to highlight important considerations for pulmonary rehabilitation in people with multimorbidity ²⁴, however further advances are needed in this area. Future clinical guidelines should consider multimorbidity early in the document development process, directly address it where possible including statements regarding confidence in treatment effects for common co-existing conditions, acknowledge cost-benefit trade-offs that may influence treatment decisions, and outline gaps where future research is needed.

Pulmonary rehabilitation - so what's in a name?

There is ample evidence that pulmonary rehabilitation is a highly successful intervention, delivering meaningful improvements for patients with respiratory disease, their communities and the health system. We should not give it up in favour of an untested, generic model of rehabilitation. The challenge is not in the name of pulmonary rehabilitation; the challenge is for our model to evolve, building on existing successes to more comprehensively address the needs of people with multimorbidity. This presents an exciting opportunity to place pulmonary rehabilitation at the forefront of person-centred care.

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Table 1: Fried's five markers of frailty

Item	Type of measure	Criteria
Weight Loss	Direct measurement of weight	Unintentional loss of ≥ 10 pounds in the previous year.
Weakness	Handheld dynamometer	Maximum grip strength (kilograms) of the dominant hand adjusted for gender and body mass index (BMI). (For example, a male with a BMI of 26.1-26 would require grip strength at least 30kg to be defined as not frail).
Exhaustion	Two questions taken from the Center for Epidemiological Studies – Depression scale (CES-D) ('I felt that everything I did was an effort' and 'I could not get going').	A score of 2 or 3 (felt this way for a moderate amount of the time in the last week (3-4 days) or most of the time).
Physical activity	Minnesota leisure time activity questionnaire	Kcals per week expended are calculated using standardized algorithm and stratified by gender. Men with Kcals of physical activity per week less than 383 are frail and women with Kcals per week less than 270 are frail.

Slowness (or gait speed)	15 foot walk test	Time taken to walk 15 feet adjusting for gender and standing height. (For example, a female with height greater than 159cm would be required to walk 15 feet in 6 seconds or less to be identified as not frail).
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Table 2: The Frailty Staging System as applied by Galizia et al., 2011

Item	Type of measure	Criteria
Visual function	Self-report	Could not recognize a friend across the street.
Hearing function	Self-report	Need people to raise their voices to hear and understand them.
Mobility	Self-report	Having great difficulty or being unable to walk around the house, walk outside, climb stairs or walk half a mile.
Urinary function	Self-report	Total incontinence
Cognitive function	Mini Mental State Examination (MMSE)	A score less than 24
Disability	Basic Activities of Daily Living (BADL)	Need assistance with at least one BADL
Social support	Social support scale used in an elderly population (Mazella et al 2010).	A score of 13-17

Table 3: The Tilburg Frailty Indicator as applied by Park et al., 2013.

Item		Type of measure	Criteria
Physical frailty	Nutrition	A direct measure of weight	Unintentional weight loss of more than 10 pounds over the previous year.
	Mobility	Self-report	Difficulty walking without any special equipment or having at least moderate difficulty walking up 10 steps.
	Physical activity	Actigraph (ActiGraph Model 7164 accelerometer, LLC; Ft. Walton Beach, FL)	Less than 85.35 counts per minute.
	Strength	Self-report	Some difficulty carrying or lifting something weighing 10 pounds.
	Vision	Self-report	Poor vision, even when wearing corrective eyewear.
	Hearing	Self-report	Moderate trouble hearing without a hearing aid.
Psychological frailty	Cognition	Self-report	Difficulties in remembering or experiencing periods of confusion
Social frailty	Social	Self-report	Not having anyone to provide emotional

	support		support.
	Social relations	Self-report	Having no close friends.

Figure 1. Concepts of comorbidity and multimorbidity.

Comorbidity refers to co-existing chronic conditions, whereas multimorbidity acknowledges that there may not be a ‘dominant’ problem, that conditions interact and vary in severity, importance and burden.

COPD – chronic obstructive pulmonary disease; HT – hypertension; OA – osteoarthritis; OP – osteoporosis; T2DM – type 2 diabetes mellitus.

Figure 2. Top five exclusion criteria in randomised controlled trials of pulmonary rehabilitation.

Data from McCarthy et al (2015).