

Perspective

A Conceptual Framework for Use of Increased Endurance Time During Constant Work Rate Cycle Ergometry as a Patient-Focused Meaningful Outcome in COPD Clinical Trials

Richard Casaburi, MD, PhD¹ Debora D. Merrill, MBA² Gale Harding, MA³ Nancy Kline Leidy, PhD³
Harry B. Rossiter, PhD¹ Ruth Tal-Singer, PhD² Alan Hamilton, PhD⁴ on behalf of the CBQC Constant Work Rate Exercise Working Group

Abstract

The Chronic Lung Disease Biomarker and Clinical Outcome Assessment Qualification Consortium (CBQC) evaluates the potential of biomarkers and outcome measures as drug development tools. Exercise endurance is an objective indicator of treatment benefit, closely related to daily physical function. Therefore, it is an ideal candidate for an outcome for drug development trials. Unfortunately, no exercise endurance measure is qualified by regulatory authorities for use in trials of chronic obstructive pulmonary disease (COPD) and no approved COPD therapies have claims of improving exercise endurance. Consequently, it has been challenging for developers to consider this outcome when designing clinical trials for new therapies.

Endurance time during constant work rate cycle ergometry (CWRCE), performed on an electronically braked stationary cycle ergometer, provides an exercise endurance measure under standardized conditions. Baseline individualized work rate for each participant is set using an incremental test. During CWRCE the patient is encouraged to continue exercising for as long as possible. Although not required, physiological and sensory responses (e.g., pulmonary ventilation, heart rate, dyspnea ratings) are frequently collected to support interpretation of endurance time changes. Exercise tolerance limit is reached when the individual is limited by symptoms, unable to maintain pedaling cadence or unable to continue safely. At exercise cessation, exercise duration is recorded.

An CWRCE endurance time increase from the pre-treatment baseline is proposed as a key efficacy endpoint in clinical trials. In COPD, improved exercise endurance has a direct relationship to the experience of physical functioning in daily life, which is a patient-centered, meaningful benefit.

Abbreviations: Chronic Lung Disease Biomarker and Clinical Outcome Assessment Qualification Consortium, **CBQC**; chronic obstructive pulmonary disease, **COPD**; constant work cycle ergometry, **CWRCE**; U.S. Food and Drug Administration, **FDA**; drug development tool, **DDT**; clinical outcome assessment, **COA**; St George's Respiratory Questionnaire, **SGRQ**; concept of interest, **COI**; American Thoracic Society, **ATS**; European Respiratory Society, **ERS**; forced expiratory volume in 1 second, **FEV₁**; 6-minute walking test, **6MWT**; incremental shuttle walk test, **ISWT**; endurance shuttle walk test, **ESWT**; peak oxygen uptake, **VO₂ peak**; pulmonary carbon dioxide output, **VCO₂**; pulmonary ventilation, **V_E**

Funding Support: Funding for the CBQC Constant Work Rate Exercise project was provided by Boehringer Ingelheim, GlaxoSmithKline, Novartis, AstraZeneca, and Chiesi.

Date of Acceptance: January 5, 2022 | **Published Online Date:** January 10, 2022

Citation: Casaburi R, Merrill DD, Harding G, et al. A conceptual framework for use of increased endurance time during constant work rate cycle ergometry as a patient-focused meaningful outcome in COPD clinical trials. *Chronic Obstr Pulm Dis*. 2022;9(2):252-265. doi: <https://doi.org/10.15326/jcopdf.2021.0258>

1. Rehabilitation Clinical Trials Center, Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, California, United States
2. COPD Foundation, Washington, DC, United States
3. Evidera, Bethesda, Maryland, United States
4. Medical Department, Boehringer Ingelheim, Burlington, Ontario, Canada

Address correspondence to:

Richard Casaburi, PhD, MD
 Rehabilitation Clinical Trials Center
 The Lundquist Institute at Harbor
 UCLA Medical Center, CDCRC Building
 Torrance, CA 90502
 Email: casaburi@ucla.edu
 Phone: (424) 201-3000 x7269

Keywords:

COPD; exercise endurance; physical functioning; clinical outcome assessment; drug development

Introduction

In 2006, the U. S. Food and Drug Administration (FDA) issued the “Critical Path Opportunities Report,”¹ which described 6 key areas along the path to improved therapies. The report noted that attention to a needed drug development tool (DDT) often only occurs when the clinical study protocols to facilitate the registration of a drug are being developed, at which time it is recognized that the available DDTs are inadequate. The report further noted that the efficiency of drug development could be improved by developing a new product development toolkit containing innovative scientific and technical methods. New and improved DDTs are among the methods that can help streamline the drug development process, improve the chances for clinical trial success, and yield more information about the treatment and/or disease.

In 2010, the FDA issued a draft guidance intended to represent the agency’s thinking on the qualification process for DDTs; the final guidance² was formally adopted in January 2014 and was recently updated³ in November 2020. According to the final DDT guidance, as well as other relevant sources,⁴⁻⁷ establishing a well-understood relationship of a clinical outcome assessment (COA) to a meaningful aspect of how a patient feels or functions in his or her usual life is central to the conclusion that the observed effect is actually a treatment benefit, i.e., an aspect of health that the patient cares about and has a preference that this aspect either

does not become worse, improves, or is prevented. As an illustrative example of this important initial phase of the COA development process, we describe here the necessary first steps in establishing endurance time during constant work rate cycle ergometry (CWRCE) as a COA for use in interventional studies by describing its link to physical function. We discuss:

1. How the disease process that characterizes COPD has meaningful effects on patient symptoms and physical functioning during everyday life.
2. How limitations in physical functioning are directly linked to exercise endurance among people with COPD.
3. How endurance time during CWRCE can be objectively measured, yielding consistent interpretable results.

Combining these elements, we conclude that endurance time during CWRCE is an appropriate candidate COA for the measurement of exercise endurance in interventional studies. In future publications, we will describe the validation requirements to support the COA as a qualified DDT.

Background: The COPD Biomarker Qualification Consortium Initiative

Stimulated by the publication of the FDA’s DDT guidance, the COPD Biomarker Qualification Consortium (CBQC) was formed under the management of the COPD Foundation to focus efforts on the qualification of DDTs in COPD, following processes consistent with the newly released draft DDT guidance. The organizational structure of the CBQC was set-up to foster contributions of clinical and scientific expertise from both academia and the pharmaceutical industry.^{8,9} To date, the work of the CBQC has resulted in qualification of plasma fibrinogen as a stratification tool¹⁰ and qualification of the St George’s Respiratory Questionnaire (SGRQ) as a COA in interventional studies.⁸ Based on the recognition that many COAs are relevant across chronic lung diseases such as bronchiectasis, pulmonary fibrosis, alpha-1 antitrypsin deficiency, and asthma, the CBQC was refocused as the Chronic Lung Disease Biomarker and Clinical Outcome Assessment Qualification Consortium (CBQC) in 2020.

A working group within the CBQC was formed in 2013 to evaluate opportunities for qualification of a COA based on exercise endurance. Within the working group (see list in Acknowledgements), a broad request for input from both academia and the pharmaceutical

industry has resulted in a significant contribution from clinical/scientific experts in clinical exercise testing; National Heart, Lung, and Blood Institute staff members have served in an advisory capacity, while independent contractors have assisted with data collection and analysis. Feedback from the FDA has helped to shape the project's progress.

Physical Functioning in Daily Life: A Meaningful Aspect of Health Impacted by COPD

Qualitative research among people with COPD consistently shows that limitations in the ability to perform activities of daily life are a significant burden to patients. Table 1 provides a summary of relevant qualitative research conducted among people with COPD, highlighting the specific ways in which people with COPD adapt their physical functioning.¹¹⁻¹⁴

The qualitative research described in this table offers important insight into the experience of living with COPD. There is a consistent theme; people with COPD describe the impact of the disease in terms of the adverse effects and necessary adaptations they must make in physical functioning:

- Sustained symptom burden (breathlessness, fatigue) resulting in loss of physical functioning; breathlessness impacts every aspect of life, including everyday activities.
- On good days there is an increase in physical activity and on bad days a reduction in physical activity.
- When expecting a high level of discomfort from an activity, people impacted by COPD consider alternative methods of performance, reducing standards of performance, or relinquishing the activity altogether.
- People with COPD frequently describe the course of their COPD in terms of symptom-induced changes in activity that are discouraging and frustrating and express a desire to return to previous levels of performance.

Of particular relevance, people with COPD express the need to modify activity patterns with progressing disease:

- Utilize pacing (self-regulated performance to

minimize symptoms), planning (devising strategies to accomplish the activity within known constraints on capacity), assistive devices, and personal assistance to accomplish activities they want to perform.

- Report unpredictable symptoms that gradually worsen over time, and this results in pacing or slowing down, interrupting activities to recover, or allowing for a longer recuperation period.

Exercise Endurance: A Specific, Relevant Concept of Interest Related to Physical Functioning

An explanatory conceptual model of the progressive limitations in physical functioning over time in COPD patients (the “downward spiral of disability”)¹⁵⁻¹⁸ postulates that:

1. In the face of expiratory flow limitation, the respiratory response required to support the increased metabolic demands of a given intensity of muscular work results in disproportionate breathlessness.
2. In an effort to avoid breathlessness, patients reduce the intensity and/or amount of activity performed during daily life.
3. The reduced activity leads to muscular de-conditioning, especially of the leg muscles.
4. Other extra-pulmonary intrinsic factors related to COPD (e.g., systemic inflammation) also contribute to muscle dysfunction.
5. The consequences of muscle dysfunction (e.g., early onset of lactic acidosis during exercise) further stimulate breathing, increase breathing work, and increase breathlessness, amplifying the downward spiral of disability.

In people with COPD, adaptations to their activity patterns such as pacing, slowing down, interrupting activities to recover, and allowing for a longer recuperation, reflect a reduced exercise endurance. Exercise endurance may be defined as the ability to sustain intense aerobic exercise or activity (intense relative to the individual's peak capabilities). Thus, as a concept of interest (COI) of meaningful treatment benefit, exercise endurance has a direct relationship to the experience of physical functioning in daily life. Figure 1 presents

Table 1. Qualitative Research Highlighting the Specific Ways in Which People With COPD Adapt Their Physical Functioning

Author	Research Question / Methodology	Results
Jones et al ¹¹	<p>Objective: To evaluate COPD health status and explore how people with COPD experience their condition and the language they use to describe it.</p> <p>Methodology: Rigorous qualitative research methods, including one-to-one interviews and focus groups, which allowed identification of key concepts that were meaningful and important to people with COPD.</p> <p>Focus: Individuals were asked to describe the symptoms they experience on a typical or usual day, a better-than-usual day (i.e., “good” day), and a day worse than usual but not bad enough to seek medical assistance (i.e., “bad” day). For each type of day (“usual/typical,” “good,” or “bad”), they also described the frequency and severity of symptoms and the impact these symptoms had on their daily lives.</p>	<p>Irrespective of COPD severity, individuals consistently reported symptoms of shortness of breath, chest tightness, and cough with or without sputum, as well as wheezing, fatigue, weakness, anxiety, sleep disruption, and limitations in daily activities.</p> <p>Breathing and its impact on their daily lives and emotional well-being were of particular concern to individuals.</p> <p>“Good” days were characterized by reduced symptoms, most frequently improved breathing and coughing, as well as less wheezing, chest tightness and tiredness, better sleep, use of fewer rescue medications, increased physical activity, and improved emotional well-being.</p> <p>“Bad” days were characterized by increased shortness of breath, worsening of cough and wheezing, loss of energy, and problems with sleep, as well as increased rescue medication use and feelings of fear, frustration, anxiety, and depression. As a result of these symptoms, individuals were less active and rested or stayed in bed instead of seeking help.</p>
Disler et al ¹²	<p>Objective: To better understand the experience and ongoing needs of people with COPD.</p> <p>Methodology: Thematic synthesis and expert panel discussion of extractions from 22 individual qualitative studies.</p>	<p>Seven descriptive themes emerged: better understanding of condition, breathlessness, fatigue, frailty, anxiety, social isolation, and loss of hope and maintaining meaning. These were condensed into 3 analytical themes: need for better understanding of condition; sustained symptom burden; unrelenting psychological impact of living with COPD.</p> <p>Sustained symptom burden, breathlessness, fatigue, and the resulting loss of physical functioning were consistently identified in studies.</p> <ul style="list-style-type: none"> • As the most common and debilitating symptom, breathlessness impacted every aspect of the life of people with COPD, including everyday activities such as walking within their home or to a destination. • Fatigue, which individuals described as unrelenting tiredness and exhaustion, was found to change the behavior of people with COPD and prevented access to the outside world, thereby disrupting daily life. <p>The loss of physical capability impacted daily tasks such as taking a shower, cleaning the house, washing dishes, and participating in social activities.</p> <p>As a result of dependence on others for such tasks and self-care, individuals expressed embarrassment, frustration, and reduced feelings of self-worth.</p> <p>Overall, people with COPD have a high symptom burden that restricts daily activities despite treatment of breathlessness and fatigue.</p>
Leidy et al ¹³	<p>Objective: To better understand the functional performance of people with COPD by developing contextual descriptions of the major areas of functional activities and to describe the factors individuals perceive as</p>	<p>Activities described by individuals were categorized as household maintenance, movement, family activities, social activities, work, altruistic avocation, and recreation.</p> <p>Movement consisted of deliberative motion for purposeful activities (e.g., carrying objects, walking, stair climbing), therapeutic movement (e.g., less demanding or intense movement such as stretching, leg or arm lifts, twisting and bending associated with work), and exercise</p>

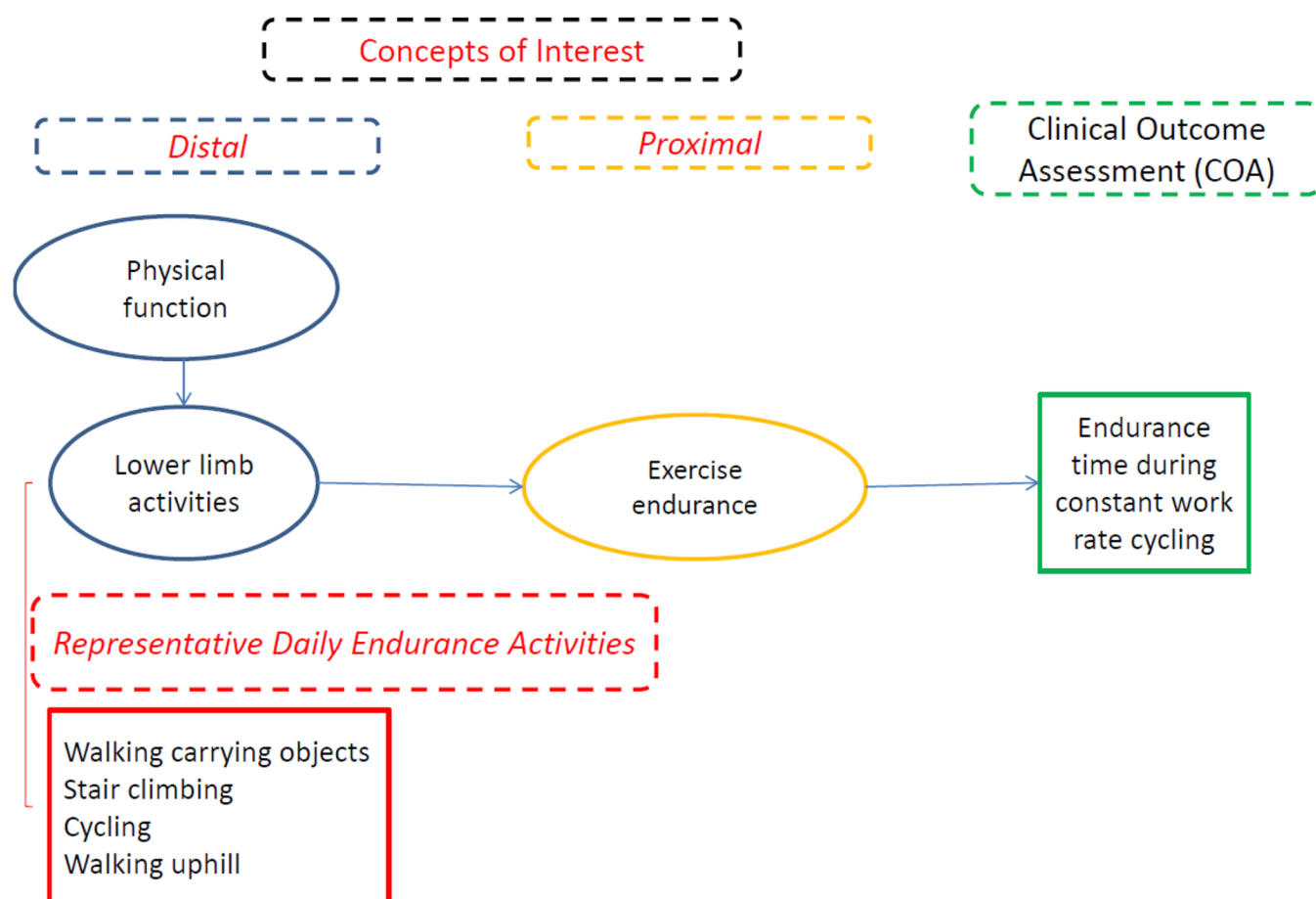
continued on next page

	<p>contributing to or impeding performance.</p> <p>Methodology: Functional performance was defined as the physical, psychological, social, occupational, and spiritual activities that people choose in the normal course of their lives. One-on-one interviews were conducted, with participants asked to describe a typical day. Thematic analyses uncovered present and past activities performed, satisfaction and meaning they derived through these activities, factors impeding their performance, how people managed to continue the most important activities, and when, why, and how certain activities were relinquished.</p>	<p>(e.g., walking at a mall).</p> <p>An individual's decision to perform an activity was based on its anticipated satisfaction in light of possible symptomatic or psychological discomfort.</p> <ul style="list-style-type: none"> • When expecting a high level of discomfort from an activity, individuals considered alternative methods of performance, reducing standards of performance, or relinquishing the activity altogether. • Discomfort typically consisted of symptoms, mainly fatigue, generalized breathing difficulty, and activity-related shortness of breath. <p>Individuals frequently described the course of their COPD in terms of symptom-induced changes in activity that were discouraging and frustrating and expressed a desire to return to previous levels of physical performance.</p>
Dobbels et al ¹⁴	<p>Objective: To design a conceptual framework for patient-reported outcome instruments capable of assessing the experience of physical activity in people with COPD.</p> <p>Methodology: One-on-one interviews, focus groups, and debriefings</p> <p>Focus: People with COPD were asked to describe their experience with activity using core questions such as "what does physical activity mean to you?" and "do you experience limitations in your activities? If so, what are these?"</p>	<p>Three core themes emerged related to the individual's experience of physical activity:</p> <ul style="list-style-type: none"> • Amount of physical activity (what activities they do) • Symptoms during physical activity (how do they feel when doing these activities), • Need for physical adaptations (how they perform these activities). <p>Reduction in activities, activity-related symptoms, and physical adaptation mechanisms were interrelated.</p> <p>Individuals reported that climbing the stairs and walking (first uphill and then also on the flat) were the first activities affected by COPD, followed by almost all physical activities of daily life as disease progressed (such as carrying objects, household activities and, ultimately, self-care activities such as dressing or bathing).</p> <p>Symptoms during physical activity included breathlessness, physical exhaustion, fatigue, or lack of strength as well as leg problems (including leg fatigue) in some people.</p> <p>Individuals reported having both good days and bad days, with unpredictable symptoms that gradually worsened over time and resulted in individuals pacing themselves or slowing/ interrupting their activities to recover or requiring a long recuperation period.</p> <p>While using aids (e.g., a rollator or electric scooter) to facilitate physical activities, individuals discontinued some activities that they could no longer perform.</p> <p>Problems with physical activity were influenced by external factors (e.g., humid air, extreme temperatures), comorbid conditions (e.g., back pain), and COPD exacerbations.</p> <p>Activity-related problems resulted in some individuals reporting feeling sad, frustrated, dependent, or isolated by their inability to do activities as they had done previously.</p> <p>Physical activity is both universally relevant for the majority of people with COPD and described with a common language.</p>

a conceptual framework of this relationship. In the figure, the concept of physical function refers to relevant physical tasks in everyday life that are impacted among people with COPD. Physical function is identified as a distal concept in that many contextual factors, including environmental (e.g., air quality, products or substances for personal consumption, most especially cigarette

smoking) and demographic (e.g., age, psychosocial status, ethnicity) factors, influence physical function in addition to the effects of the impairment in bodily function caused by the disease and its associated comorbidities (including skeletal muscle dysfunction, cardiovascular abnormalities, and orthopedic limitations). Within the domain of physical function, the separation into upper

Figure 1. Relationship Between Physical Function, Exercise Endurance, and Endurance Time During Constant Work Rate Cycle Ergometry



This figure shows the conceptual relationship between the distal concept of physical function (for lower limb activities), the proximal concept of exercise endurance, and the clinical outcome assessment of endurance time during constant work rate cycle ergometry.

limb and lower limb activities has value in general.¹⁹ This separation has particular relevance when considering physical function among people with COPD due to the significantly larger muscle mass involved in lower limb activities compared with upper limb activities, and the consequently greater ventilatory response required to support lower limb activities. COPD imposes difficulty performing upper extremity activities (especially those requiring lifting arms above the head), in part related to recruitment and use of accessory muscles of respiration. However, the central role of the muscles of ambulation in supporting activities most important to people with COPD (see Table 1) justifies a primary focus on the lower limbs.

Therefore, our work in the CBQC has focused on lower limb activities since limitations in these types of activities are ubiquitous among people with COPD. In

developing our conceptual framework, the next step was to identify a proximal concept of treatment benefit that was more directly associated with the disease-defining concepts of impaired pulmonary function and muscle dysfunction. An important concept relates to the reduced physiological capacity (pulmonary dysfunction, muscle dysfunction) and its impact on the ability to sustain aerobic muscular work (i.e., muscular work requiring a significant cardiorespiratory response to support bioenergetic requirements), which defines exercise endurance.

In summary, exercise endurance (the ability to sustain intense aerobic exercise or activity) provides an appropriate link between pulmonary and muscular dysfunction and limitations in lower limb activities experienced by people with COPD, observed in daily life as limitations in the ability to complete a given physical

task.

Exercise endurance as a relevant COI in COPD is also supported by guidance developed by clinical and scientific bodies and regulatory authorities. The American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force on Outcomes for COPD Pharmacological Trials,²⁰ assembled with the aim of informing the COPD research community about current outcomes and markers for evaluating the impact of a pharmacological therapy, identified exercise tolerance as a necessary supplement to the measurement of lung function among people with COPD. From the task force:

“Changes in forced expiratory volume in 1 second (FEV₁) with therapy should not be regarded as a surrogate for changes in dyspnea, exercise performance, or health-related quality of life. These variables should be measured separately to complement other markers of physiological impairment when assessing a therapy for COPD.”²⁰

The FDA issued a draft guidance for developing drugs in COPD⁸ in 2016 which described exercise tolerance (which is synonymous with exercise endurance) as a potential objective physiological assessment. The draft guidance was withdrawn for undisclosed reasons in 2018 and a final guidance has not been released. In this document, efficacy assessments were grouped into the following broad categories: (1) objective physiological assessments, (2) patient- or evaluator-reported outcome measures, and (3) biomarkers and surrogate endpoints. Within this framework, reduced capacity for exercise was described as a potential objective physiological assessment:

“...reduced capacity for exercise is a typical consequence of airflow obstruction in COPD patients, particularly because of dynamic hyperinflation occurring during exercise. Assessments of exercise capacity by treadmill or cycle ergometry combined with lung volume assessment potentially can be a tool to assess efficacy of a drug.”⁸

The European Medicines Agency considers exercise testing among people with COPD to be useful in the clinical setting to assess the degree of impairment, prognosis, and the effects of treatment interventions,²¹ and recommends its use as a co-primary endpoint in confirmatory trials for therapies intended for the symptomatic treatment of COPD:

“...measurement of lung function parameters alone

is considered to be insufficient in the assessment of therapeutic effect. If lung function is selected as a primary endpoint (FEV₁ would be the parameter of choice), additional evidence of efficacy must be demonstrated through the use of a co-primary endpoint, which should either be a symptom-based endpoint or a patient-related endpoint. In moderate/severe COPD this might be the number of exacerbations and/or symptoms such as dyspnea on exertion, or health status assessed through the use of a disease-specific questionnaire such as the SGRQ and/or assessment of exercise capacity.”²¹

Thus, there is general consensus that exercise endurance represents a clinically meaningful aspect of patient function in COPD. Currently, no products approved for treatment of COPD in the United States have claims related to exercise endurance and, as such, the regulatory pathway in the United States is not established.²² Therefore, there is a clear need to develop and qualify COAs associated with the concept of exercise endurance within the framework of the FDA DDT qualification process.

Identification of an Appropriate Clinical Outcome Assessment for the Measurement of Exercise Endurance

There are several exercise tests that have been used in the evaluation of patients with COPD. An ERS Task Force conducted a comprehensive review of the value and limitations of different exercise tests for the assessment of therapeutic interventions.²³ The task force summarized the available evidence for:

- laboratory-based incremental work-rate tests (cycle ergometer; motorized treadmill),
- high-intensity constant work rate tests (cycle ergometer; motorized treadmill),
- field tests (6-minute walk test [6MWT], incremental shuttle walk test [ISWT], endurance shuttle walk test [ESWT]).

Laboratory-based incremental work rate tests (using a cycle ergometer or a motorized treadmill) permit evaluation of both submaximal and peak exercise responses and have an important role in establishing exercise prescriptions for exercise training. Peak oxygen uptake ($\dot{V}O_{2peak}$) is a key measurement during these tests and is closely reflective of the individual's maximum

oxygen uptake ($\dot{V}O_2$), the gold-standard index of aerobic capacity. However, in terms of a measure of exercise performance, the necessary incremental nature of the work rate control during the test means that the exercise test is not representative of the type of activity pattern performed in everyday life; it is analogous to climbing up a hill that becomes steeper and steeper as the individual climbs. Furthermore, individuals do not habitually choose to perform exercise at peak work rate or peak $\dot{V}O_2$. As such, the measurement of peak work rate (i.e., the work rate associated with $\dot{V}O_{2\text{peak}}$) is not a relevant measure of exercise endurance in the context of activity limitation in COPD. Similarly, the ISWT, in which walking speed increases progressively, was developed as a field test for the estimation of peak aerobic capacity²⁴ and, as such, is also not a relevant measure of exercise endurance within the present context.

The task required of the individual performing the 6MWT is to “walk as far as possible during a 6-minute period.”²⁵ The individual, therefore, has the task to self-select a walking speed that he/she assesses to be appropriate for maximizing the distance walked in the 6-minute testing period. As the test continues, the individual has the option to adjust the walking speed based on a continuous re-assessment of the time to test-end within the requirement to maximize distance walked. If necessary, the individual is allowed to rest during the test. Therefore, the 6MWT is a suitable test for the measurement of “walking performance,” but is not a measure of exercise endurance, defined as “the ability to sustain intense aerobic exercise or activity.” Importantly, it has been demonstrated operationally²⁶ that the 6MWT does not consistently elicit limitation in physiologic variables. Most individuals self-select walking speeds that are comfortable, rather than maximal. As a result, pharmacological interventions that ameliorate physiologic limitations to exercise have generally not been found to increase 6MW distance.²⁶

The ESWT is a field test that was developed based on the same construct as laboratory-based CWR tests²⁷; the individual is tasked with walking for as long as possible (i.e., to the point of exercise intolerance) at an externally regulated walking speed that is pre-determined to be at a high relative intensity compared with peak walking speed. The ESWT was developed to reflect a specific functional activity performed in daily life (walking along level ground); the ESWT is the focus of a separate COA qualification initiative that focuses on the concept of

interest of “walking endurance.”

CWR tests (cycle or treadmill) require the patient to perform an activity that reflects the symptom-limited exercise intolerance experienced while performing activities of daily living; the duration for which a given task can be sustained. Importantly, it standardizes the intensity of the activity performed by the individual, thus avoiding the confounding influence of the behavioral adaptations seen in everyday life, consistent with the recommendations in the International Classification of Functioning, Disability, and Health published by the World Health Organization.¹⁹ Constant work rate tests have the following important characteristics:

- A physical task that is continued until the point of symptom limitation (“symptom-limited”).
- A high intensity activity (relative to the individual’s exercise capacity) involving large muscle groups, which most commonly brings the person with COPD to 1 of 2 physiologic limitations:
 - a limitation in pulmonary ventilation and/or gas exchange, which elicits a limiting intensity of breathlessness;
 - a limitation in leg muscle oxidative metabolism and/or accumulation of fatigue-associated metabolites, which elicits a limiting intensity of neuromuscular fatigue.

Both CWRCE²⁸ and CWR treadmill walking are recognized as appropriate measurement tools for exercise endurance.²³ The CBQC CWR Exercise Working Group decided to focus its initial qualification efforts on CWRCE due to the more extensive evidence available for CWRCE compared with CWR treadmill walking.²⁸ Specifically, the Working Group agreed to move forward with an evaluation of endurance time during CWRCE as a potentially important COA for drugs developed for COPD that reflects the concept of interest “exercise endurance.” As a basis for the evaluation, the context of use was stipulated as a key efficacy endpoint in clinical trials that incorporate standard features, e.g., randomization and double-blind study treatment(s). In such a trial setting, the endpoint assessed with this COA is anticipated to be defined as an increase in exercise endurance measured as change from pre-treatment baseline endurance time during CWRCE.

Description of the Clinical Outcome Assessment: Endurance Time During Constant Work Rate Cycle Ergometry

CWRCE is performed on an electronically braked stationary cycle ergometer (specifically, an ergometer in which the work rate is controlled and is independent of the pedaling cadence). At baseline, an individualized work rate is established for each individual, based on a preceding incremental cycle ergometer exercise test in which work rate is incremented in a pre-specified protocol.

During the CWRCE, the individual begins to pedal at a self-selected pedaling cadence (usually 60rpm) and is encouraged to maintain this frequency throughout the exercise test. A stopwatch (or other time recording device) is started when the work rate is increased to the pre-determined level. The individual is encouraged to continue exercising for as long as possible (i.e., to intolerance or maximal exertion).

Although not an absolute requirement (and engendering additional complexity), measurement of physiological and sensory responses are typically collected during this laboratory-based exercise test to allow changes in endurance time to be interpreted in relation to changes in physiological and sensory responses: e.g., $\dot{V}O_2$, pulmonary carbon dioxide output ($\dot{V}CO_2$) pulmonary ventilation (\dot{V}_E) inspiratory capacity, breathing frequency, heart rate, or patient-reported ratings of dyspnea and leg effort.

The individual supervising the exercise test provides standardized and continuous encouragement to the individual. If an individual selects a pedaling rate of 60rpm, the encouragement during the test would focus on ensuring that the patient is motivated to maintain the pedaling rate of 60rpm. Should the pedaling cadence drop below the selected rpm, the individual is encouraged immediately to increase the pedaling cadence back to the selected rpm, and to maintain it for as long as possible.

The limit of exercise tolerance is defined as the point at which the individual is: (1) limited by symptoms (i.e., is unwilling to continue exercising because of the discomfort associated with the exercise), or (2) unable to maintain the self-selected pedaling cadence (e.g., the cadence drops more than 10rpm below the self-selected cadence and is not increased even with continued encouragement), or (3) unable to continue safely (in the opinion of supervising personnel). It should be noted

that the latter reason for termination is uncommon, as CWRCE is preceded by an incremental cycle ergometer test in which a safety evaluation is conducted.

At the end of exercise, the duration of exercise is recorded (in minutes and seconds).

Comparing Work Rate During Constant Work Rate Cycle Ergometry and During Lower Limb Activities in Daily Life

A critical issue in CWRCE is the selection of a work rate that is a relevant indicator of work rates required during daily activities. There is a critical relationship between the intensity of the muscular work performed, degree of muscular conditioning, and the associated ventilatory response, which interacts with the magnitude of the individual's expiratory flow limitation resulting in the degree of breathlessness experienced. While the work rate imposed during CWRCE can be measured in a straightforward manner, this is generally not the case for activities of daily living. However, the well-established relationship between work rate and $\dot{V}O_2$ allows for a close approximation of the work rate during daily life activities by using $\dot{V}O_2$ as the critical linkage parameter.

The *Compendium of Physical Activities*²⁹ documents the metabolic requirements for a multitude of daily activities. In the document, metabolic requirements are described as metabolic equivalents (METs), defined as a multiple of the metabolic requirement at rest. One MET is defined as the oxygen uptake required in the resting state, which by convention is approximated as 3.5 milliliters of oxygen uptake per minute per kilogram of body weight (mL/kg/min). For example, "stair climbing, slow pace" requires 4.0 METs, which means a metabolic requirement that is 4 times the resting metabolic requirement. While the concept of METs has value in describing activity intensity to the lay public, the $\dot{V}O_2$ requirement has greater value for relating the work rate during CWRCE to the work rate required during everyday activities. So, the example of "stair climbing, slow pace" equates to a $\dot{V}O_2$ of 14.0mL/kg/min. The $\dot{V}O_2$ requirement may then be transformed into an estimate of the associated work rate by using the well-established relationship between work rate and $\dot{V}O_2$; for a 70kg individual, based on a $\dot{V}O_2$ requirement of 14.0mL/kg/min, "stair climbing, slow pace" has an associated work rate of 42 watts (W). Table 2 and Figure 2 illustrate a representative list of activities

Table 2. Activities in Daily Life Involving the Lower Limbs with the Metabolic Equivalent, the Approximate Oxygen Uptake Requirement, and the Associated Work Rate^{a,b}

METs	Description	$\dot{V}O_2$ (mL/kg/min)	External Work Rate–70kg (W) ^c
2.3	Food shopping, standing	8.1	0.6
2.5	Walking from house to car or bus	8.8	5.5
2.8	Standing, playing with child(ren) light effort, only active periods	9.8	12.8
3.0	Ballroom dancing, slow	10.5	17.6
3.0	Standing tasks, light effort (e.g., store clerk)	10.5	17.6
3.3	Vacuuming, moderate effort	11.6	24.9
3.5	Walking on job, 3.0 mph, not carrying anything	12.3	29.8
3.5	Descending stairs	12.3	29.8
3.8	Cleaning, sweeping, slow, moderate effort	13.3	37.0
3.8	Gardening, general, moderate effort	13.3	37.0
4.0	Sweeping garage, sidewalk or outside of house	14.0	41.9
4.0	Stair climbing, slow pace	14.0	41.9
4.3	Golf, walking, carrying clubs	15.2	50.0
4.8	Walking 3.5 mph carrying objects less than 25 lbs	16.8	61.3
4.8	Golf, general	16.8	61.3
5.0	Mowing lawn, walk, power mower	17.5	66.1
5.0	Carrying load 1–15 lbs upstairs	17.5	66.1
5.3	Walking, 2.9–3.5 mph, uphill, 1%–5% grade	18.6	73.4
6.0	Mowing lawn, walk, hand mower	21.0	90.4
6.0	Running 4 mph	21.0	90.4
6.3	Climbing hills, no load	22.1	97.7
7.0	Skiing, general	24.5	114.7
7.5	Carrying groceries upstairs	26.3	126.8
8.0	Tennis, singles	28.0	138.9
8.8	Stair climbing, fast pace	30.8	158.3

Source: Wasserman et al,³⁰ 1975; Wasserman et al,³¹ 2004

^afor a 70kg individual

^badapted from Ainsworth et al²⁹

^cPredicted $\dot{V}O_2$ (mL/min)= $5.8 \times \text{body weight (kg)} + 151 + 10.1 \times \text{work rate (W)}$; METs= $3.5 \dot{V}O_2$ (mL/min)/ body weight (kg).

Therefore: work rate (W)=($\dot{V}O_2$ (mL/kg/min)- 5.8) \times body weight [kg]- 151)/ 10.1

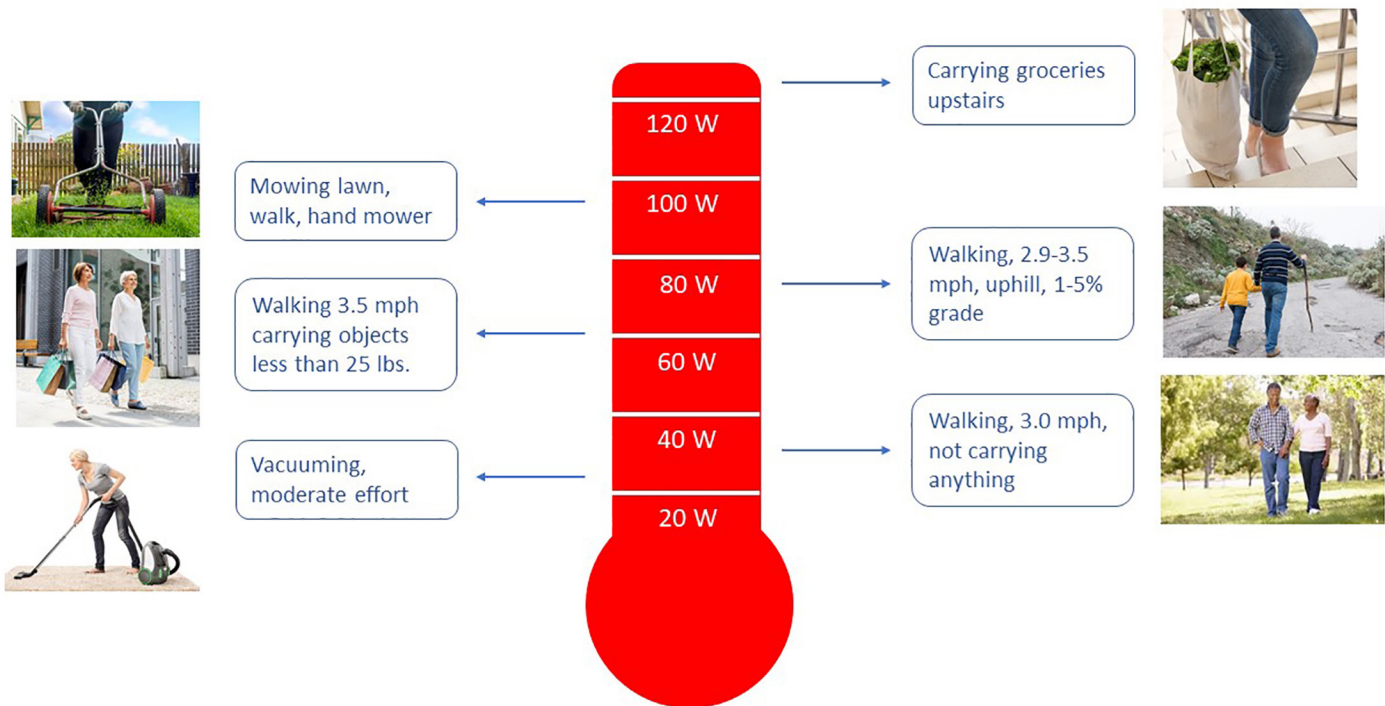
METs=metabolic equivalents; $\dot{V}O_2$ =oxygen uptake; W=watts

in daily life involving the lower limbs, accompanied by the MET equivalent, the associated $\dot{V}O_2$ requirement and the estimated work rate (for a 70kg individual^{30,31}; the equations in the footnote of Table 2 allow calculations for individuals of other body weights). Thus, the work rates performed (and the associated cardiorespiratory response) during CWRCE are representative of the work rates (and the associated cardiorespiratory response) of many lower limb activities that people with COPD perform during daily life.

Work rates for CWRCE testing are selected to be ones that the given individual with COPD can sustain

for only a limited period of time (e.g., 6 minutes). Using Table 2, that work rate can be related to a relevant activity the individual may wish to perform. **An improvement in CWR exercise time as a result of an intervention implies that the individual will be capable in everyday life of performing that activity for a longer duration without stopping.**

In conclusion, endurance time during CWRCE is proposed as an efficacy endpoint for use in clinical trials evaluating drugs or other interventions such as pulmonary rehabilitation. We have demonstrated here that improved exercise endurance time has a direct

Figure 2. External Work Rates Required for Everyday Tasks^a^afor a 70kg individual

relationship to an individual with COPD's experience of physical functioning in daily life, which is a meaningful patient-centered benefit. Future publications will focus on the process of assembling a database of endurance time responses of individuals with COPD to endurance-enhancing interventions and subsequent characterization of the factors contributing to endurance time improvement.

Acknowledgements

Author contributions: All authors have significantly contributed to the intellectual content of this article and have given final approval of the version that has been submitted for publication.

Medical writing assistance, provided by Nena O'Keefe, was funded by the CBQC Constant Work Rate Exercise project funders.

COPD Biomarkers Qualification Consortium Constant Work Rate Exercise Working Group Members:

Richard Casaburi, PhD, MD, (academic co-chair), the Lundquist Institute for Biomedical Innovation at

Harbor-UCLA Medical Center, Torrance, California; Alan Hamilton, PhD, (industry co-chair), Boehringer Ingelheim, Canada, Ltd; Christopher B. Cooper, MD, University of California, Los Angeles; Gale Harding, MA, Evidera, Bethesda, Maryland; Nick Hopkinson, FRCP, Brompton Hospital, London, United Kingdom; Nancy Kline Leidy, PhD, Evidera, Bethesda, Maryland; Nicholas Locantore, PhD, GlaxoSmithKline, Collegeville, Pennsylvania (at the time of the study); Debora Merrill, MBA, COPD Foundation, Washington, DC; Francois Maltais, MD, Université Laval, Quebec, Canada; Divya Mohan, MRCP, PhD, GlaxoSmithKline, Collegeville, Pennsylvania (at the time of this study); Alberto Neder, MD, Queens University, Kingston, Canada; Andrea Noronha, Syneos Research, Morrisville, North Carolina; Dennis O'Donnell, MD, Queens University, Kingston, Canada; Michael Polkey, PhD, FRCP, Brompton Hospital, London, United Kingdom; Janos Porszasz, MD, PhD, the Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, California; Stephen Rennard, MD, University of Nebraska Medical Center, Omaha, Nebraska; Harry B. Rossiter, PhD, the Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, California; Frank Sciurba, MD, University of Pittsburgh, Pittsburgh, Pennsylvania;

Sally J. Singh, PhD, University of Leicester, United Kingdom; Martijn A. Spruit, PhD, CIRO, Expertise Centre for Chronic Organ Failure, Horn, Netherlands; Ruth Tal-Singer, PhD, COPD Foundation, Washington, DC, (formerly at GlaxoSmithKline); Martyn Walker, Syneos Research, Ebchester England, United Kingdom; Susan Ward, PhD, Crickhowell, Wales, United Kingdom; Ren Yu, Evidera, Bethesda, Maryland;

All Working Group members were provided this manuscript prior to submission for publication.

Declaration of Interest

Richard Casaburi reports consulting fees/honoraria from Boehringer Ingelheim, GlaxoSmithKline, Regeneron, Abbott, and Respinova. He is involved in contracted clinical research with Regeneron, United Therapeutics, and Boehringer Ingelheim. Debora Merrill has no conflicts to disclose. Gale Harding is employed by Evidera, a health care research firm that provides consulting and other research services to pharmaceutical, device, government, and non-government organizations. In this salaried position, she works with a variety of companies and organizations and receives no payment or honoraria directly from these organizations for services rendered.

Nancy Kline Leidy is employed by Evidera, a health care research firm that provides consulting and other research services to pharmaceutical, device, government, and non-government organizations. In this salaried position, Dr. Leidy works with a variety of companies and organizations. She receives no payment or honoraria directly from these organizations for services rendered, with the exception of honoraria received for her advisor role on several National Institutes of Health and FDA-funded programs: PATIENTS, PCAR, and NUOAT. Harry Rossiter is supported by grants from the National Institutes of Health (R01HL151452, R01HL153460, P50HD098593, R01DK122767, P2CHD086851), the Tobacco-Related Disease Research Program (T31IP1666), and the University of California, Office of the President. He reports consulting fees from Omnix Inc., and is involved in contracted clinical research with Boehringer Ingelheim, GlaxoSmithKline, Novartis, AstraZeneca, Astellas, United Therapeutics, Genentech, and Regeneron. Ruth Tal-Singer is a former employee (retiree) and current shareholder of GlaxoSmithKline. She reports personal fees from Immunomet, Vocalis Health, Teva and ENA Respiratory. She is a member of ENA Respiratory Board of Directors. Alan Hamilton was an employee of Boehringer Ingelheim during the writing of this manuscript.

References

- Woodcock J, Woosley R. The FDA critical path initiative and its influence on new drug development. *Annu Rev Med*. 2008;59:1-12. doi: <https://doi.org/10.1146/annurev.med.59.090506.155819>
- U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Qualification process for drug development tools. CDER website. Published January 2014. Accessed December 2021. <https://www.c-path.org/wp-content/uploads/2014/01/FDA-releases-guidance-for-drug-development-tool-qualification.pdf>
- U.S. Food and Drug Administration (FDA). Qualification process for drug development tools guidance for industry and FDA staff. FDA website. Published November 2020. Accessed December 2021 <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/qualification-process-drug-development-tools-guidance-industry-and-fda-staff>
- Walton MK, Powers JH, Hobart J, et al. Clinical outcome assessments: conceptual foundation-report of the ISPOR clinical outcomes assessment - emerging good practices for outcomes research task force. *Value Health*. 2015;18(6):741-752. doi: <https://doi.org/10.1016/j.jval.2015.08.006>
- Woodcock J, Buckman S, Goodsaid F, Walton MK, Zineh I. Qualifying biomarkers for use in drug development: a US Food and Drug Administration overview. *Expert Opin Med Diagn*. 2011;5(5):369-374. doi: <https://doi.org/10.1517/17530059.2011.588947>
- Amur SG, Sanyal S, Chakravarty AG, et al. Building a roadmap to biomarker qualification: challenges and opportunities. *Biomark Med*. 2015;9(11):1095-1105. doi: <https://doi.org/10.2217/bmm.15.90>
- Amur S, LaVange L, Zineh I, Buckman-Garner S, Woodcock J. Biomarker qualification: toward a multiple stakeholder framework for biomarker development, regulatory acceptance, and utilization. *Clin Pharmacol Ther*. 2015;98(1):34-46. doi: <https://doi.org/10.1002/cpt.136>
- United States Food and Drug Administration (FDA). Guidance for industry: chronic obstructive pulmonary disease: developing drugs for treatment. FDA website. Published May 2016. Accessed December 2021. <https://www.federalregister.gov/documents/2016/05/20/2016-11855/chronic-obstructive-pulmonary-disease-developing-drugs-for-treatment-draft-guidance-for-industry>
- Casaburi R, Celli B, Crapo J, et al. The COPD Biomarker Qualification Consortium (CBQC). *COPD*. 2013;10(3):367-377. doi: <https://doi.org/10.3109/15412555.2012.752807>
- Miller B. Plasma fibrinogen qualification as a drug development tool in chronic obstructive pulmonary disease. Perspective of the Chronic Obstructive Pulmonary Disease Biomarker Qualification Consortium. *Am J Respir Crit Care Med*. 2016;193(6):607-613. doi: <https://doi.org/10.1164/rccm.201509-1722PP>
- Jones P, Harding G, Wiklund I, Berry P, Leidy N. Improving the process and outcome of care in COPD: development of a standardised assessment tool. *Prim Care Respir J*. 2009;18(3):208-215. doi: <https://doi.org/10.4104/pcrj.2009.00053>
- Disler RT, Green A, Luckett T, et al. Experience of advanced chronic obstructive pulmonary disease: meta-synthesis of qualitative research. *J Pain Symptom Manage*. 2014;48(6):1182-1199. doi: <https://doi.org/10.1016/j.jpainsymman.2014.03.009>
- Leidy N, Haase J. Functional performance in people with chronic obstructive pulmonary disease: a qualitative analysis. *ANS Adv Nurs Sci*. 1996;18(3):77-89. doi: <https://doi.org/10.1097/00012272-199603000-00008>
- Dobbels F, de Jong C, Drost E et al. The PROactive innovative conceptual framework on physical activity. *Eur Respir J*. 2014;44(5):1223-1233. doi: <https://doi.org/10.1183/09031936.00004814>
- Ramon MA, Ter Riet G, Carsin A-E, et al. The dyspnoea-inactivity vicious circle in COPD: development and external validation of a conceptual model. *Eur Respir J*. 2018;52:1800079. doi: <https://doi.org/10.1183/13993003.00079-2018>
- Cooper CB. Exercise in chronic pulmonary disease: limitations and rehabilitation. *Med Sci Sports Exerc*. 2001;33:S643-S646. doi: <https://doi.org/10.1097/00005768-200107001-00001>
- Reardon JZ, Lareau SC, ZuWallack R. Functional status and quality of life in chronic obstructive pulmonary disease. *Am J Med*. 2006;119(10A):S32-S37. doi: <https://doi.org/10.1016/j.amjmed.2006.08.005>
- Kawagoshi A, Kiyokawa N, Sugawara K, et al. Effects of low-intensity exercise and home-based pulmonary rehabilitation with pedometer feedback on physical activity in elderly patients with chronic obstructive pulmonary disease. *Respir Med*. 2015;109(3):364-371. doi: <https://doi.org/10.1016/j.rmed.2015.01.008>
- World Health Organization (WHO). Towards a common language for functioning, disability and health ICF. WHO website. Published 2002. Accessed December 2021. <http://www.who.int/classifications/icf/training/icfbeginnersguide.pdf>
- Cazzola M, MacNee W, Martinez FJ, et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J*. 2008;31(2):416-468. doi: <https://doi.org/10.1183/09031936.00099306>

21. European Medicines Agency (EMA). Clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD). EMA website. Published September 2012. Accessed December 2021. <https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-chronic-obstructive-pulmonary-disease-copd>
22. United States Food and Drug Administration (FDA). Briefing Document for the Pulmonary-Allergy Drugs Advisory Committee (PADAC) Meeting (Jan 29th, 2013): NDA 203108 - olodaterol (proposed trade name Striverdi Respimat) for the proposed indication of long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. FDA website. Published 2013. Accessed December 2021. <http://web.archive.org/web/20161024105010/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM336760.pdf>
23. Puente-Maestu L, Palange P, Casaburi R, et al. Use of exercise testing in the evaluation of interventional efficacy: an official ERS statement. *Eur Respir J*. 2016;47:429-460. doi: <https://doi.org/10.1183/13993003.00745-2015>
24. Singh SJ, Morgan MDL, Scott S, Walters D, Hardman AE. Development of a shuttle walking test of disability in patients with chronic airways obstruction. *Thorax*. 1992;47(12):1019-1024. doi: <https://doi.org/10.1136/thx.47.12.1019>
25. ATS Statement. Guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111-117. doi: <https://doi.org/10.1164/ajrccm.166.1.at1102>
26. Celli B, Tetzlaff K, Criner G, et al. The 6-minute walk test as a COPD stratification tool: insights from the COPD Biomarker Qualification Consortium. *Am J Respir Crit Care Med*. 2016;194(12):1483-1493. doi: <https://doi.org/10.1164/rccm.201508-1653OC>
27. Revall SM, Morgan MD, Singh SJ, et al. The endurance shuttle walk: a new field test for the assessment of endurance capacity in chronic obstructive pulmonary disease. *Thorax*. 1999;54:213-222. doi: <https://doi.org/10.1136/thx.54.3.213>
28. Borel B, Provencher S, Saey D, Maltais F. Responsiveness of various exercise-testing protocols to therapeutic interventions in COPD. *Pulm Med*. 2013;2013:410748. doi: <https://doi.org/10.1155/2013/410748>
29. Ainsworth BE, Haskell WL, Herrmann SD, et al. Compendium of physical activities: a second update of codes and MET values. *Med Sci Sports Exerc*. 2011;43(8):1575-1581. doi: <https://doi.org/10.1249/MSS.0b013e31821ece12>
30. Wasserman K, Whipp BJ. Exercise physiology in health and disease. *Am Rev Respir Dis*. 1975;112:219-249. doi: <https://www.atsjournals.org/doi/citedby/10.1164/arrd.1975.112.2.219>
31. Wasserman K, Hansen J, Sue D, Stringer W, Whipp B, eds. *Principles of Exercise Testing and Interpretation*. 4th ed. Lippincott Williams & Wilkins; 2004.