Clinical Outcome Assessments (COA) Qualification Program
DDT COA #000072: Endurance Time during Constant Work Rate Cycle Ergometry (CWRCE)
Qualification Plan

Section 1: Proposed COA Qualification

1.1 Introduction and overview

- **Concise description of the disease and the clinical trial setting in which the planned or existing COA would be used**

1.1.1. Concise description of the disease

According to the United States (US) Food and Drug Administration (FDA) Guidance for Industry and FDA Staff Qualification Process for Drug Development Tools (January 2014), as well as other relevant sources (e.g., Walton et al, 2015 [1]), establishing a well-understood relationship of a clinical outcome assessment (COA) with 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). In this section, we discuss how the disease process that characterizes chronic obstructive pulmonary disease (COPD) impacts on how the patient feels and functions during performance of physical tasks during everyday life. We then introduce the concept of exercise endurance as a relevant limitation in physical functioning in patients with COPD.

COPD is a common, preventable and treatable disease that is characterized by expiratory flow limitation (EFL) due to airway and / or alveolar abnormalities usually caused by significant exposure to noxious particles or gases (2). The chronic EFL characteristic of COPD is caused by a mixture of small airways disease (e.g., chronic bronchitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person. These changes do not always occur together and evolve at different rates over time. Chronic inflammation causes structural changes, narrowing of the small airways, and destruction of the lung parenchyma that leads to a loss of alveolar attachments to the small airways and decreases lung elastic recoil. In turn, these changes diminish the ability of the airways to remain open during expiration. A loss of small airways also contributes to EFL. Mucociliary dysfunction is another characteristic feature of the disease. EFL is usually measured by post-bronchodilator spirometry because this is the most widely available and reproducible test of lung function (2). There are also extra-pulmonary manifestations of COPD that contribute to symptomatology and prognosis; key among them is dysfunction of the muscles of ambulation, related to both the sedentary lifestyle that most patients exhibit as well as intrinsic factors related to COPD (3).

Patients with COPD have a variety of symptoms, including shortness of breath (breathlessness), chest tightness, wheezing, and cough with or without sputum as well as systemic symptoms such as fatigue and weakness (4). Breathlessness on exertion is a defining symptom of COPD and is often what provokes initial health care contact prior

to diagnosis. Breathlessness on exertion is a key indicator used in the diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (2); it is a ubiquitous symptom that is persistent and progressive over time and identified as a major concern by patients due to its impact on daily life and emotional well-being (4).

It has been long recognized that the breathlessness experienced by patients with COPD needs to be viewed alongside the intensity of the activity associated with the breathlessness episode. For example, the Medical Research Council breathlessness scale (5), developed in the 1950s, is recommended as a primary assessment tool for the description of symptoms at time of diagnosis (2). Using the modified Medical Research Council scale (6), the patient grades the degree of breathlessness in the context of the intensity of activity that is causing the breathlessness:

0: “not troubled by breathlessness except on strenuous exercise”

1: “short of breath when hurrying on the level or walking up a slight hill”

2: “walks slower than most people on the level, stops after a mile or so, or stops after
15 minutes walking at own pace”

3: “stops for breath after walking about 100 yards or after a few minutes on level ground”

4: “too breathless to leave the house, or breathless when undressing”

In an effort to avoid breathlessness during daily life, patients reduce the intensity and/or amount of activity performed. Patients have reported that on days when their COPD symptoms are worse, they reduce their activity, opting to “rest” or “stay in bed” with increased rescue medication use and feelings of fear, frustration, anxiety, and depression (4). In the multinational PERCEIVE (Perception of Exacerbations of Chronic Obstructive Pulmonary Disease) study that conducted telephone interviews with >1000 COPD patients, shortness of breath was identified as the primary symptom (78%) while patients most frequently complained about their inability to complete the activities they enjoy because of COPD (7). Furthermore, the chronic EFL and persistent respiratory symptoms that limit patients’ activities, and the consequent reduction in physical activity, leads to a reduction in patients’ physical conditioning; dysfunction of the muscles of ambulation yields early onset of lactic acidosis during exercise, which stimulates breathing and increases breathlessness. (8). This explanatory conceptual model of the progressive limitations in physical functioning over time in COPD patients has been termed the “dyspnea-inactivity vicious cycle”,(8) “disease spiral,”(9) “dyspnea spiral,”(10) or “downward spiral of disability”(11).

In seeking to develop a conceptual framework for the experience of physical activity in patients with COPD, Dobbels et al. asked patients 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?” (12) Three core themes were identified that reflect the patients’ experience of physical activity, i.e., ‘‘amount of physical activity’’ (what activities they do), ‘‘symptoms during physical activity’’ (how do they feel when doing these activities), and ‘‘need for physical adaptations’’ (how they perform these activities). While the activities affected first were climbing stairs and walking (first uphill and then also on the flat), with disease progression, patients reported that almost all activities of daily life became affected, such as carrying objects, household activities and, ultimately, self-care activities such as dressing or bathing. Patients adapted primarily by pacing or slowing down, interrupting activities to take a break to recover, or allowing a longer recuperation period; these adaptations reflect reduced exercise endurance, defined as the duration for which an individual is able to sustain intense aerobic exercise or activity. Thus, exercise endurance is a relevant aspect of physical functioning during everyday life that is impacted by COPD.

In this Full Qualification Package (FQP), we present evidence to support Endurance Time during Constant Work Rate Cycle Ergometry (CWRCE) as a COA that provides a directly observed, objective measure of exercise endurance under standardized conditions, as recommended in the International Classification of Functioning, Disability and Health (ICF) published by the World Health Organization (WHO)[2] (13). A conceptual framework that further describes the linkage between the COA of Endurance Time during CWRCE, the proximal concept of interest of exercise endurance, and the distal concept of interest of physical function is presented in Section 1.2.

1.1.2. Clinical trial setting for use of COA

This FQP proposes that Endurance Time during CWRCE be used 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 in endurance time during CWRCE. The anticipated study population and study design are further detailed in Section 1.3.

- **Limitations of existing assessments, brief description of the COA, and rationale for use in drug development**

1.1.3. Limitations of existing assessments

Currently, there is no qualified COA for the measurement of exercise endurance; no products approved for treatment of COPD in the US have claims related to exercise endurance.

Following a brief description of the proposed COA, below, Section 1.2 presents a summary of other related exercise tests that were not taken forward, because they were not considered to measure the specific concept of interest of exercise endurance.

1.1.4. Brief description of COA

A CWRCE test is performed on an electronically braked stationary cycle ergometer (i.e., an ergometer where the work rate is controlled and independent of the pedaling cadence). At baseline, an individualized work rate is established for each subject, based on a preceding incremental cycle ergometer (ICE) exercise test in which work rate is incremented in a prespecified protocol.

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

Although not an absolute requirement, 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., pulmonary oxygen uptake, $\dot{V}O_2$; 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).

Standardized and continuous encouragement to the patient is provided by a member of the trial team; e.g., if a patient selects a pedaling rate of 60 rpm, the encouragement during the test would focus on ensuring that the patient is motivated to maintain the pedaling rate of 60 rpm. Should the pedaling cadence drop below the selected rpm, the patient 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 patient is: (i) limited by symptoms (i.e., is unwilling to continue exercising because of the discomfort associated with the exercise), or (ii) unable to maintain the self-selected pedaling cadence (i.e., the cadence drops more than 10 rpm below the self-selected cadence and is not increased even with continued encouragement), or (iii) 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 ICE test in which a safety evaluation is conducted.

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

1.1.5. Rationale for use of COA in drug development

Endurance time during CWRCE is intended to be a standardized COA to assess exercise endurance in clinical trials (see Section 1.2). Assessment of exercise endurance has been identified as a necessary supplement to the measurement of lung function in patients with COPD by the American Thoracic Society (ATS) / European Respiratory Society (ERS) Task Force. In addition, the FDA Draft Guidance for developing drugs in COPD (recently withdrawn by the Agency) (14) described exercise tolerance (which is synonymous with exercise endurance) as a potential objective

physiological assessment, and the European Medicines Agency (EMA) considers exercise testing in patients with COPD to be useful in the clinical setting to assess the degree of impairment, prognosis and the effects of interventions (15).

The ATS / ERS Task Force on outcomes for COPD pharmacological trials (16), 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 in patients with COPD:

> "Changes in forced expiratory volume in 1 second (FEV_1) 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 (16)."

In the FDA Draft Guidance for developing drugs in COPD (14), efficacy assessments were grouped into the following broad categories: (i) objective physiological assessments, (ii) patient or evaluator-reported outcome measures, and (iii) 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." (14)

A similar perspective is stated by the EMA (15) with the recommendation for use as a coprimary 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 (FEV_1 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 St. George's Respiratory Questionnaire (SGRQ) and/or assessment of exercise capacity." (15)

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 US have claims related to exercise endurance and, as such, the regulatory pathway in the US is not established (17). Therefore, there is a clear

need to develop and qualify COAs associated with the concept of exercise endurance within the framework of the FDA Drug Development Tool (DDT) qualification process.

1.2 Concept of Interest for meaningful treatment benefit

- **Describe the meaningful aspect of patient experience that will represent the intended benefit of treatment (e.g., the specific symptom and/or sign presence or severity or limitations in performance or daily activities relevant in the targeted context of use)**

1.2. Concept of interest for meaningful treatment benefit

In Section 1.1.1, we noted the FDA's position that establishing a well-understood relationship of a COA with 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. We also asserted that, for COPD patients, physical function while performing everyday activities is a meaningful aspect of patient functioning that is impacted by COPD.

In this section, we first discuss the linkage between physical function (a distal concept of treatment benefit) and exercise endurance (a proximal concept of treatment benefit that can be directly observed and objectively measured). We then present the rationale for endurance time during a constant work rate (CWR) exercise test as an appropriate measure of exercise endurance. Finally, we provide a brief overview of other potentially relevant exercise tests, including our rationale for the conclusion that these tests are not suitable measures of exercise endurance.

1.2.1. Exercise endurance as a relevant proximal concept of interest within the domain of physical function in patients with COPD

As described in Section 1.1.1, the explanatory conceptual model of the progressive limitations in physical functioning over time in COPD patients (the "downward spiral of disability") postulates that: (i) in the face of EFL that is characteristic of COPD, the respiratory response required to support the increased metabolic demands of a given intensity of muscular work results in increased breathlessness; (ii) in an effort to avoid breathlessness, patients reduce the intensity and/or amount of activity performed during daily life; (iii) the reduced activity leads to muscular de-conditioning, especially of the leg muscles; (iv) other extra-pulmonary intrinsic factors related to COPD, e.g., systemic inflammation, also contribute to muscle dysfunction; (iv) the consequences of muscle dysfunction, e.g., early onset of lactic acidosis during exercise, stimulate breathing and further increase breathlessness, amplifying the downward spiral of disability.

Figure 1 presents a conceptual framework of the relationship between relevant concepts of interest for a meaningful treatment benefit in patients with COPD. In the figure, the concept of "physical function" refers to relevant physical tasks in everyday life that are impacted in patients 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 personal (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. Within the domain of physical function, the separation into upper limb and lower limb activities has value in general (13); this separation has particular relevance when considering physical function in patients 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.

We have focused on lower limb activities, since limitations in these types of activities are ubiquitous in patients 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 metabolic requirements), which defines exercise endurance.

The concept of exercise endurance (the ability to sustain intense aerobic exercise or activity) provides an appropriate link between pulmonary / muscular dysfunction and limitations in lower limb activities experienced by COPD patients, observed in daily life as limitations in the ability to complete the physical task (see Section 3).

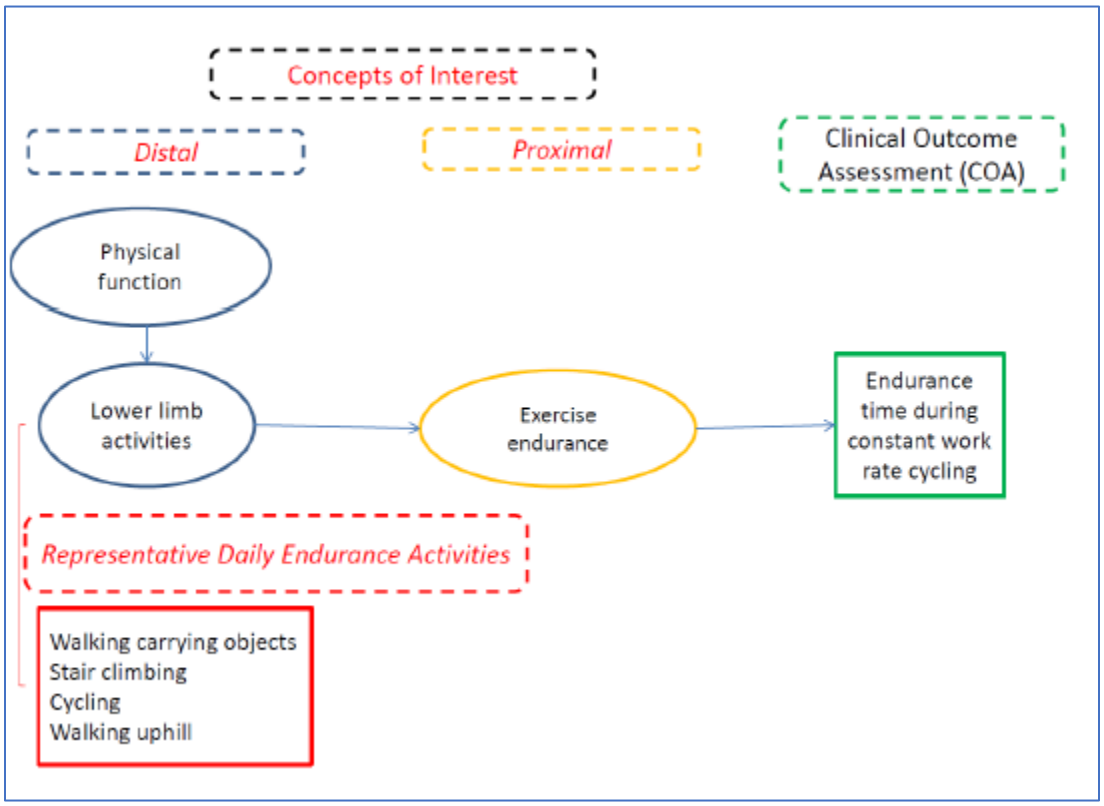

Figure 1. Conceptual relationship between the distal concept of physical function (for lower limb activities), the proximal concept of exercise endurance and the COA of endurance time during constant work rate cycle ergometry

1.2.2. Endurance time during CWRCE: an appropriate COA for measurement of exercise endurance

In the performance of lower limb activities in daily life, patients adapt by modifying behavior in the face of increasing breathlessness (abandoning activities, pacing, slowing down, longer recovery periods). Constant work rate tests require the COPD patient to perform an activity that reflects the symptom-limited exercise intolerance experienced while performing activities of daily living: the time a given task can be sustained. Importantly, it standardizes the intensity of the activity performed by the COPD patient, thus avoiding the confounding influence of the behavioral adaptations seen in everyday life. 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 brings the patient to one of two 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 leg muscle fatigue.

Both CWRCE (18) and CWR treadmill walking are recognized as appropriate measurement tools for exercise endurance (19). The decision to focus on CWRCE in this COA qualification initiative is based on the more extensive evidence available (18) for CWRCE compared with CWR treadmill walking.

In conclusion, as a reflection of the concept of interest "exercise endurance", measurement of endurance time during CWRCE is a potentially important COA for drugs developed for COPD.

1.2.3. Exercise intensity: comparing work rate during CWRCE and during lower limb activities in daily life

As mentioned above, there is a critical relationship between the intensity of the muscular work performed, the associated ventilatory response which interacts with the magnitude of the individual's EFL resulting in the degree of breathlessness experienced. While the work rate imposed during CWRCE can be measured in a straight-forward manner, this is generally not the case for activities of daily living. However, the well-established relationship between work rate and oxygen uptake ($\dot{V}O_2$) allows for the ascertainment of the work rate during daily life activities by using $\dot{V}O_2$ as the critical linkage parameter.

The Compendium of Physical Activities (20) documents the metabolic requirements for a multitude of daily activities. In the document, metabolic requirements are described as metabolic equivalents (MET), defined as a multiple of the metabolic requirement at rest (1 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 actual $\dot{V}O_2$ 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 14.0 ml/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 70 kg individual, based on a $\dot{V}O_2$ requirement of 14.0 ml/kg/min, “stair climbing, slow pace” has an associated work rate of 42.0 W. Table 1 and Figure 2 illustrate a representative list of activities 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 70 kg individual). This range of work rates may be compared with the range of work rates generally performed by COPD patients during CWRCE (e.g., in Table 1, median work rate of 53 W, with an interquartile range of 38-70 W). It is clear that the intensity of the work performed (and the associated cardiorespiratory response) during CWRCE is representative of the intensity of work (and the associated cardiorespiratory response) of many lower limb activities performed during daily life.

Table 1. A representative list of activities 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 70 kg individual) (adapted from Ainsworth et al.[20])

METS	Description	$\dot{V}O_2$ (mL/kg/min)	External Work Rate – 70 kg (W)*
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

* Predicted $\dot{V}O_2$ (ml/min) = 5.8 x body weight (kg) + 151 + 10.1 x Work rate (W); METS = 3.5 $\dot{V}O_2$ (ml/min)/ body weight (kg). Therefore: Work rate (W; 70 kg individual) = ([$\dot{V}O_2$ (ml/kg/min) - 5.8] x body weight (kg) - 151) / 10.1

Source: Wasserman et al, 1975 (21); Wasserman et al, 2004 (22).

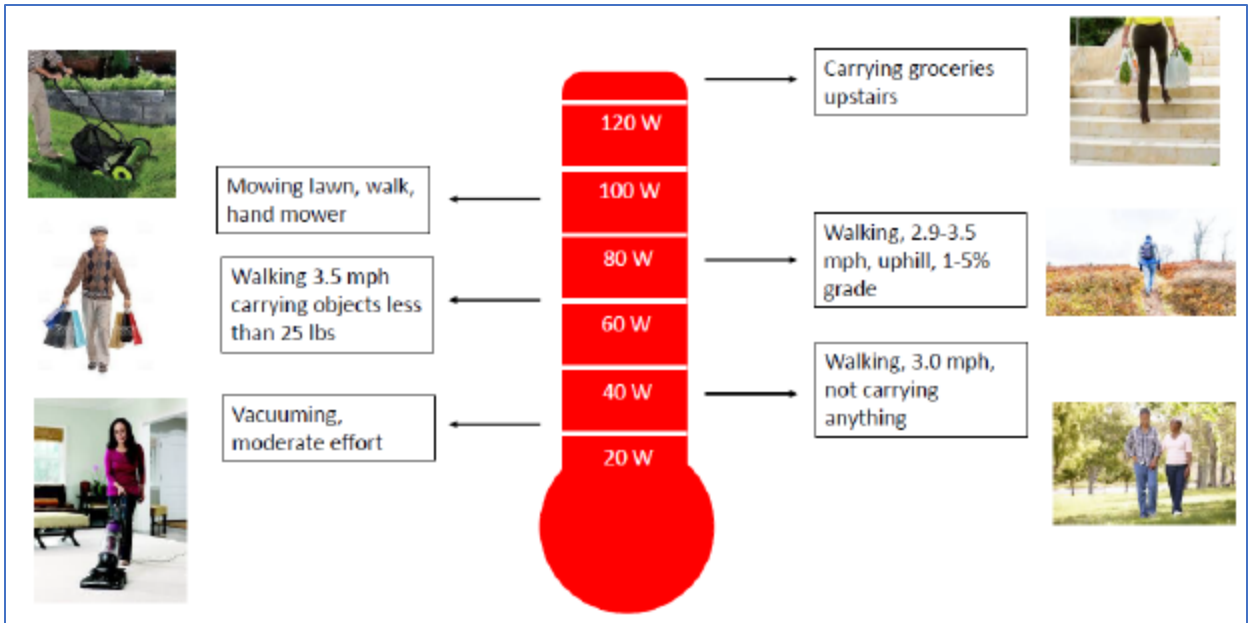

Figure 2. External work rates for everyday tasks (20 – 120 W; 70 kg individual)

Work rates for CWRCE testing are selected to be ones that the given COPD patient can sustain for only a limited period of time (e.g., 6 minutes). Using the table above, that work rate can be related to a patient relevant activity the patient may wish to perform. An improvement in CWR exercise time as a result of an intervention implies that the patient will be capable of performing that activity for a longer duration without stopping in everyday life.

1.2.4. Brief overview of other exercise tests and functional tests

In addition to CWR tests, there are several other 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 (19). In addition to high-intensity CWR tests, the task force summarized the available evidence for:

- laboratory-based incremental work-rate tests (cycle ergometer; motorized treadmill)
- field tests (six 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. Peak oxygen uptake ($\dot{V}O_2$peak) is a key measurement during these tests, and is closely reflective of the subject's "maximum" $\dot{V}O_2$, 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 subject 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 $\dot{V}O_2$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 capacity (23), 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;" (24) the subject 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 subject 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 subject 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 operationally (25 and see below) that the 6MWT does not consistently elicit physiologically-limiting levels of exercise. Most subjects self-select walking speeds that are comfortable, rather than maximal. As a result, pharmacological interventions that increase physiological ability to exercise have generally not been found to increase 6MW distance (25).

The ESWT is a field test that was developed based on the same construct as laboratory-based CWR tests; the subject 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 an independent COA qualification initiative that focuses on measurement of the concept of interest of "walking endurance".

1.3 Context of Use

- **Targeted study population, including a definition of the disease and selection criteria for clinical trials (e.g., baseline symptom severity, patient demographics, language/culture groups)**

1.3.1. Study population

COPD management guidelines (e.g., GOLD) recommend that COPD diagnosis be based upon spirometric determination of expiratory airflow limitation (EFL) (2), specifically FEV_1/forced vital capacity (FVC) <0.7.

It is anticipated that clinical trials that use CWRCE will incorporate traditional inclusion criteria for identifying COPD patients. For trials that include patients with a diagnosis of COPD, these inclusion criteria may include the following:

- Post-bronchodilator FEV_1/FVC <0.7
- Male or female patients, at least 40 years of age

- Current or ex-smokers with a smoking history of more than 10 pack-years.

Other inclusion criteria might include: degree of lung function impairment (mild, moderate, severe, and very severe), evidence of a ventilatory limitation to exercise (e.g., dynamic hyperinflation, low breathing reserve), evidence of activity-related breathlessness, and evidence of impaired exercise endurance.

- **Targeted study design; most commonly the COA will be used to assess the change (compared to a control) induced by a medical treatment**
- **Targeted study objectives and endpoint positioning (i.e., planned set of primary and secondary endpoints with hierarchy). Usually, the COA will serve to support a primary or secondary efficacy endpoint**

1.3.2. Study design

It is anticipated that the target study design for trials that include CWRCE in the evaluation of pharmacologic interventions will incorporate standard features such as randomization, and double-blind study treatment(s) where appropriate, so that the COA can be used to assess the change compared to a comparator group. It should be noted that the database developed for the evaluation of CWRCE includes rehabilitative exercise training studies, which enables comparison with pharmacologic interventions; most of these exercise training studies did not have a blinded study design and often did not include a control group.

The duration of treatment will be dependent on the specific treatment(s) being studied while being of a sufficient duration to allow the treatment to have its full effects on physiologic factors that determine exercise endurance.

The study endpoint for CWRCE is anticipated to be defined as:

- Change from pre-treatment baseline in endurance time during CWRCE.

The primary comparison of interest (primary analysis) is anticipated to be Intervention X vs. Comparator. Endurance time during CWRCE is intended for use as either a primary, co-primary, or secondary endpoint in the study.

1.4 Critical details of the measure to the degree known

- **Type of COA (e.g., patient-reported outcome [PRO]) and intended respondent(s), if applicable**
- **Item content or description of the instrument (for existing instruments, provide the specific version of the instrument and a copy from which quantitative evidence has been or will be derived)**
- **Method of administration (i.e., self-administered, interview-administered, etc.)**
- **Mode of data collection (i.e., electronic, interactive voice response system, etc.)**

A brief methodologic description of CWRCE is described in Section 1.1.4. CWRCE is to be conducted according to the technical standards and user manual to be provided in the full qualification package.

1.5 Description of the involvement of external expertise, including scientific communities or other international regulatory agencies, if applicable (i.e., working group, consortia)

In recognition of the importance of COAs to advance the development of new treatments, the FDA in the US initiated the Biomarker and COA Qualification processes to support new tool development in the early 2000's. In 2010, the COPD Biomarker Qualification Consortium (CBQC) was formed under the auspice of the COPD Foundation to undertake the qualification of new DDTs consistent with these processes. The focus of the initial efforts of the CBQC was on qualification of plasma fibrinogen as a stratification tool (26) and qualification of the SGRQ as an endpoint in interventional studies. In 2016, the FDA recognized SGRQ score in their draft guidance for the development of drugs to treat COPD as a COA for the measurement of health status, appropriate for use as co-primary or lower order endpoint demonstrating efficacy in clinical development (14). This was a significant step forward; however, CBQC believes that a wider range of tools, rigorously developed according to new regulatory standards and important to patients, will be a valuable addition to the COPD toolbox. Exercise endurance, as assessed by Endurance Time during CWRCE, is a concept that is important to both patients and researchers.

The organizational structure of the CBQC fosters contributions of clinical and scientific expertise from both academia and the pharmaceutical industry (Figure 3) (27, 14). Within the working group for the CWRCE initiative (see CBQC Working Group Members above), a broad request for input from academia has resulted in a significant contribution from clinical/scientific experts in clinical exercise testing; several CBQC working group members contributed to the recently published official ERS statement on the use of exercise testing in the evaluation of interventional efficacy.

Figure 3. CBQC Organizational Structure

Section 2: Executive Summary
High-level summary of what is included in the full qualification package and results to be described in the sections below

In patients with COPD, physical function (a distal concept of treatment benefit) can be linked to exercise endurance (a proximal concept of treatment benefit that can be directly observed and objectively measured). Currently, no COA is qualified for the measurement of exercise endurance, and therefore, no products approved for treatment of COPD in the US have claims related to exercise endurance.

As described in this FQP, as a concept of interest of meaningful treatment benefit, exercise endurance has a direct relationship to a COPD patient's experience of physical functioning in daily life. Endurance Time during the CWRCE is shown to be a COA that provides a directly observed, objective measure of exercise endurance under standardized conditions.

A CWRCE test is performed on an electronically braked stationary cycle ergometer (i.e., an ergometer where the work rate is controlled and independent of the pedaling cadence). At baseline, an individualized work rate is established for each subject, based on a preceding ICE exercise test in which work rate is incremented in a pre-specified protocol. During the CWRCE the patient begins to pedal at a self-selected pedaling cadence (usually 60 rpm) and is encouraged to maintain this frequency throughout the exercise test. The stopwatch (or other time recording device) is started when the work rate is increased to the pre-determined level. The patient is encouraged to continue exercising for as long as possible (i.e., to intolerance or maximal exertion). Although not an absolute requirement, 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., pulmonary oxygen uptake, $\dot{V}O_2$; 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 limit of exercise tolerance is defined as the point at which the patient is: (i) limited by symptoms, or (ii) unable to maintain the self-selected pedaling cadence (ie, the cadence drops more than 10 rpm below the self-selected cadence and is not increased even with continued encouragement), or (iii) unable to continue safely (in the opinion of supervising personnel). At the end of exercise, the duration of exercise is recorded (minutes and seconds).

Endurance Time during the CWRCE is proposed to be used as a key efficacy endpoint in clinical trials that incorporate standard features such as 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 in endurance time during the CWRCE.

References:

1. 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 in Health 2015; 18: 741-752.
2. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2019 Report. https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf
3. Maltais F, Decramer M, Casaburi R, et al. ATS/ERS Ad Hoc Committee on Limb Muscle Dysfunction in COPD. An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2014;189(9):e15-62.
4. 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. Primary Care Respiratory J. 2009;18(3): 208-215.
5. Stenton C. The MRC breathlessness scale. Occupational Medicine. 2008;58:226–227.
6. Williams N. The MRC breathlessness scale. Occupational Medicine 2017; 67(6):496–497.
7. Miravitlles M, Anzueto A, Legnani D, et al. Patient's perception of exacerbations of COPD – the PERCEIVE study. Respir Med 2007; 101: 453–460.
8. 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; in press (https://doi.org/10.1183/13993003.00079-2018).
9. Cooper CB. Exercise in chronic pulmonary disease: limitations and rehabilitation. Med Sci Sports Exerc 2001; 33: S643-6.
10. Reardon JZ, Lareau SC, ZuWallack R. Functional Status and Quality of Life in Chronic Obstructive Pulmonary Disease. The American Journal of Medicine (2006) Vol 119 (10A), S32–S37.
11. Kawagoshi A, Kiyokawa N, Sugawara K, Takahashi H, Sakata S, Satake M, Shioya T. Effects of low-intensity exercise and home-based pulmonary rehabilitation with pedometer feedback on physical activity in elderly patients with chronic obstructive pulmonary disease. Respiratory Medicine 2015; 109(3): 364-371.

12. Dobbels F, Corina de Jong C, Drost E et al. and the PROactive consortium. The PROactive innovative conceptual framework on physical activity. Eur Respir J 2014; 44: 1223–1233.
13. World Health Organization. Towards a common language for functioning, disability and health ICF. International Classification. 2002;1149:1–22. Available from: http://www.who.int/classifications/icf/training/icfbeginnersguide.pdf
14. United States Food and Drug Administration. Guidance for industry: chronic obstructive pulmonary disease: developing drugs for treatment (draft guidance, May 2016). Rockville: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) (2016).
15. European Medicines Agency (EMA) Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD) (21 June 2012, EMA/CHMP/483572/2012). www.emea.europa.eu (2012).
16. Cazzola M, MacNee W, Martinez FJ, et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J 2008; 31: 416–468.
17. United States Food and Drug Administration. 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.
18. Borel B, Provencher S, Saey D, Maltais F. Responsiveness of Various Exercise-Testing Protocols to Therapeutic Interventions in COPD. Pulmonary Medicine 2013(4):410748 2013.
19. 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.
20. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR Jr, Tudor-Locke C, Greer JL, Vezina J, Whitt-Glover MC, Leon AS. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc. 2011; 43(8):1575-81
21. Wasserman K, Whipp BJ. Exercise physiology in health and disease. ARRD 1975; 112:219-249.
22. Wasserman K, Hansen J, Sue D, Stringer W, Whipp B, eds (2004). Principles of Exercise Testing and Interpretation, 4th ed. Lippincott Williams & Wilkins, Philadelphia, USA. ISBN 7-7817-4876-3; 612 page
23. Singh et al
24. ATS Statement. Guidelines for the Six-Minute Walk Test. American Thoracic SocietyAm J Respir Crit Care Med. 2002;166(1): 111–117.
25. 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 Resp and Critical Care Medicine. 2016;194:10.1164/rccm.201508-1653OC.
26. 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. AJRCCM. 2016;193(6).
27. Casaburi R, Celli B, Crapo J, et al. The COPD Biomarker Qualification Consortium (CBQC) COPD 2013; 10:367–377.