Clinical Outcome Assessments (COA) Qualification Program
DDT COA #000125: Endurance Time during the Endurance Shuttle Walking Test (ESWT)
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. Introduction and overview

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), 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 walking 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 (Gold, 2019). 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 (Gold, 2019). 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 (Maltais, 2014).

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 (Jones, 2009). 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 (Gold, 2019); 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 (Jones, 2009).

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 (Stenton, 2008), developed in the 1950s, is recommended as a primary assessment tool for the description of symptoms at time of diagnosis (Gold, 2019). Using the modified Medical Research Council scale (Williams, 2017), 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 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 (Jones, 2009). 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 (Miravitlles, 2007). 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 (Ramon, 2018). This explanatory conceptual model of the progressive limitations in physical functioning over time in COPD patients has been termed the “dyspnea-inactivity vicious cycle,” (Ramon, 2018) “disease spiral,”(Cooper, 2001) “dyspnea spiral,”(Reardon, 2006) or “downward spiral of disability” (Kawagoshi, 2015).

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?” (Dobbels, 2014) 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 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. When considered in the context of walking as a ubiquitous functional activity limitation in patients with COPD, walking endurance (the duration for which an individual is able ability to sustain walking) 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 the Endurance Shuttle Walk Test (ESWT) as a COA that provides a directly observed, objective measure of walking endurance under standardized conditions, as recommended in the International Classification of Functioning, Disability and Health (ICF) published by the World Health Organization[2] (WHO, 2002). A conceptual framework that further describes the linkage between the COA of Endurance Time during ESWT, the proximal concept of interest of walking 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 the ESWT 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 walking endurance measured as change from pre-treatment baseline in endurance time during the ESWT. 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

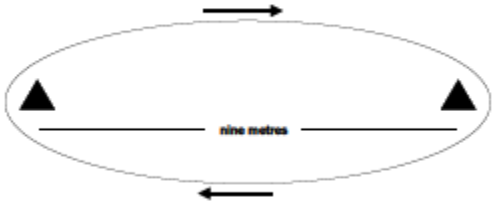
Currently, there is no qualified COA for the measurement of walking endurance; no products approved for treatment of COPD in the US have claims related to walking endurance. Following a brief description of the proposed COA, below, Section 1.2 presents a summary of other related tests that were not taken forward, because they were not considered to measure the specific concept of interest of walking endurance.

1.1.4. Brief description of COA

The ESWT is to be conducted according to previously published standards (Revill, 1999; Holland, 2014; Singh, 2014).

The ESWT is performed on a flat, straight walking course that is 10 m in length (defined as a “shuttle”) with two markers (such as cones) inset 0.5 m from either end (Figure 1). The patient walks around the markers, thus avoiding abrupt changes in direction.

Figure 1. Course Layout for the ESWT



A pre-treatment baseline ESWT is preceded by establishing an individualized peak walking speed in a preliminary incremental shuttle walk test (ISWT [Singh, 1994]). The ESWT is performed at a constant walking speed calculated as a predefined percentage of peak walking speed from the preceding ISWT. The walking speed established in the pre-treatment ESWT is used at each post-treatment time the ESWT is performed.

At the beginning of the test, instructions are played from a recording, the patient is positioned at one end of the course and a triple beep indicates the test has started. The initial stages of the test are at a slower speed and are a “warm up” for the participant (approximately 1.5 min). Participants are then paced by the operator for the first two shuttles at the pre-determined constant speed. During the test, only one verbal cue can be used to encourage the patient to pick up their speed: “You need to increase your speed to keep up with the test.” This is delivered if the patient fails to be within 0.5 m of the cone when the bleep sounds.

The test is terminated when either:

1. The patient indicates that he/she is unable to continue,
2. The operator determines that the patient is not fit to continue, or
3. The operator assesses that the patient is unable to sustain the speed and cover the distance to the cone prior to the beep sounding. The operator stops the test if the patient fails to reach the cone/marker in the time allowed. This is defined as the patient being more than 0.5 m away from the cone when the beep sounds on a second successive 10 m length. When the patient is just outside the 0.5 m marker, he/she is advised to increase the speed of walking; if the patient fails to do so, the test is terminated and the distance recorded.

At the end of the test, the time of exercise is recorded (in minutes and seconds), excluding the warm up time.

1.1.5. Rationale for use of COA in drug development

Endurance time during the ESWT is intended to be a standardized COA to assess walking endurance in clinical trials (see Section 1.2); walking endurance (the ability to sustain a walking activity) falls within the general concept of exercise endurance (the ability to sustain intense aerobic exercise or activity) and applies to a specific functional activity (walking). 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) (FDA, 2016) 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 (EMA, 2012).

The ATS/ ERS Task Force on outcomes for COPD pharmacological trials (Cazzola, 2008), 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 (Cazzola, 2008)."

In the FDA Draft Guidance for developing drugs in COPD (FDA, 2016), 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." (FDA, 2016)

A similar perspective is stated by the EMA (EMA, 2012) with the recommendation for 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 (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." (EMA, 2012)

Thus, there is general consensus that exercise endurance represents a clinically meaningful aspect of patient function in COPD; walking endurance is an important sub-category of exercise endurance specific to ambulatory activities, which are often limited in patients with COPD. Currently, no products approved for treatment of COPD in the US have claims related to walking endurance and, as such, the regulatory pathway in the US is not established (FDA, 2013). Therefore, there is a clear need to develop and qualify COAs associated with walking endurance within the framework of the FDA Drug Development Tool 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 treatment effect is beneficial to the patient. 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 walking endurance (a proximal concept of treatment benefit that can be directly observed and objectively measured). We then present the rationale for endurance time during the ESWT as an appropriate measure of walking endurance. Finally, we provide a brief overview of other potentially relevant functional assessment tests, including our rationale for the conclusion that these tests are not suitable measures of walking endurance for the proposed context of use.

1.2.1. Walking 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 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 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.

Figure 2 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; 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 respiratory response required to support lower limb activities). We have focused on lower limb activities, and more specifically ambulatory 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 concept of impaired respiratory function and muscle dysfunction. An important concept relates to the reduced physiological capacity (respiratory 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. When applied to ambulatory activities, the concept of interest “walking endurance” is regarded as a specific concept within the general concept of exercise endurance and is intended to describe the concept of the maximal ability (“capacity”) of the patient to sustain a given walking task.

The concept of walking endurance provides an appropriate link between respiratory / muscular dysfunction and limitations in physical functioning experienced by COPD patients, observed in daily life as limitations in the ability to complete ambulatory tasks.

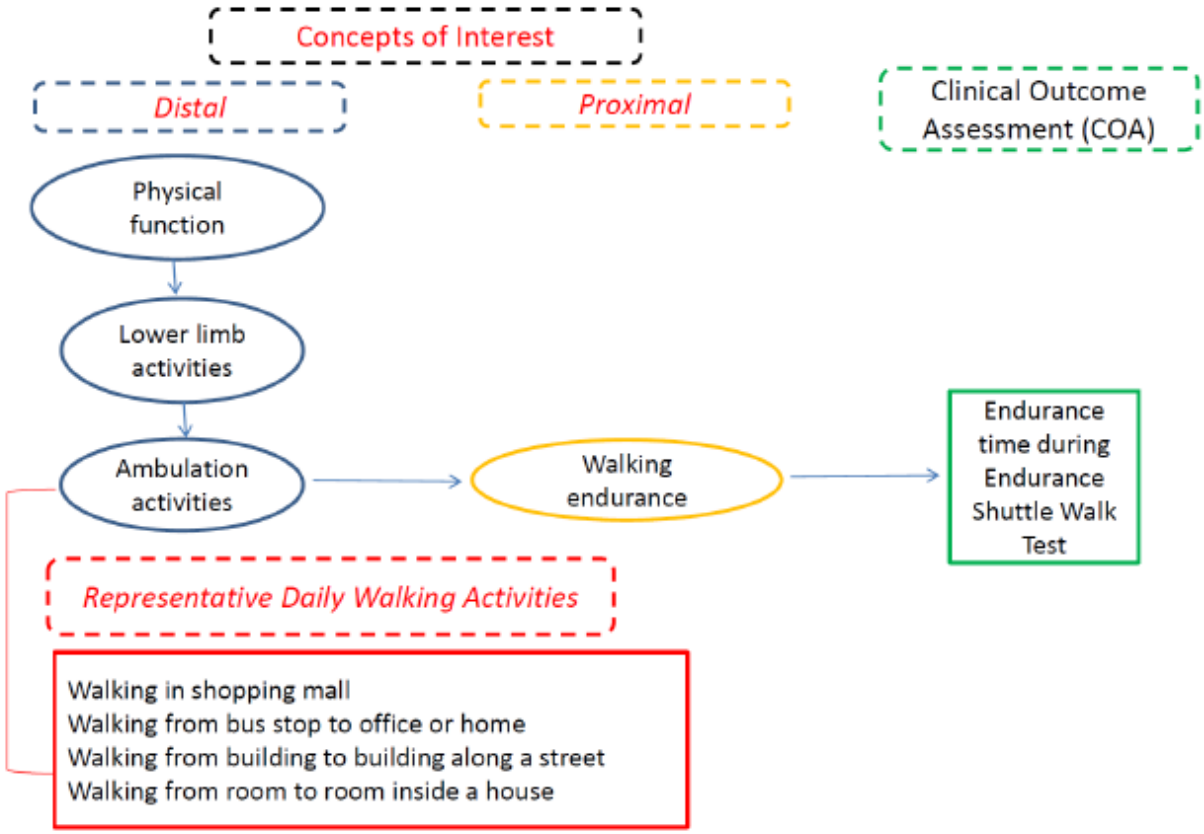


Figure 2. Conceptual relationship between the distal concept of physical function (with a specific focus on ambulatory activities), the proximal concept of walking endurance and the COA of endurance time during ESWT

1.2.2. Endurance time during ESWT: an appropriate COA for measurement of walking endurance

In the performance of ambulatory activities in daily life, patients adapt by modifying behavior in the face of increasing breathlessness (abandoning activities, pacing, slowing down, longer recovery periods). The ESWT is a constant pace walking test that requires the COPD patient to perform an activity that reflects the symptom-limited exercise intolerance experienced by patients with COPD while performing activities of daily living: the time a given task can be sustained. Importantly, the ESWT standardizes walking pace, thus avoiding the confounding influence of the behavioral adaptations seen in everyday life. The ESWT has the following important characteristics:

- A physical work task that is continued until the point of symptom limitation ("symptom-limited")
- A high intensity activity (relative to the individual's peak walking capacity) involving large muscle groups, which brings the patient to one of two interdependent physiologic limitations:
    - A limitation in pulmonary ventilation and/or gas exchange, which elicits a limiting intensity of breathlessness

- A limitation to limb muscle oxidative and glycolytic metabolism, which elicits a limiting intensity of leg muscle fatigue.

In conclusion, as a reflection of the concept of interest “walking endurance”, measurement of endurance time during the ESWT is a potentially important COA for drugs developed for COPD.

1.2.3. Walking pace during the ESWT and comparison with walking pace during daily life

In the development of the ESWT as a standardized, field assessment of endurance capacity, Revill and colleagues (Revill, 1999) investigated three endurance intensities, which were related to 75%, 85%, and 95% of individual maximal capacity. The mean walking speeds at these intensities (3.8, 4.1, and 4.4 km/h, respectively) are viewed as slow to moderate (when conducted on a level, firm surface) according to the Compendium of Physical Activities (Ainsworth, 2011):

- slow pace: walking @ 3.2 km/h [2.8 METS]
- moderate pace: walking @ 4.5 to 5.1 km/h [3.5 METS]
- brisk pace: walking @ 5.6 km/h [4.3 METS]
- very brisk pace: walking @ 6.4 km/h [5.0 METS]
- very, very brisk pace: walking @ 7.2 km/h [7.0 METS]

Based on the results of the development study, Revill and colleagues proposed an intensity related to 85% of maximum walking speed capacity as an appropriate intensity for further development. It is worth noting that for individuals with COPD this pace of walking represents a significant work rate and can only be sustained for a limited duration as an activity of daily living. A recent publication (including 513 COPD patients) reported a mean duration the ESWT of 3.25 (standard deviation [SD]=1.97) minutes (Zatloukal, 2019).

1.2.4. Brief overview of other exercise tests

In addition to the ESWT, 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. In addition to the ESWT, the task force summarized the available evidence for the following walking tests:

- laboratory-based incremental work-rate tests (motorized treadmill)
- laboratory-based constant work-rate tests (motorized treadmill)
- field tests (6-minute walking test [6MWT], ISWT

Laboratory-based incremental work rate tests (using a motorized treadmill) permit evaluation of both submaximal and peak exercise responses. Peak oxygen uptake (VO_2peak) is a key measurement during these tests and is closely reflective of the subject’s “maximum” VO_2, the gold-standard index of aerobic capacity. However, in terms of a measure of functional performance, the necessary incremental nature of the work rate regulation during the test means that the test is not representative of the type

of activity pattern performed in everyday life; it is analogous to walking up a hill that becomes steeper and steeper as the subject climbs. Furthermore, individuals do not habitually choose to perform exercise at peak WR or peak VO_2. As such, the measurement of peak work rate (i.e., the work rate associated with VO_2peak) is not a relevant measure of walking 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 and, as such, is also not a relevant measure of walking endurance within the present context.

Laboratory-based constant work-rate tests on a motorized treadmill have a similar construct to the ESWT. In contrast to the ESWT, which is conducted on level ground, treadmill walking protocols generally use a combination of walking speed and treadmill grade to select an appropriate work rate as a specific percentage of an individual's peak work rate, established during a preceding incremental treadmill test. As such, both endurance time during ESWT and endurance time during treadmill walking are considered as measures of "walking endurance"; the ESWT is specific to walking along level ground, while treadmill walking is specific to walking up a slope.

The task required of the individual performing the 6MWT is to "walk as far as possible during a 6 minute period"; 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 walking endurance, defined as "the ability to sustain a walking activity". Importantly, it has been demonstrated operationally (see below) that the 6MWT generally does not 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. Thus, while the 6MWT test focuses on ambulatory activities, which is a clinically meaningful aspect of health in patients with COPD, it is a COA that is associated with walking performance and not 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 obstruction (Gold, 2019), specifically FEV_1/forced vital capacity (FVC) <0.7.

It is anticipated that clinical trials that use the ESWT will use 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 $FEV_1/FVC < 70\%$
- 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, very severe), evidence of a ventilatory limitation to exercise (e.g., dynamic hyperinflation, low breathing reserve), evidence of activity-related breathlessness, evidence of impaired walking 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 the ESWT 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 for the evaluation of the ESWT includes rehabilitative exercise training studies, which enables comparison with pharmacologic interventions; several of these exercise training studies did not have a blinded study design and often did not include a control group.

The duration of treatment would 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 capacity. The study endpoint for the ESWT is anticipated to be defined as:

- Change from pre-treatment baseline in endurance time during the ESWT.

The primary comparison of interest (primary analysis) is anticipated to be Intervention X vs. Comparator for the ESWT. The ESWT endpoint is intended for use as either a primary, coprimary, 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.)**

The ESWT is described in Section 1.1.4. The ESWT is to be conducted according to the technical standards and user manual provided by the ERS and ATS (Singh, 2014).

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 2000s. In 2010, the COPD Biomarker Qualification Consortium (CBQC) was formed under the auspice of the COPD Foundation to undertake the qualification of new drug development tools consistent with these processes. The focus of the initial efforts of the CBQC was on qualification of plasma fibrinogen as a stratification tool (Miller, 2016) 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 (FDA, 2016). 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 tolerance, as assessed by tests such as the ESWT, is a measurement 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 (see Figure 1 in [FDA, 2016]). Within the working group for the ESWT 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.

In addition to the valuable input received during the development of this qualification package, recognized leaders in the field have also contributed to the development of the technical standards for the ESWT, which achieved consensus status by the ERS/ATS as a valid field walking test for patients with COPD.

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 walking endurance (a proximal concept of treatment benefit that can be directly observed and objectively measured). Currently, no COA is qualified for the measurement of walking endurance, and therefore, no products approved for treatment of COPD in the US have claims related to walking endurance. Walking endurance,

specifically, the ability to sustain a walking activity, falls within the general concept of exercise endurance (the ability to sustain intense aerobic exercise or activity) and applies to a specific functional activity (walking).

As described in this Qualification Plan (QP), Endurance Time during the ESWT is shown to be a COA that provides a directly observed, objective measure of walking endurance under standardized conditions. As specified in previously published standards, the ESWT is performed on a flat, straight walking course that is 10 m in length with two markers inset 0.5 m from either end that the patient walks around. For each patient, an individualized peak walking speed is established in a preliminary ISWT, after which a pre-treatment baseline ESWT is performed at a constant walking speed calculated as a predefined percentage of peak walking speed from the preceding ISWT. The walking speed established in the pre-treatment ESWT is used at each posttreatment time the ESWT is performed. The test continues until the patient indicates that he/she is unable to continue, the operator determines that the patient is not fit to continue, or the patient is unable to sustain the speed and cover the distance.

Endurance Time during the ESWT 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 walking endurance measured as change from pre-treatment baseline in endurance time during the ESWT.

References:

Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc. 2011;43(8):1575-81.

Cazzola M, MacNee W, Martinez FJ, et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J. 2008;31:416–68.

Cooper CB. Exercise in chronic pulmonary disease: limitations and rehabilitation. Med Sci Sports Exerc 2001;33:S643-6.

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.

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).

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.

Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44:1428–46.

Jones P, Harding G, Wiklund I, et al. Improving the process and outcome of care in COPD: development of a standardised assessment tool. Primary Care Respiratory J. 2009;18(3):208-215.

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. Respiratory Medicine. 2015;109(3):364-71.

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.

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).

Miravitlles M, Anzueto A, Legnani D, et al. Patient's perception of exacerbations of COPD – the PERCEIVE study. Respir Med 2007;101:453–460.

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(3):pii: 1800079.

Reardon JZ, Lareau SC, ZuWallack R. Functional Status and Quality of Life in Chronic Obstructive Pulmonary Disease. The American Journal of Medicine. 2006 119(10 Suppl 1):s32-7.

Revill 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.

Singh SJ, Morgan MDL,Hardman AE,et al. Comparison of oxygen uptake during a conventional treadmill test and the shuttle walking test in chronic airflow limitation. Eur Respir J. 1994;7:2016–20.

Singh SJ, Puhan MA, Andrianopoulos V, et al. An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. Eur Respir J. 2014;44:1447–78.

Stenton C. The MRC breathlessness scale. Occupational Medicine. 2008;58:226–227.

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.

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).

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.

Williams N. The MRC breathlessness scale. Occupational Medicine 2017;67(6):496–97.
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

Zatloukal J, Ward S, Houchen-Wolloff L, et al. The minimal important difference for the endurance shuttle walk test in individuals with chronic obstructive pulmonary disease following a course of pulmonary rehabilitation. Chron Respir Dis. 2019;16:1479973119853828.