Physical activity end-points in trials of chronic respiratory diseases: summary of evidence

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Physical activity (PA) is a challenging domain to measure accurately. Patient-centric measures have been developed for the COPD population; however, the appropriateness of PA measures used in asthma and IPF populations remains sporadic and controversial. https://bit.ly/3HmmaGp

Cite this article as: Rist C, Karlsson N, Necander S, *et al*. Physical activity end-points in trials of chronic respiratory diseases: summary of evidence. *ERJ Open Res* 2022; 8: 00541-2021 [DOI: 10.1183/23120541.00541-2021].

Received: 6 Sept 2021
Accepted: 19 Jan 2022

Abstract

Background Physical activity contributes to improving respiratory symptoms. However, validated end-points are few, and there is limited consensus about what is a clinically meaningful improvement for patients. This review summarises the evidence to date on the range of physical activity end-points used in COPD, asthma and idiopathic pulmonary fibrosis (IPF) whilst evaluating their appropriateness as end-points in trials and their relation to patients' everyday life.
Methods Trials reporting physical activity end-points were collected using Citeline's database Trialtrove; this was supplemented by searches in PubMed.
Results The daily-patient-reported outcome (PRO)active and clinical visit-PROactive physical activity composite end-points appeared superior at capturing the full experience of physical activity in patients with COPD and were responsive to bronchodilator intervention. Time spent in moderate-to-vigorous physical activity is a recently validated end-point for IPF that correlates with exercise capacity and quality of life. Step count appears the best available physical activity measure for asthma, which consistently declines with worse disease status. However, evidence suggests a time lag before significant improvement in step count is seen which may reflect the impact of human behaviour on physical activity.
Conclusions Physical activity represents a challenging domain to accurately measure. This is the first review evaluating physical activity measures used specifically within the respiratory field. Whilst physical activity can be effectively captured using PROactive in patients with COPD, this review highlights the unmet need for novel patient-focused end-points in asthma and IPF which would offer opportunities to develop efficacious medicines with impact on patients' therapeutic care and quality of life.

Introduction

Physical activity is defined as "any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level" [1]. It is important to distinguish physical activity from exercise, and subsequently separate measures of exercise capacity from assessments of physical activity [1]. Beyond exercise, physical activity includes everyday activities such as leisure-time, domestic, transportation and occupational activities [1]. The ability to meet the physical requirements of daily life is imperative in disease management and an important aspect of health-related quality of life, both in healthy and disease settings [2, 3]. However, there is limited consensus what a meaningful measure in physical activity is for patients with respiratory diseases.

Over the past decades, it has been widely accepted that physical activity improves worsening of respiratory symptoms [4]. Consistent evidence has linked low levels of physical activity with increased frequency of exacerbations and mortality in patients with COPD [5]. There is accumulating evidence that increasing physical activity improves asthma control, reduces exacerbation rates and healthcare utilisation [6]. Despite its importance, physical activity is an often-overlooked interventional method to optimise asthma management strategies. Research into the implications of idiopathic pulmonary fibrosis (IPF) on physical activity is largely sparse and exploratory. However, fatigue is increasingly documented by IPF patients [7], which may lead to reduced physical activity. The respiratory symptoms experienced by patients with COPD, asthma and IPF are similar, despite differences in the underlying pathogenesis [8]. Patients with respiratory diseases are often subject to a vicious downward cycle comprising reduced lung function, a worsened clinical presentation of dyspnoea, reduced physical activity, deconditioning of muscle mass, reduced exercise capacity and ultimately disability or mortality [9]. Patients with severe respiratory conditions often complain of breathlessness, and limited exercise capacity, which hinder physical abilities, such as basic daily activities, and social interactions [9]. To address these complaints, firstly, physical activity end-points sensitive to improvements by efficacious drugs need to be identified, whilst indicating improvements in dyspnoea, exercise limitation and disease severity. This would then enable the discovery of medicines with the greatest impact on physical activity and quality of life for the patient.

The aim of this review is to investigate the use of physical activity measures in respiratory clinical trials to date, evaluating the most prevalent physical activity measures for their appropriateness as end-points in trials and how they relate to patients' everyday lives. This may allow clinicians to assess which end-point may be of most relevance to patients with respiratory disease and thus optimal to use in clinical trials going forward. Additionally, this will highlight where the unmet needs for novel relevant physical activity end-points are within the clinical landscape.

Search strategy and overview of the outcomes

To evaluate physical activity measures with a focus on patient relevance, the variety of end-points was first assessed using Citeline's database Trialtrove (a database, constantly updated, covering the entire public domain using major – and over 40 000 unique information sources – *i.e.* trial registries, portals, PubMed; figure 1). We searched for the terms "Trial Title contains Physical Activity" OR "Trial Title contains exercise" OR "End-point is Daily Physical Activity" OR "Primary End-point contains Physical Activity". It is noteworthy that the inclusion criteria included "Trial title contains Exercise": frequently studies claim to measure exercise when they record daily physical activity levels through end-points such as steps per day. To prevent inclusion of studies truly measuring exercise and endurance, any exercise intervention or exercise challenge studies were then manually excluded from the search results (figure 1). For each indication, the top two to four most frequently used end-points were cross-compared using resources from Trialtrove, supplemented with primary literature found through end-point-specific Google Scholar and PubMed searches. The choice of end-point comparison was owing to the availability of evidence relating to each end-point, with both time and resource limitation taken into consideration. The end-points were compared across multiple factors, including their construct and content validity. Construct validity refers to ensuring the end-point measures what it claims to be measuring, whereas content validity ensures the end-point is measuring appropriate content.

The search criteria returned 15 studies in patients with COPD, 6 in patients with asthma and 2 in patients with IPF (table 1). The COPD studies identified were published between 2007 and 2018, whereas the asthma and IPF studies were published more recently, between 2017 and 2018 and between 2018 and 2019, respectively. Step count was used most frequently across all the indications, appearing in 16 out of 23 clinical trial results. This was followed by time spent in moderate-to-vigorous physical activity (MVPA) in 10 out of 23 clinical trials, the 6-min walk distance (6MWD) in 9 studies and activity-related energy expenditure (AEE) in 5 studies. Two novel instruments have been used specifically in patients with COPD: the daily-patient-reported outcome (PRO)active and clinical visit-PROactive physical activity (D-PPAC and C-PPAC). D-PPAC and C-PPAC are hybrid instruments which combine a patient-reported outcome (PRO) with accelerometer-derived data, to capture the amount of physical activity and patient experience during activity [10]. Both instruments were developed and validated specifically within the COPD patient population. Other end-points used included time spent in light physical activity, sedentary time, active time, "healthy lifestyle", duration of exercise, intensity of exercise and time spent in degrees of activity as determined by the metabolic equivalent of task (METs). The variety and inconsistency of end-points used reflects the unmet need for relevant and validated physical activity measures for use in clinical trials.

Assessing physical activity in patients with COPD

The European Medicines Agency (EMA) qualified both D-PPAC and C-PPAC as suitable instruments to capture physical activity experience in patients with COPD and are supported as end-point use in clinical trials [11]. Both instruments demonstrate strong construct validity, content validity, with scores reflecting

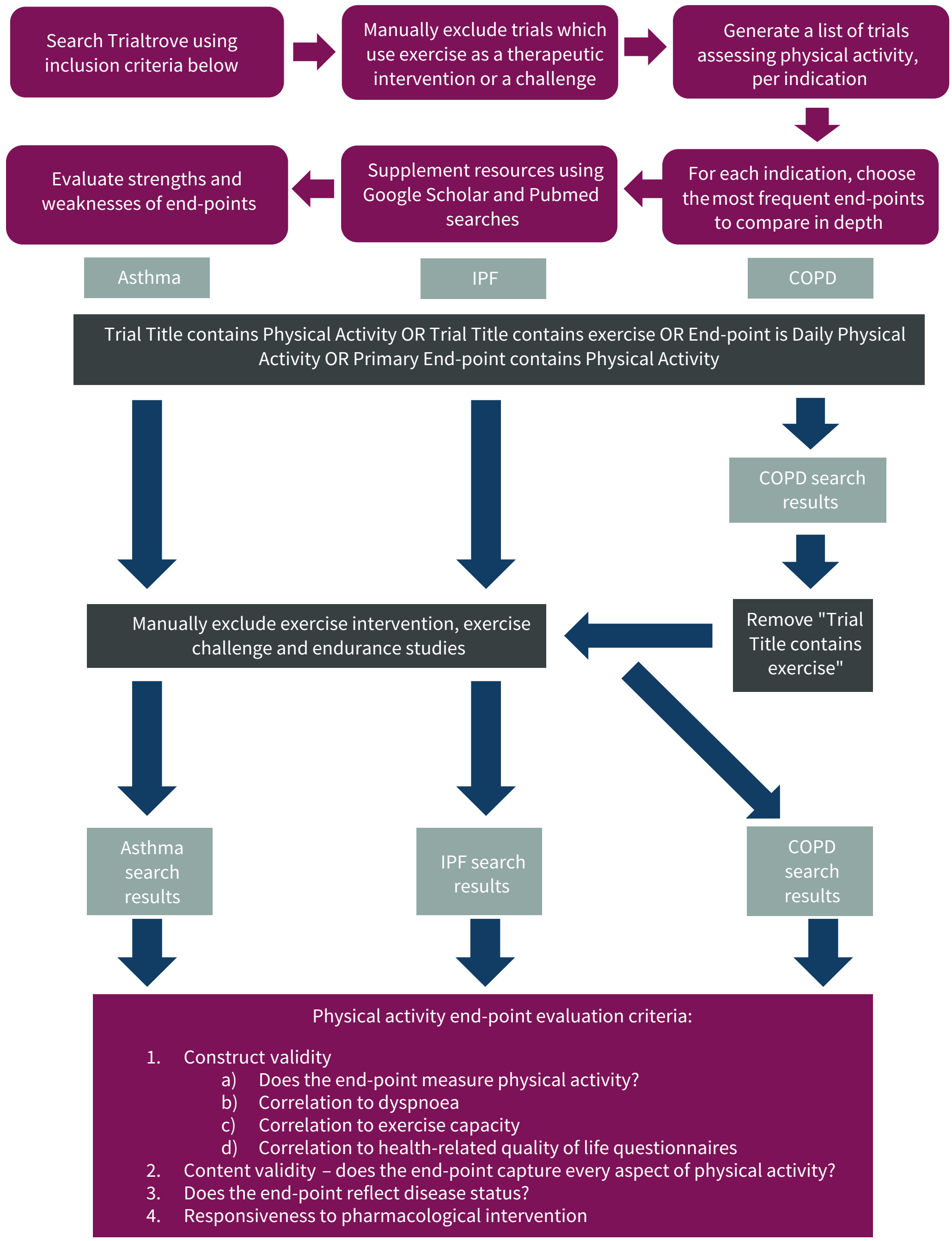

FIGURE 1 Search strategy diagram. Workflow to assess landscape of end-points which assess physical activity in respiratory trials; details of inclusion/exclusion criteria used for Trialtrove searches; and end-point evaluation criteria. IPF: or idiopathic pulmonary fibrosis.

COPD status, positively affected by bronchodilator therapy, and negatively affected by exacerbations (table 2) [10]. Additionally, out of 1595 patients who participated in 7 validation studies, 83% of patients produced sufficient data from both accelerometer (8 h wearing time on at least 3 days across 1 week recording) and respective questionnaires, confirming sufficient acceptability from a patient perspective, across multiple nations, disease severities and languages [10].

TABLE 1 Out of 23 clinical trials measuring physical activity in COPD, asthma or idiopathic pulmonary fibrosis (IPF) studies; step count, time spent in moderate-to-vigorous physical activity (MVPA), 6-min walk distance (6MWD) and activity-related energy expenditure (AEE) were the measures used most frequently

Indication	Protocol/trial identification	Completion	Physical activity measure(s)	Number of patients/ patient target
COPD	NCT00523991	Complete	Time spent in light physical activity Time spent in MVPA AEE Step count Healthy lifestyle (30 min of activity >3 metabolic equivalent levels for 70% of eligible days)	457
COPD	jRCTs071180021	Complete	Sedentary time (METs 1–1.5) Time in METs >2 Time in METs >3 6MWD	80
COPD	NCT01783808	Complete	No specified end-point. "Physical activity level measured with accelerometer and questionnaire" 6MWD	144
COPD	NCT02205242	Complete	Step count Time in MVPA Sedentary time (lying, sitting) Active time (standing, locomotion, shuffling)	60
COPD	NCT03357341	Complete	Step count Median daily activity level based on vector magnitude counts C-PPAC	98
COPD	NCT03359473	Complete	No specified end-point, measured using triaxial accelerometer 6MWD	80
COPD	NCT03123692	Complete	Daily physical activity – no specified end-point 6MWD	12
COPD	NCT03123692	Complete	Step count Time active AEE	171
COPD	NCT02629965	Complete	Step count 6MWD Time in >4 METs Time in >3 METs Time in >2 METs	180
COPD	NCT02424344	Complete	Step count D-PPAC	269
COPD	NCT02153489	Complete	Step count Time in MVPA	30
COPD	NCT02085161	Complete	6MWD PROactive Daily walking time Daily walking intensity	304
COPD	NCT01996319	Complete	AEE Step count Time in at least light physical activity	194
COPD	PMC3534442	Complete	6MWD Step count Time in MVPA AEE	23
COPD	NCT01012765	Complete	Step count Time in MVPA	173
Asthma	NCT04724278	Incomplete	Step count Duration of exercise per day Intensity of exercise per day	50
Asthma	NCT04203797	Incomplete	Step count AEE Time in MVPA	140
Asthma	NCT04195958	Incomplete	Physical activity min per day – no specified end-point	60
Asthma	NCT04184284	Incomplete	Step count	500

Continued

TABLE 1 Continued

Indication	Protocol/trial identification	Completion	Physical activity measure(s)	Number of patients/ patient target
Asthma	NCT03739320	Complete	Daily moving time Daily moving intensity Time in MVPA Step count	50
Asthma	NCT03357341	Complete	Step count Daily activity levels based on vector magnitude units	96
IPF	NCT03717012	Complete	6MWD Daily accelerometer activity – no specified end-point	290
IPF	NCT03737409	Incomplete	Step count 6MWD Time in MVPA Sedentary time	260

METs: metabolic equivalent of task; D-PPAC and C-PPAC: daily-patient-reported outcome (PRO)active and clinical visit-PROactive physical activity.

In comparison, step count displays some aspects of construct validity such as correlations to dyspnoea and exercise capacity [12, 13], but an inconsistent relationship with health-related quality of life questionnaires (HRQoL) [12, 14]. Content validity is poor, as it cannot portray intensity of activity nor patient experience during daily activities. Step count does however show sensitivity to severity of COPD [12] and improvement following pharmacological intervention [13, 15, 16]. The 6MWD has commonly been used as a surrogate end-point for physical activity prior to introduction of pedometers and commercialisation of activity monitors. Despite the fact the 6MWD captures functional capacity and not daily activity (demonstrating poor content validity), it remains a popular end-point within respiratory research to indicate patient activity levels. 6MWD shows some correlation with levels of dyspnoea [17] and HRQoL [18], inverse correlation with disease severity [18] and sensitivity to therapeutic intervention [15, 17].

Assessing physical activity in patients with asthma

In contrast to the COPD population, less work has thus far been conducted in patients with asthma with respect to physical activity. The majority of studies have utilised the end-points step count and time spent in MVPA (table 3). Of the two end-points, step count offers more advantages: it is an intuitive end-point, easily understood by patients, and easily assessed by wearable user-friendly gadgets. Fundamentally, step count is an important measure owing to the fact that patients with asthma do not complete the recommended 10 000 daily steps per day and the consistent (but limited) findings that step count declines with worsening disease status [8, 21, 22]. Step count is responsive to intervention, specifically improving with anti-5 therapy [23]. Furthermore, step count associates with dyspnoea and exercise capacity [8], two end-points which significantly impact quality of life. Conversely, step count can be viewed as a crude representation of physical activity which is impacted by occupation and does not at first glance reflect patient experience. However, recent evidence may suggest otherwise; in 2020, Neale and colleagues [24] showed that step count in patients with asthma is inversely correlated with HRQoL.

The concept of measuring time spent in MVPA by patients is meaningful and perhaps has potential to be a clinically useful physical activity end-point. Increasing the time spent in MVPA has endless physical, mental and social benefits for patients, and largely this end-point is not impacted by occupation. Unfortunately, the initial studies present inconsistent findings. Firstly, the raw values of time spent in MVPA by both asthma and healthy populations varies substantially between studies [8, 22, 24]. Secondly, time spent in MVPA is not significantly different between asthma and healthy populations in the studies describing it, once adjusting for confounding factors, such as in a study by Bahmer and colleagues in 2017 [22]. Finally, there are no data available looking at the effect of treatment on time spent in MVPA in patients with asthma.

Assessing physical activity in patients with IPF

There are few clinical trials that have investigated physical activity in patients with IPF (table 4). Patients are reportedly completing 2728±2475 steps per day on average, a variation in steps almost as large as the step count itself [26]. A study by Nakayama and colleagues in 2015 [27] found that patients averaged 6520 steps per day, and that during the monitoring period over 1 month, there was no significant day-to-day variation. Both studies show that IPF patients complete less steps than the recommended 7000

TABLE 2 Evaluation of the daily-patient-reported outcome (PRO)active and clinical visit-PROactive physical activity (D-PPAC and C-PPAC) instruments against Step Count and 6-min walk distance (6MWD) to assess physical activity in patients with COPD

	C-PPAC, D-PPAC (PROactive)	Step count	6MWD
Construct validity			
1. Does the end-point measure physical activity?	Scores for "amount of physical activity" and "difficulty during physical activity" showed good internal consistency and construct validity across sex, age, COPD severity, countries and languages [10] EMA supports C-PPAC & D-PPAC as end-points to measure physical activity in COPD [11]	Good indicator of day-to-day activity in healthy subjects; however, pure step count cannot indicate relative effort required to complete steps in subjects with respiratory diseases Subject to seasonal variation and potentially skewed by occupation [12]	Historically the most used field test to assess functional capacity Surrogate for physical activity prior to introduction of activity monitors Limited functional capacity indicates muscle depletion caused by physical inactivity [19] The test is self-paced and therefore subject to motivational effects
2. Correlation to dyspnoea	Pooled data showed "difficulty during physical activity" scores correlated moderately to strongly with dyspnoea [10]	21 days of fixed dose combination LABA/LAMA therapy reduced lung hyperinflation as measured by inspiratory capacity. This was accompanied by a significant increase in step count [16] mMRC score was weakly associated with daily step count of patients [12]	8 weeks of dual bronchodilator therapy elicited a reduction in dyspnoea intensity experienced during the 6MWD [17]
3. Correlation to exercise capacity	Pooled data showed "amount" scores from both D-PPAC and C-PPAC moderately correlated with exercise capacity. Difficulty scores showed moderate-to-strong correlations with exercise capacity [10]	Bronchodilator therapy improved step count and was accompanied by improvements in exercise capacity during constant cycle ergometry [13] 6MWD weakly correlated with daily step count of patients [12]	Inherently an end-point used to indicate exercise capacity and therefore an exact correlation to exercise capacity
4. Correlation to HRQoL	Pooled data showed "difficulty" scores had moderate-to-strong correlations with HRQoL [10]	A 4-month pedometer-based exercise programme, which improved step count, improved SGRQ by the minimum clinically important difference [14] SGRQ was not found to be associated with daily step count [12]	Significant negative correlation between 6MWD and HRQoL, as measured by SGRQ symptoms domain, SGRQ impact domain and the SGRQ total score [18]
Content validity			
1. Does the end-point capture every aspect of physical activity?	The wide distribution of scores for all domains supports the use of these instruments to capture the diversity of amount and difficulty experienced during physical activity by patients with COPD. Qualitative and quantitative data from development and validation studies of both instruments support the hypothesis that amount and difficulty are two different dimensions of physical activity experience [10]	Poor indicator of vigorous activity (crucial for long-term health) Poorly reflects patient experience, cannot indicate any pain experienced during essential mobility	Exercise capacity comprises only one of the important dimensions which determine physical activity Behaviours and environmental factors play huge roles in the amount and frequency of physical activity performed by people; exercise capacity does not directly translate to physical activity
2. Reflects respiratory disease state	All D-PPAC and C-PPAC scores differentiated across severity of COPD [10] Instruments detected negative impacts on physical activity in patients who experienced exacerbations in the follow-up period [10]	Average step count decreased with increasing GOLD stage [12] Completing an additionally 1000 steps at a low intensity corresponds to a 20% reduction in the risk of hospitalisations [20] An improvement of daily step count by 780 (as facilitated by a	6MWD is inversely correlated with severity of COPD [18]

Continued

TABLE 2 Continued

	C-PPAC, D-PPAC (PROactive)	Step count	6MWD
	"Amount", "difficulty" and total scores derived from D-PPAC and C-PPAC vary fittingly to patients with a range of clinical characteristics [10] The wide distribution of scores for all domains supports the use of these instruments to capture the diversity of amount and difficulty experienced during physical activity by patients with COPD [10]	4-month pedometer-based programme) was associated with significant improvements in health status of patients [14] Decline in average step count by 393 seen annually in patients with COPD monitored over 3 years, independent of COPD severity at baseline [19]	
3. Responsiveness to pharmacological intervention	ACTIVATE and PHYSACTO studies showed improvements in D-PPAC difficulty score following bronchodilator treatment [10]	21 days of fixed dose combination LABA/LAMA therapy improved step count in moderate-to-severe COPD patients by an average of 358 steps [16] Short-term LABA therapy improved daily step count by an average of 1616 steps [15] Short term dual bronchodilator therapy improved step count by approximately 10% [13]	4 weeks of LABA therapy improved 6MWD by an average of 24.7 m [15] 8 weeks of dual bronchodilator therapy improved 6MWD by 21 m [17]

EMA: European Medicines Agency; LABA/LAMA: long-acting β2-adrenoreceptor agonist/long-acting muscarinic receptor antagonist; mMRC: modified British Medical Research Council questionnaire; HRQoL: health-related quality of life questionnaire; SGRQ: Saint George's Respiratory Questionnaire; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

per day for older adults, and other studies show initial indications of associations between step count and clinically important end-points such as serum Krebs von den Lungen (KL)-6 [27], dyspnoea [28], lung function measures [28], HRQoL [28] and 6MWD [26–28].

Time spent in MVPA was recently approved by the Food and Drug Administration (FDA) as a Phase III primary end-point in Bellerophon Therapeutics Inc's study investigating the inhaled nitric oxide treatment of pulmonary hypertension associated with interstitial lung disease, confirming the validity of MVPA as a clinically meaningful end-point [29]. This was due to the positive results reported from cohort 1 of their ongoing Phase 2b/3 study, where patients on active treatment demonstrated a 34% placebo-adjusted improvement in MVPA after 8 weeks [29]. It is noteworthy that this Phase 2b/3 study also measured step count, but the largest difference in activity between treatment arms was shown through MVPA. A study by Hur and colleagues in 2018 estimated that an increase of MVPA by 26 min a week is a realistic but beneficial goal for patients with fibrotic interstitial lung disease; this study included a subset cohort of IPF patients. Time in MVPA has proven to correlate with exercise capacity in patients with IPF [30] and HRQoL [31].

AEE is the relative energy expended to perform a task above resting metabolism [26]. AEE recorded in IPF patients is significantly less than expended in healthy controls, averaging 133±127 kcal per day in IPF patients compared to 201±111 kcal per day in healthy controls [26]. AEE has been shown to be correlated with 6MWD and survival of IPF patients [26], dyspnoea and serum KL-6 [27]. Two papers measuring 6MWD in IPF patients have shown the end-point's unsuitability as a surrogate marker for physical activity, as it accounts for a low percentage of the variance observed in step count [28, 32]. There is initial data suggesting that 6MWD associates with dyspnoea and quality of life [28], and predicts mortality [32]. However, there are no published data to suggest 6MWD reflects IPF severity or treatment response.

Discussion

The patient-centric trend within the healthcare sector is causing a paradigm shift in which we are moving beyond disease treatment towards disease management and prevention. This reshaping of the healthcare sector calls for change in several aspects of the drug development process. We can no longer view the patients' perspective through the lens of a physician or regulator, requiring novel patient-focused end-points which incorporate the patients' voice and seeks to address patient-identified outcomes.

TABLE 3 Evaluation of step count and time spent in moderate-to-vigorous physical activity (MVPA) to assess physical activity in patients with asthma

	Step count	Time in MVPA
Construct validity		
1. Does the end-point measure physical activity?	Most common end-points used to assess physical activity in patients with asthma Good indicator of day-to-day activity in healthy subjects; however pure step count cannot indicate relative effort required to complete steps in subjects with respiratory diseases Subject to seasonal variation and potentially skewed by occupation [12]	Captures moderate-to-intense activities. Useful end-point to capture as people with asthma intuitively avoid intense exercise to avoid exercise-induced bronchoconstriction [36] Patients' long-term habits may prevent an improvement in MVPA despite efficacious treatment Substantial variability in results between subjects and between studies: with averages ranging between 22.3 min per day and 125 min per day for patients with severe asthma [8, 22, 24]
2. Correlation to dyspnoea	Step count is correlated with dyspnoea [8]	MVPA correlated with dyspnoea [8]
3. Correlation to exercise capacity	100-m increase in 6MWD equals to an increase of 1500 steps [8]	MVPA independently correlated with 6MWD [8]
4. Correlation to HRQoL	The reduced step count completed by patients with severe asthma *versus* healthy controls was associated with a worse HRQoL, as measured by EuroQoL, Chronic Respiratory Questionnaire and Asthma QoL Questionnaire [24]	Both total time in MVPA and time spent doing sustained bouts of MVPA was positively associated with HRQoL measures [24]
Content validity		
1. Does the end-point capture every aspect of physical activity?	Step count is a poor indicator of vigorous activity (crucial for long-term health) End-point poorly reflects patient experience, cannot indicate any pain experienced during essential mobility	Doesn't capture majority of daily movement, *e.g.* walking
2. Reflects respiratory disease state	Patients with severe asthma (averaging 5385 steps) are less active than the healthy control cohort (median of 2270 less steps) [8] Severe asthmatic patients averaged 6174 steps. Patients with mild-to-moderate asthma performed significantly better with 7831 steps ($p<0.001$), and healthy controls averaged better still with 8912 steps [22] Both studies found the differences in step count between cohorts to be significantly different once adjusting for confounding factors [8, 22] Step count is a reliable long-term marker for asthma control – persistent uncontrolled asthmatic patients averaged 6614 steps at baseline, 6195 steps at follow-up 2 years later. Patients with controlled asthma averaged 8670 and 9058 at baseline and follow-up respectively. This is a sustained difference of at least 2000 steps [21]	Patients with severe asthma spend less time in MVPA than healthy controls, at 22.3 min per day and 42 min per day, respectively [8] Patients with severe asthma spent less time doing sustained (>10-min bouts) of MVPA a day than healthy controls [24] There was no significant difference in MVPA between patients with severe asthma and healthy controls, once adjusting for age, sex, obesity and smoking [22]
3. Responsiveness to pharmacological intervention	12 months of anti-IL-5 therapy in 13 patients with severe eosinophilic asthma improved step count by 14% [23]. 12 months of biologic (mepolizumab/ omalizumab) therapy in patients with severe asthma improved physical activity, measured by step count and total energy expenditure [25]	No data available

6MWD: 6-minute walking distance; HRQoL: health-related quality of life questionnaire; EuroQoL: European Quality of Life Scale; QoL: quality of life questionnaire; anti-IL-5: anti-interleukin-5.

The PROactive consortium produced validated tools accepted by a diverse range of countries, ages and disease severities. These novel instruments are first of their kind, measuring the experience of physical activity in patients with COPD as a bi-dimensional concept and showed strong correlations to dyspnoea and exercise capacity, the two main complaints voiced by patients with COPD. Further attempts to measure physical activity in either asthma or IPF should adopt a similar approach to PROactive, whereby

TABLE 4 Evaluation of step count, time spent in moderate-to-vigorous physical activity (MVPA) and activity-related energy expenditure (AEE) to assess physical activity in patients with idiopathic pulmonary fibrosis (IPF)

	Step count	Time in MVPA	AEE	6-min walk distance (6MWD)
Construct validity				
1. Does the end-point measure physical activity?	Most common end-points used to assess physical activity in patients with IPF Good indicator of day-to-day activity in healthy subjects; however, pure step count cannot indicate relative effort required to complete steps in subjects with respiratory diseases Subject to seasonal variation and potentially skewed by occupation [12]	Captures moderate–intense activities. Useful to capture as patients with IPF intuitively avoid intense exercise to avoid exercise-induced bronchoconstriction Patients' long-term habits may prevent an improvement in MVPA despite efficacious treatment	Relative energy expended to perform a task above resting metabolism	Historically the most used field test to assess functional capacity Surrogate for physical activity prior to introduction of activity monitors Despite 6MWD being a strong predictor of reduced step count in IPF patients in two studies, the end-point only accounted for 42% and 31% of the step count variance, respectively, indicating this end-point is not a good surrogate for daily physical activity [28, 32] Limited functional capacity indicates muscle depletion caused by physical inactivity [19] The test is self-paced and therefore subject to motivational effects
2. Correlation to dyspnoea	Step count correlated with dyspnoea, patients with an mMRC >2 averaged 1900 steps per day, a 70% reduction compared to patients with mild dyspnoea (mMRC <2) [28]	No data available	AEE associated with dyspnoea score [27, 33]	Patients with a poor 6MWD completed a similar step count to patients with low mMRC [28]
3. Correlation to exercise capacity	Step count correlated with 6MWD [26, 27]	Time in MVPA correlated with 6MWD in 17 IPF patients [30]	AEE correlated with 6MWD in patients with IPF [26, 27]	Inherently an end-point used to indicate exercise capacity
4. Correlation to HRQoL	Step count correlated with HRQoL [28] Step count did not correlate with SGRQ and HADS score, which indicates HRQoL and anxiety/depression, respectively, within IPF cohort [26]	Time in MVPA showed moderate-to-strong correlations with the EQ-5D index score in 111 patients with fibrotic interstitial lung disease [31]	No data available	Patients with a poor 6MWD completed a similar step count to patients with low QoL (12-Item Short Form Survey, SF-12) [28]
Content validity				
1. Does the end-point capture every aspect of physical activity?	Poor indicator of vigorous activity (crucial for long-term health)	Doesn't capture majority of daily movement, *e.g.* walking	Captures energy expended during physical activity in a day	Exercise capacity comprises only one of the important dimensions which

Continued

TABLE 4 Continued

	Step count	Time in MVPA	AEE	6-min walk distance (6MWD)
	Poorly reflects patient experience, cannot indicate any pain experienced during essential mobility			determines physical activity Behaviours and environmental factors play huge roles in the amount and frequency of physical activity performed by people; exercise capacity does not directly translate to physical activity
2. Reflects respiratory disease state	Patients averaged a daily step count of 2728±2475, significantly fewer than the healthy cohort at 5953 ±3578 [26] Step count associated with lung function measures such as FVC % predicted normal value and D_{LCO} % predicted normal value [28]	No data available	Patients averaged 133 ±127 kcal·day^{-1}, whilst healthy controls expended 201±111 kcal·day^{-1} [26]	No data available
3. Responsiveness to pharmacological intervention	No data available	Inhaled nitric oxide improved MVPA by 34% in patients with IPF [29]	No data available	No data available
4. Impact on survival	Step count correlated with serum KL-6, an important predictor of survival in IPF [27, 33]	No data available	Following adjustment for the prognostic factors age, sex and % FVC, AEE was the only end-point significantly associated with survival of IPF patients [26] AEE associated with serum KL-6 [27]	6MWD significantly and independently predicted mortality, with a 6MWD of >360 m having an 80% survival probability after 30 months [32]

mMRC: modified British Medical Research Council questionnaire; HRQoL: health-related quality of life questionnaire; EQ-5D: European Quality of Life Five Dimension; QoL: quality of life; SGRQ: Saint George's Respiratory Questionnaire; HADS: hospital and anxiety depression score; FVC: forced vital capacity; D_{LCO}: diffusion capacity for carbon monoxide; QoL: quality of life.

thoughtfully designed trials can endure scrutiny, prevent time and resource wasting and facilitate consistency in data. Novel instruments must be developed based upon a conceptual framework to follow FDA best practice, and a patient-centred methodology should be used to develop outcome assessments, where the patients' voice is central to the work of clinical experts in the respective therapeutic area. Patient-reported outcome item selection should address an unmet need for assessments that directly measure or indirectly reflect an aspect of the disease or illness which, if relieved, improved or prevented, is meaningful for patients. Careful consideration over any accompanying activity monitor should be taken so that it is validated against the correct disease assessed, comfortable to wear for the specified length of time and easy to use by the relevant population, ideally uploading data automatically to mobile applications or clinical trial systems to facilitate decentralised trials.

The influence of behaviour and motivational factors on physical activity is a major limitation of traditional one-dimensional end-points such as steps per day and time spent in MVPA. The engrained behaviours of patients pose the risk of hindering transition into a more active lifestyle, despite efficacious treatment. Behaviour, in addition to the multitude of other variables which affect physical activity, such as disease severity, body mass index, season and comorbidities, may be the root of high variability of MVPA baseline values observed among asthmatic patients. Consequently, individual improvements observed in MVPA across a cohort of patients tend to have a lower statistical significance. Additionally, it is plausible to think there can also be a time lag between treatment efficacy and a significant improvement in frequency or intensity of activity, potentially reflecting a personal adjustment of a patient's habits over time. For example, recent studies showed anti-interleukin-5 (IL-5) therapy increasing lung function in patients with severe eosinophilic asthma as early as 3 months, and positive impacts on patient-reported outcomes as early as 3 days after initial treatment [34, 35]. Yet, when investigating efficacy on physical activity in patients with severe asthma, a significant improvement in step count was only apparent after 12 months and 6 months of anti-IL-5 treatment, respectively [23, 25].This suggests that measuring physical activity in patients with asthma may be more relevant in trials of longer duration (Phase 3 and 4) and thus not a viable efficacy measure for early clinical development (*i.e.* Phase 2). Nonetheless, in considering patients with chronic respiratory diseases, improving levels of physical activity should remain a vital part of respiratory disease management.

Conversely, behaviour can be harnessed to encourage improvements in physical activity using motivational tools and individualised targets. The PHYSACTO PROactive study [17] tested the rationale that behaviour modification is a pre-requisite to improving daily physical activity levels in patients. The paper concluded that a 12-week self-management behaviour-modification programme exhibited a clinically meaningful improvement in step count by 20%, without bronchodilator therapy [17]. The combination of pharmacological intervention with behavioural therapy to improve activity levels may be a useful strategy to uncover benefits for patients, whilst setting a foundation for a more active lifestyle.

When trials are contemplating assessing physical activity, one should carefully consider which specific outcome to measure. More specifically, is the aim to measure an aspect of daily physical activity, or exercise capacity? Research has largely concerted its efforts into evaluating exercise capacity through endurance tests such as the 6MWD; however, it is only over the past decades that research has moved on to assessing physical activity. Physical activity is a multifactorial concept, where a patient's willingness to engage is paramount. This willingness is determined by a complex interplay of motivation, environmental factors, perception of exercise-related symptoms, past experiences and confidence in fitness capabilities. As maximal exercise performance does not sufficiently correlate with daily physical activity [36], measuring daily physical activity can be regarded as more informative than assessing exercise capacity.

This review exhibits various strengths and weaknesses. It is a first of its kind as it attempts to evaluate physical activity measures for their relevance to respiratory patients, reflecting the shift in healthcare towards a more patient-centred approach. In doing so, this review highlights the unmet needs for patient-centric physical activity measures, particularly within disease areas such as asthma and IPF. However, we are judging patient relevance of end-points by association with symptomatic burden, such as breathlessness and limited exercise capacity [37, 38], self-reported quality of life questionnaires and indication of treatment efficacy. We are additionally limited by choice of end-points in available research to provide data that can be analysed. This review would benefit from direct patient input to guide evaluating criteria. For example, a social media listening study revealed that relief from cough, mucus production and shortness of breath are the most desirable aspects of COPD management from a patient's perspective [39]. The effort of mucus expulsion early in the morning is particularly relevant as it leaves patients exhausted for the rest of the day [39]. Similar patient insights should be gained within asthma and IPF populations and evaluated against physical activity measures in future trials. Other limitations lie in the methodology and search strategy. This is not a systematic review of all existing literature: this review has only evaluated the physical activity measures which were used more frequently, owing to the preference to evaluate end-points with a breadth of available evidence. The search strategies were not consistent across all therapeutic areas: within asthma and IPF populations, the lack of available literature meant that both complete and incomplete studies were consulted, to gain insight into which end-points are currently being used in exploratory studies. Whereas within COPD, owing to the larger amount of studies, only completed studies were consulted so study results could be analysed in greater depth with the time available.

Conclusion

Within the respiratory therapeutic areas, a variety of physical activity measures and surrogates have been used to assess physical activity. However, few disease-specific measures are available. D-PPAC and C-PPAC are truly patient-centric measures developed specifically for the COPD population. The significance of physical activity measures used within asthma and IPF populations, such as step count, time spent in MVPA and AEE, are controversial given the lack of relevant primary literature in these populations. Within asthma, step count may be the most patient relevant assessment of physical activity available, correlating with disease severity and associated symptom of dyspnoea, exercise capacity and HRQoL. Furthermore, time spent in MVPA has proven useful at progressing an inhaled nitric oxide treatment for interstitial lung disease to late-stage development.

To the best of our knowledge, this is the first review which evaluates physical activity measures used within the respiratory field for patient-centric and clinically relevant criteria, whilst highlighting the unmet need for novel patient-focused end-points validated in the asthmatic population. Despite its behavioural challenges, breaking the vicious cycle associated with poor physical activity levels is crucial to progress patient-centric healthcare, and thus represents a meaningful goal. Utilisation of patient-centric measures of physical activity (or the best currently available) in trials provides the best opportunity to achieving this goal and uncovering efficacious medicines with the biggest impact on patients' quality of life.

Provenance: Submitted article, peer reviewed.

Conflict of interest: C. Rist reports financial support for the present manuscript received from AstraZeneca. The author also reports to be a current employee of AstraZeneca. N. Karlsson reports financial support for the present manuscript received from AstraZeneca. The author also reports to be a current employee of AstraZeneca who holds stock or stock options through a remuneration package. S. Necander reports financial support for the present manuscript received from AstraZeneca. The author also reports to be a current employee of AstraZeneca who holds stock or stock options through a remuneration package. C.A. Da Silva reports financial support for the present manuscript received from AstraZeneca. The author also reports to be a current employee of AstraZeneca who holds stock or stock options through a remuneration package.

Support statement: All authors were full-time employees of AstraZeneca at the time of the work. No additional financial support was provided. Funding information for this article has been deposited with the Crossref Funder Registry.

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