

## Review

# Towards precision in defining COPD exacerbations

COPD is the most prevalent chronic respiratory disease worldwide and a major cause of disability and death. Acute exacerbations of COPD remain a key feature of the disease in many patients and research assessing interventions to prevent and treat them requires a robust definition with high sensitivity and specificity. To date, no such definition exists, and multiple different definitions are used in clinical studies depending on the research question. The strengths and weaknesses of current definitions are discussed in the context of evolving knowledge and different settings in which studies are undertaken. Whether identification and recording of exacerbations remains essentially clinical, or can be identified with a dependable biomarker, it should be sensitive and adaptable to context while retaining clarity and facilitating data collection. This is essential to progress a better understanding of the pathophysiology and phenotypic expression of exacerbations to reduce their impact and personal burden for patients.

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## Introduction

The global mortality and morbidity of COPD is high and has not changed appreciably, unlike many other noncommunicable diseases, over the past 20 years. The Global Burden of Disease Study reported that an estimated 545 million people worldwide had a chronic respiratory disease in 2017, equivalent to a 40% increase compared with the number of individuals affected in 1990, an increase disproportionate to global population growth [1]. COPD, with an overall global prevalence of 6%, remained the most prevalent chronic respiratory disease worldwide and made up 55% of chronic respiratory disease prevalence among men and women. This represents an increase in overall prevalence of 6%, with a marked increase in women

over the same period [2, 3]. Chronic respiratory disease is almost equally prevalent in high income countries and low-middle income countries (LMICs), although with vastly different aetiologies and potentially still serious underdiagnosis in LMICs. Chronic respiratory diseases account for 7% of total all-cause deaths globally, and in 2017 were the third leading cause of death, close behind cardiovascular disease and cancer.

COPD, as the major portion of this high prevalence, also confers very high morbidity [4]. Disability (disability-adjusted life years (DALYs)) due to chronic respiratory diseases increased 13% between 1990 and 2017, and COPD accounted for the lion's share of this [1]. Some gains have been made, the prevalence, mortality, and DALY rates per 100000 people dropping significantly

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**COPD exacerbations carry high risk for long-term disability and death. As the search for a standardised measure continues, study investigators must ensure definitions are explicit and justified to better understand how to prevent and manage these episodes.** <https://bit.ly/2UNqScy>



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between 1990 and 2017 when adjusted for population growth and ageing. However, COPD remains a major global health issue, with increasing numbers of people affected and several of its major causes still not addressed in many regions of the world. This is despite the fact that much of the burden of COPD can be prevented by primary and secondary interventions ranging from public health and government policy to health infrastructure, skilled workforce development and community health literacy [5]. Even in high income countries, treatment-related costs consume a major portion of healthcare budgets [6, 7], and a major portion of these is the cost of exacerbations [7, 8]. Indirect costs of work and productivity loss are also substantial and just as great a burden for the patient as for wider society [6].

## Exacerbations of COPD

Although COPD is a progressive illness marked by daily symptoms and in some patients, a slow decline in lung function and quality of life [9, 10], acute exacerbations of COPD remain a key feature of the disease in many patients. Exacerbations are more likely to occur in patients with a high symptom burden, and in themselves add further burden of disease and impairment of health status [9], as well as risk of more frequent severe events [11–13]. Patients describe exacerbations as having a major impact on their quality of life [9]. Unscheduled visits to healthcare, whether primary, secondary or tertiary, are costly [14, 15], disruptive and most importantly to the patient, moments of extreme physical [6] and emotional stress [16, 17], and for some, life-threatening [18–20].

For the purposes of this introductory discussion, I will define exacerbations of COPD clinically, as episodes of acute worsening of symptoms, leading to additional therapy and hospitalisations, that punctuate a patient's journey more frequently as lung function and ventilatory impairment worsen with time. However, as will become clear, within and between patients with COPD, exacerbations are heterogeneous events, with multiple causes, different expression, and varying impact and clinical responses. A satisfactory definition is not only a semantic challenge, but also an epistemological and environmental one. Most definitions of COPD exacerbations contain both a symptom-based component and an event-based component. There are inadequacies with an emphasis on either of these approaches [21], although alternative definitions have not proven to be superior as a general rule, even if fit for specific purposes, such as clinical trials [22], database analysis [23] or studies examining pathophysiology.

Exacerbations vary in frequency in individual patients and most patients do not exacerbate at exactly the same rate year after year [24, 25]. In many studies [26], including the Evaluation of

COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) [27] and the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) [28], a significant proportion of so-called frequent exacerbators or infrequent exacerbators change status over a 3-year period, indicating that propensity to exacerbation is not a fixed property and either naturally or through both pharmacological [29, 30] and nonpharmacological [31] interventions, patients can change their exacerbation status.

Exacerbation frequency is strongly related to severity of airflow limitation as measured by forced expiratory volume in 1 s ( $FEV_1$ ). This was demonstrated in a recent study from Norway, where the incidence rate ratios for utilisation-defined acute exacerbations of COPD were 2.45 (95% CI 1.22–4.95), 3.43 (95% CI 1.59–7.38), and 5.67 (95% CI 2.58–12.48) with Global Initiative for Obstructive Lung Disease (GOLD) spirometric stages II, III, and IV, respectively [32]. Similarly in an analysis of the Copenhagen General Population Study [23], compared to individuals with GOLD 1, the risk of exacerbations was 17-fold for GOLD 4, five-fold for GOLD 3, and two-fold for GOLD 2.

At a population level, being more prone to exacerbations is associated with being older, having worse  $FEV_1$ , lower levels of daily physical activity, more hours of sedentary time in a day, a greater number of comorbidities, higher dyspnoea scores and higher probability of anxiety and depression [25]. In the SPIROMICS population, having a consistent acute exacerbation profile ( $\geq 1$  event per year for 3 years) was associated with higher baseline symptom burden, previous exacerbations and greater evidence of small airway abnormality on computed tomography (CT), compared with having no acute exacerbations [28].

Many investigators have developed tools to enable practitioners to estimate the risk of developing an exacerbation, most recently the ASSESS tool [33]. In a study using the ECLIPSE 3-year observational study to validate the ASSESS findings, predicted exacerbation and observed exacerbation rates were similar (1.31 *versus* 1.20 events per year for all exacerbations and 0.25 *versus* 0.27 events per year for severe exacerbations). Area under the curve (AUC) was 0.73 (95% CI 0.70–0.76) for two or more exacerbations and 0.74 (95% CI 0.70–0.78) for at least one severe exacerbation. At an individual level, many factors increase exacerbation risk, particularly increasing age, worse  $FEV_1$ , having a history of exacerbations, a higher modified Medical Research Council (mMRC) dyspnoea score [34], worse health status measured by COPD Assessment Test (CAT) or St George's Respiratory Questionnaire (SGRQ), having gastro-oesophageal reflux [35] and a chronic bronchitis phenotype [9, 36].

The economic costs of COPD associated with exacerbations [8, 37] are substantial. However, the arguments for using exacerbations as an end-point extend beyond their economic impact, even

though this has proven to be a vital aspect of the regulatory process and approvals for drug availability and affordability in global markets. The strongest arguments for a robust definition primarily derive from the very severe consequences of exacerbations for patients [18, 20, 38].

## A brief history

In early clinical trials of COPD, many different clinical and physiological characteristics were studied, but in particular, measures of airway obstruction. Despite the reproducibility of the FEV<sub>1</sub> and its relationship to other important clinical outcomes in patients with COPD, it is not a sensitive measure of change during acute exacerbations, can be difficult to perform when patients are unwell, and does not relate strongly to the symptom burden and impaired quality of life that characterises acute exacerbations of COPD.

However, in 1987, significant progress was made when ANTHONISEN *et al.* [22] used a graded definition of exacerbations in a trial of antibiotics for COPD exacerbations. This definition contained objective criteria that could be used in other studies and enabled some quantification of individual components. These exacerbations were described by major and minor symptoms and somewhat arbitrarily graded by type. Type 1 was characterised by increased dyspnoea, sputum volume and sputum purulence; type 2 when two of these symptoms were present; and type 3 when one of the three major symptoms was present in addition to at least one of either an upper respiratory infection within the past 5 days, fever without other cause, increased wheezing or cough, or an increase in respiratory rate or heart rate by 20% as compared with baseline. Despite the appeal of these objective features, and their subsequent use in many clinical studies, they were not derived from a database or case series describing individual characteristics or patterns of exacerbation. They describe symptoms, but do not relate to the underlying pathophysiology or the likely evolution of the exacerbation.

Exacerbations were still variably described in the literature and in small clinical trials prior to a definition proposed in 2000 by RODRIGUEZ-ROISIN [39] in a paper summarising an expert workshop that reached a consensus definition for use in trials and studies. This definition describes an exacerbation as “*a sustained worsening of the patient’s condition from the stable state and beyond normal day to day variations, that is acute in onset and necessitates change in regular medication in a patient with underlying COPD*” [39]. This was a pivotal moment in defining exacerbations, as it introduced a standardised definition for counting exacerbations, was a realistic definition for clinical trials and aligned with clinical care. Although the requirement for symptom worsening limits its use for identifying exacerbations in databases and routinely collected healthcare data, the inclusion

of medication change could be used as a surrogate marker if associated with a healthcare visit.

Subsequent to this, many studies incorporated versions of these symptom descriptors, particularly emphasising worsening of respiratory symptoms that required treatment with oral corticosteroids or antibiotics or both, as judged by the attending clinician. Dyspnoea became the major, dominant symptom, based on evidence from studies that clearly highlighted its importance to patients and as a trigger for initiating greater intensity of treatment and seeking medical care.

The rationale behind each component of the definition by RODRIGUEZ-ROISIN [39] is explained in the paper, which succinctly summarises the subsequent challenges. 20 years of experience has made investigators, epidemiologists and clinicians well aware of its strengths and weaknesses, and it is now worth revisiting this definition, and looking at potential refinements that would add to its utility while not reducing its capacity to be applied in many different contexts. I will address each of these in the light of the experience gained by investigators as they implemented it in many different clinical trials, observational studies and database analyses.

## Dissecting the definition

### Sustained worsening from the stable state

RODRIGUEZ-ROISIN [39] suggests “The terminology, *worsening of the patient’s condition*, is relatively imprecise because of the *absence of established clinical markers, signs, or symptoms*”.

#### Sustained worsening of the stable state

Most patients find it difficult to identify the very early stages of an exacerbation and to distinguish their increased symptoms from day-to-day variability. This has several immediate consequences for patients, regarding commencing treatment [40] and achieving the best possible outcomes [41]. Under-recognition of exacerbations is a concern [41, 42], in that these events may lead to worse outcomes, specifically longer duration, poorer quality of life and increased risk of hospitalisation [43, 44], but over-reporting can also occur (events that are identified by patients as an exacerbation but are not accompanied by symptom change in diary cards [44], or do not result in healthcare contact or change of treatment [42]). In most studies, unreported exacerbations have less intense and often fewer symptoms [43] and appear to be milder events [40] even though they have a cumulative impact on health status [41, 44]. Whether in a clinical trial or through routinely collected data, worsening of the stable state is limited by its dependence on patient recognition, which it is well established can result in both over- [45] and

undercounting [46]. Compared with reported exacerbations, unreported exacerbations usually show a lower median number of key symptoms, less worsening for each key symptom, and a significantly lower proportion of exacerbations with two and three key symptoms. Conversely, more unreported exacerbations (83.3%) than reported exacerbations (28.8%) exhibited a single worsening symptom.

With regard to the absence of established clinical markers, signs, or symptoms, it is an unfortunate fact that we are still struggling to develop, test and embed these in clinical and research practice. We know the specific symptoms most often associated with an exacerbation, but we do not have an adequate scoring system to rank these, even though we have several validated tools focused on symptoms that enable us to better understand the impact of COPD in patients' lives, particularly the CAT and the SGRQ. Both are highly useful for assessments of change over time from an exacerbation, but they were not designed to detect and measure exacerbations in themselves [47]. Tools to detect and measure the onset, severity and resolution of an acute deterioration have proven challenging to develop.

What are the key symptoms of a COPD exacerbation? ANTHONISEN *et al.* [22] carefully divided exacerbation symptoms into major and minor, particularly focused on achieving a definition suitable for a clinical trial of antibiotics. A similar categorisation has been useful in other analyses, but it is crucial to acknowledge that patients' symptoms [48], their perceptions [49] and ability to grade these vary markedly. Cultural [49], age-related and gender-based [36, 50, 51] differences also influence this, as does severity of COPD [34, 52]. Patient-reported outcome (PRO) measures vary greatly in sensitivity and specificity for identification of exacerbations in patients with COPD [53, 54], and specific definitions [55] and tools for this purpose must be carefully chosen [56, 57].

Dyspnoea is a major symptom of COPD and intensifies during exacerbations [46, 58]. Most patients recognise it as a clear indication that they are more unwell [40]. Cough and sputum, and chest symptoms are also key symptoms and with dyspnoea account for most of the quantitative change from the stable state during an exacerbation [49, 59]. Many other symptoms are highly variable, dependent on underlying aetiology of the exacerbation, clinical disease features, whether the patient has a chronic bronchitic or emphysematous phenotype, the presence of comorbidities and the cultural setting of the patient and their carers. Systemic features such as marked fatigue may be prominent but lack specificity and so the respiratory symptoms are essential to identify worsening of the patient's condition as due to a COPD exacerbation.

### Severity

Severity is another aspect of worsening: how much worse? Exacerbation grading is variably defined

in clinical studies and trials. The grading most commonly accepted or used in studies involves an event-based assessment for moderate-severe exacerbations. In randomised controlled trials (RCTs) exacerbations are often classified as mild if they are treated with short-acting bronchodilators only; moderate if treated with short-acting bronchodilators plus antibiotics and/or oral corticosteroids; and severe if the patient visits the emergency room (ER) or requires hospitalisation because of an exacerbation [60]. In some RCTs, exacerbations resulting in admission to intensive care or death are categorised as very severe [61]. These definitions have varied considerably in clinical trials, often depending on the intervention and its anticipated primary effect [62]. In many RCTs mild exacerbations are defined on symptoms alone, particularly an increase in, or new onset of, cough, sputum, dyspnoea, wheezing or chest tightness [63].

Other definitions of exacerbation severity used in RCTs have included any inhaled medication increases in mild exacerbations, systemic corticosteroids only in moderate exacerbations [62, 64], and in the severe category, only hospital admissions or deaths [65]. The inclusion of ER presentations in the severe category depends on geography [66], access and affordability of care and in many settings does not indicate a severe exacerbation on clinical grounds. It may thus overestimate the prevalence of severe exacerbations. In some high income countries, patients requiring admission based on clinical severity form only a small proportion of all those with exacerbations [18, 32], whereas in other settings admissions are those most commonly recorded in a trial, and many community based events go unrecorded [67]. It is also important to note that in many countries, self-management of exacerbations is based on a written action plan [68] and a patient's own supply of antibiotics or corticosteroids, which may also result in under-reporting if the patient fails to recall the event or does not seek medical assistance at the time [54, 69]. Some RCTs of COPD therapies have required sustained symptom changes that may be purposeful in terms of the intervention [58, 70, 71], but can also result in under-recognition if prespecified criteria are not met [62, 71].

### The absence of established clinical markers

Biomarkers have the potential to identify COPD exacerbations in the real world for patients and clinicians, and in clinical trials. An ideal exacerbation biomarker would be an accessible, reproducible, externally validated objective measure that either signals an exacerbation or confirms one, when associated with symptoms. Such a biomarker would help to eliminate the subjectivity of symptom worsening beyond day-to-day variability, but no such marker has yet been identified, despite major investment in cohort studies and clinical trials.

Many investigators have tried to identify a blood test that may be an effective biomarker for COPD exacerbations. The prime contenders, based on current evidence would be C-reactive protein (CRP) or fibrinogen, as raised levels are associated with a greater probability of exacerbating. One problem with both biomarkers in COPD is that an elevation may be a continuous, almost steady state for some patients [72]. In the ECLIPSE study, inflammatory biomarkers in peripheral blood were quantified in 1755 COPD patients followed over 3 years. At baseline, 30% of COPD patients did not show evidence of systemic inflammation whereas 16% had persistent systemic inflammation evidenced by elevations in the assessed markers [72]. A high white cell count has been associated repeatedly with some exacerbations and exacerbation propensity, but is a nonspecific finding, indicative of many types of infection and likely to rise if patients have already commenced systemic steroids. High blood neutrophil counts were also associated with a frequent exacerbation phenotype and mortality in ECLIPSE [35, 73]. Similarly, elevation of blood eosinophils  $\geq 3\%$  or  $\geq 300$  cells·mm<sup>-3</sup> appears to identify a subpopulation of patients at higher risk of exacerbations and a greater probability of a positive benefit from short-course corticosteroids, but this feature varies and may be evident when clinically stable and during an exacerbation. Eosinophilia may also indicate more benefit in exacerbation reduction from inhaled corticosteroids [74], but background counts or those taken at exacerbation do not have any rule-in or rule-out utility. Given this is a long term (albeit fluctuating) phenotypic marker, it lacks sensitivity and specificity for identifying exacerbations.

Biomarker repeatability was assessed in a subset of patients with COPD, ex-smoker controls with normal lung function and healthy nonsmokers selected from the ECLIPSE cohort, at baseline and 3 months, with CRP showing wide variability [75]. Fibrinogen was the most repeatable biomarker and weakly correlated with 6-min walking distance, exacerbation rate, BODE (body mass index, airflow obstruction, dyspnoea, exercise capacity) index and MRC dyspnoea score. Several inflammatory markers appear to reflect longer term disease activity: CRP, fibrinogen, interleukin-6 and surfactant protein-D were significantly elevated in subjects with exacerbations within 30 days of the 3-month visit compared with those individuals that did not exacerbate [72]. Persistence of a high CRP in ECLIPSE was a flag for predisposition to recurrence and overall higher exacerbation frequency, but did not have specificity for accurate timing [76]. In other studies, lower interleukin-15 concentrations, and higher interleukin-8 concentrations were associated with higher probability of having >1 exacerbation per year. However, none of these biomarkers have proven to be useful for contemporaneous confirmation of an exacerbation.

### **The definition acknowledges that a patient's stable state may fluctuate, and therefore includes the wording, *beyond normal day-to-day variations***

The usefulness of daily diaries in identifying exacerbations has been well demonstrated by the evidence that has emerged from the East London cohort and others like it. This is a prospective longitudinal cohort of COPD patients recruited from outpatient clinics of the London Chest and Royal Free Hospitals, London, UK and followed for a minimum of 2 years. Daily measures of symptoms, medication use, hospitalisations and clinic visits were recorded by each participant, including symptom increases above baseline, enabling identification of COPD exacerbations. These cohorts have yielded exceptionally valuable information about symptoms, frequency of flare-ups, healthcare contact, management and outcomes. It is however crucial to appreciate that daily record keeping over months to years is arduous and those who do it well may be a subset and not necessarily representative of the broader COPD population. The development of PRO tools have enabled standardisation of these measures and have been a vital addition to understanding the pattern and impact of exacerbations at an individual level [56], as well as facilitating comparisons across different demographic groups.

Electronic diaries and smartphone-based applications that enable text entry, responses to questions and uploading of physiological data such as heart rate, respiratory rate, airflow measurements and oximetry are an inevitable development from such diaries. Automatically collected data from nanodevices and microchips have opened up a raft of possibilities for self-monitoring, home care, outreach services and early discharge [46].

Electronic diaries have the benefit of real time data entry and upload, eliminating entries based on recall and helping to prevent fictional entries, often by automatically entering a time and date stamped measurement (such as peak flow). Several PROs have been automated and embedded in electronic diaries [77], recording symptom frequency and severity of daily COPD symptoms. These diaries may also have software that computes day-to-day variability and signals to patients when symptom scores or peak flow rates deviate by more than a pre-determined margin from normal. Tools, such as the Exacerbations of COPD Tool (EXACT) questionnaire [48, 78], can be integrated into smartphones, providing a validated, sensitive questionnaire that enables acute symptom changes to be recorded for the detection of exacerbations in clinical trials.

### **A sustained worsening that is acute in onset**

A key feature of the definition provided by RODRIGUEZ-ROISIN [39] is that the exacerbation

is defined by being *acute in onset*. This is also stated in the current definition as it appears in the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: “An exacerbation of COPD is defined as an *acute worsening of respiratory symptoms* that results in additional therapy” [79]. However, there is now good evidence from a variety of sources [38, 80] that exacerbations may be of a gradual onset and this should be reflected in the definition.

In a careful and highly informative analysis of the East London COPD cohort data, AARON *et al.* [80] defined an exacerbation commencement date as the first of two or more consecutive days on which the patient recorded two or more new or worsening symptoms, at least one of which was a major symptom, 55% of these resolved spontaneously. Amongst those who developed an exacerbation, the onset was sudden in 56% and the exacerbation threshold was crossed on the same day symptoms began. By contrast, 44% of exacerbations were characterised by gradual onset of symptoms with a median duration from symptom onset to exacerbation of 4 days. Patients who experienced sudden onset exacerbations had greater mean daily symptom scores, greater peak symptom scores, earlier peak symptoms and shorter median recovery times back to baseline health status. Gradual onset exacerbations were statistically associated with a longer duration of exacerbation recovery (OR 1.28, 95% CI 1.06–1.54,  $p < 0.010$ ). Others have also shown that COPD exacerbations may exhibit a gradual onset, and these may also be more likely to be slower to resolve.

Further, several studies suggest that the particular symptom thresholds and definitions within a symptomatic event clearly influence the identification of those events [44, 81]. Establishing a low threshold, however, has risks and may distort treatment effects. These risks include over-sensitivity and the inclusion of small changes in symptoms that are part of day-to-day variability, or milder exacerbations that may be shorter-lived or have only a small impact [46]. In some study designs, low treatment thresholds may have been deliberately included to enable a primary end-point to be reached more rapidly, or an intervention to appear to have greater efficacy in reducing exacerbations. However, the nature of the treatment that is changed is also important in counting exacerbations. Some clinical trials have defined an exacerbation as an event in which bronchodilators and/or inhaled medications are increased, and there are different impacts depending on which these are. Medications such as short-acting  $\beta_2$ -agonists treat the symptoms, primarily dyspnoea, whereas others, such as inhaled corticosteroids, can address the underlying mechanisms in some patients and may reverse the exacerbation.

### **The definition requires that the change in condition necessitates a change in regular medication**

As already noted, a problem with symptom or treatment defined COPD exacerbations, is what constitutes a *change in regular medication*. Not only does the word “change” matter, but also regular medication [82]. This is more of an issue than it used to be because patients across the world are taking very different medications as their regular medications [32]. In medium-high income countries, patients may be prescribed best practice medications based on current guidelines and a well-resourced healthcare system and affordable medications [79]. For some patients in high income settings and most in low income countries, their regular medications are short-acting  $\beta_2$ -agonists and antimuscarinics alone [83, 84].

Most commonly, prescription of systemic corticosteroids or antibiotics signifies the recognition of an exacerbation by the health professional or the patient. These two players, the patient and the health professional involved in exacerbation identification can have very different perspectives [85, 86], and may alter treatments for different reasons [40, 49]. In RCTs, the randomisation may be trusted to distribute this variability evenly between the intervention arms, but the problem of identifying reasons for treatment change, and sometimes the true severity of the event remains. It is now well known that in winter, the prescription of antibiotics during exacerbations is more common [34, 87], but this may be empiric and does not necessarily indicate careful clinical assessment for a bacterial aetiology.

Local access to healthcare services and affordability of care are immensely important in determining whether a moderate-severe exacerbation is recorded. People living in regional and remote communities, even in high income countries [66], often have much more significant difficulty accessing timely medical care, more hospital admissions and longer length of stay. People in low income countries may not have access to short-acting inhaled medications unless they present to hospital [84, 88]. Given the burden of COPD falls disproportionately on these communities, there is a need to address this deficiency in the definition of COPD exacerbations in order to accurately estimate the burden of COPD and the urgent need for preventative measures to reduce this. Health literacy, poverty, geographical access to care and affordability of medications all influence the measurement of exacerbations in socioeconomically deprived areas, whether an event-based or symptom/treatment-based definition is used. The mechanisms for the development of COPD in low income settings result from exposure to a range of noxious agents and inhalations that extend far beyond tobacco [89, 90], and along with early life respiratory insults [84] may also contribute to failure to achieve normal lung growth in early adult life [90, 91]. Symptom

worsening and treatment response may be different in these diverse aetiologies of COPD and much more research is needed to fully explore this.

## What do we need for the future?

In summary, the definition of a COPD exacerbation proposed in 2000 has served well as a template for many carefully conducted RCTs, clinical cohort studies and database analyses. Each of these purposes has necessitated slightly modified versions of the definition, based on the rationale for the study and the data collected. This has led to a plethora of exacerbation definitions which although only superficially different, can have very marked repercussions for estimations of burden of COPD and the effects of treatment.

It is essential that we acknowledge the imprecise aspects of our different exacerbation definitions, particularly as healthcare is changing so rapidly and events previously associated with most severe exacerbations, such as hospitalisations, are much less common. Other contemporary influences may lead to changes in our capacity to record the true burden of exacerbations. As an example, the trend to phenotype patients and their exacerbations for targeted treatment approaches, would result in fewer recorded events if guidelines advise against systemic corticosteroids for an exacerbating patient with low eosinophils. Administrative pressures to reduce admissions, the increase in patient self-management capacity and the wider availability of home-based care through clinical outreach services must be considered as changes that could also influence the recording of severe exacerbations if the commonly used definitions in large RCTs are retained.

We focus on exacerbations because of their impact on patients and healthcare systems. In the past 20 years, billions of dollars have been

spent conducting RCTs to assess the efficacy of medications and interventions to reduce their frequency and severity, with mean reductions of ~20% through optimal treatment regimens in highly selected patients, but there is a persistent residual exacerbation rate which remains a major burden. I have not addressed the aetiology of COPD exacerbations in this review, but the experience of the coronavirus disease 2019 (COVID-19) pandemic has demonstrated that social distancing, masking and hand hygiene have had a major impact in reducing exacerbations [92] and hospital admissions [93], an observation that has been made around the world in vastly different settings [94]. We must make immediate use of this information for the good of our patients and clinical trials with careful counting of exacerbations are probably not needed to demonstrate the benefits of avoiding exposure to respiratory viruses.

It is likely that the different definitions of a COPD exacerbation will evolve as the search for a standardised measure continues, and probable that there will never be a single definition that can meet all purposes. Whether identification and recording of exacerbations remains essentially clinical, or can be identified with a dependable biomarker, it should be sensitive and adaptable to context while retaining clarity and facilitating data collection. In every study, investigators should ensure that variations on the commonly accepted definition are made explicit and entirely justified. Research is urgently needed to explore the use of definitions in low income countries to enable a better understanding of the impact of the causes, impact and management of COPD exacerbations in circumstances dramatically different to middle to high income countries where the majority of large COPD trials are undertaken. Finally, we have much more to do to progress a better understanding of the pathophysiology, aetiology and phenotypic expression of exacerbations to reduce their impact and personal burden for patients.

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### Conflict of interest

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