ERS statement: a core outcome set for clinical trials evaluating the management of COPD exacerbations

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Shareable abstract (@ERSpublications)
@EuroRespSoc Statement: A core outcome set and outcome measurement instruments for #ClinicalTrials evaluating #COPD exacerbations management was developed, based on evidence-informed, global, multi-stakeholder consensus https://bit.ly/3maLXIa

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Abstract

Clinical trials evaluating the management of acute exacerbations of COPD assess heterogeneous outcomes, often omitting those that are clinically relevant or more important to patients. We have developed a core outcome set, a consensus-based minimum set of important outcomes that we recommend are evaluated in all future clinical trials on exacerbations management, to improve their quality and comparability. COPD exacerbations outcomes were identified through methodological systematic reviews and qualitative interviews with 86 patients from 11 countries globally. The most critical outcomes were prioritised for inclusion in the core outcome set through a two-round Delphi survey completed by 1063 participants (256 patients, 488 health professionals and 319 clinical academics) from 88 countries in five continents. Two global, multi-stakeholder, virtual consensus meetings were conducted to 1) finalise the core outcome set and 2) prioritise a single measurement instrument to be used for evaluating each of the prioritised outcomes. Consensus was informed by rigorous methodological systematic reviews. The views of patients with COPD were accounted for at all stages of the project. Survival, treatment success, breathlessness, quality of life, activities of daily living, the need for a higher level of care, arterial blood gases, disease progression, future exacerbations and hospital admissions, treatment safety and adherence were all included in the core outcome set. Focused methodological research was recommended to further validate and optimise some of the selected measurement instruments. The panel did not consider the prioritised set of outcomes and associated measurement instruments to be burdensome for patients and health professionals to use.

Background

Acute exacerbations punctuate the natural history of COPD and are largely responsible for the adverse disease outcomes [1–3]. Every year, approximately a third of those diagnosed with COPD experience at least one moderate or severe exacerbation, while 9–16% experience these events even more frequently [4–7]. More importantly, every year, one in 20 unselected patients with COPD and one in four of those monitored in secondary care for their COPD experience severe exacerbations [6], which are associated with a 90-day mortality that approximates 15% [8–10].

While novel maintenance treatments have reduced the occurrence of exacerbations [11], their management remains suboptimal and has not changed for decades [8, 12, 13]. However, over recent years, the complexity and heterogeneity of exacerbations, as well as their underlying mechanisms, are increasingly being understood [3, 14–17]. In addition, the clinical validation of promising biomarkers paves the way for the introduction of precision medicine interventions, that could revolutionise the approaches to managing exacerbations [18–21]. Therefore, it is anticipated that an increased number of clinical trials will be conducted in the coming years, to evaluate novel treatments, including precision medicine interventions.

However, the design and conduct of clinical trials on managing COPD exacerbations are complicated by methodological and practical challenges [22]. Selection and consistent use of relevant, comparable, well-defined and patient-important outcomes represent a critical challenge. A recent meta-epidemiological study revealed remarkable heterogeneity in the outcomes evaluated and reported in COPD exacerbation trials, as well as the definition of these outcomes and instruments used to assess them [23, 24]. This has led recent relevant systematic reviews and meta-analyses to report limited certainty in the available evidence [19, 25, 26].

To address this issue, the European Respiratory Society (ERS) formed this task force:

1) to develop a core outcome set for clinical trials evaluating the management of COPD exacerbations. A core outcome set is an agreed minimum set of critically important outcomes that should be evaluated in all future trials in a specific area of healthcare, aiming to improve their quality and comparability [27].

2) To prioritise a single instrument for measuring each of the core outcomes. The core outcome measurement instruments describe how each of the core outcomes should be evaluated in clinical trials [28].

The outputs of this project were based on global, multi-stakeholder consensus.

Methods

Detailed methodology of the Core Outcome set for the Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COS-AECOPD) ERS task force was prospectively registered with the Core Outcome Measures in Effectiveness Trials (COMET) database (https://comet-initiative.org), published [29] and is available in appendix 3 (supplementary material). This study was conducted and reported following the methodology recommended by the COMET initiative [27], the Core Outcome Set Standards for Development (COS-STAD) [30] and Standards for Reporting (COS-STAR) [31]. This project consisted of three components.

First, we developed a comprehensive list of all outcomes related to COPD exacerbations. Through a methodological systematic review, we identified outcomes that were evaluated in 123 randomised controlled trials and 38 systematic reviews on the management of COPD exacerbations [23, 24]. This list was enriched with additional outcomes considered important by patients, that have not been evaluated in trials so far. These were identified through a focused systematic review of qualitative studies [32–35], complemented by a focus group and individual interviews with a total of 86 patients from 11 countries globally. After removing duplicate entries, the list included 47 unique outcomes. This list was further enriched by the respondents of the subsequent Delphi survey.

Next, prioritisation of the most critical outcomes for inclusion in the core outcome set was facilitated by a Delphi survey and a consensus panel. An online, two-stage, global, multi-stakeholder Delphi survey was employed, which was developed in plain language and was available in 10 languages, to facilitate global participation (www.comet-initiative.org/delphimanager/index.html). Three stakeholder groups were invited to participate in the survey: 1) patients diagnosed with COPD, who had experienced exacerbations, and personal caregivers or representatives of such patients (*e.g.* patient organisations); 2) health professionals caring for patients (*e.g.* doctors, nurses or physiotherapists); and 3) clinical researchers (health professionals who care for patients, but are also involved in designing research studies). After the second round of the survey, consensus was assessed based on prospectively selected thresholds for inclusion or exclusion, considering responses of the three stakeholder groups separately and using data from respondents who completed both survey rounds.

Prioritisation was finalised during the first consensus meeting (21 April 2021). Outcomes with an inconclusive survey result that were prioritised for inclusion in the core outcome set by at least one, but not all stakeholder groups, were discussed in detail. Participants were classified into two groups: 1) health professionals or researchers and 2) patients diagnosed with COPD and their representatives. Thorough discussion in which both groups were invited to share their views about the importance of each of these outcomes was followed by polls. Only outcomes that were rated as critical by ⩾70% of the participants in both groups were added to the core outcome set.

The final component of this project consisted of the selection of a single, optimal instrument for measuring every core outcome, to ensure consistency and comparability across trials. Evidence-informed consensus was achieved during a second panel meeting (28 April 2021), in which a pragmatic methodology was followed for prioritising measurement instruments. Instruments that are already in use were identified through our methodological systematic review [23]. Since our aim was to promote consistency, for outcomes that are often evaluated by the same instrument, that instrument was considered for prioritisation during the consensus meeting, upon evaluating its strengths and methodological limitations. For other outcomes, including all patient-reported outcomes, we conducted focused literature searches of MEDLINE/PubMed and the Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN) database, to identify studies evaluating the quality and measurement properties of the different instruments. The panel reviewed available evidence, which was circulated in advance of the consensus meeting *via* email, and developed consensus on a simple instrument for each outcome considering 1) the frequency that each instrument is used in clinical trials; 2) the time and resources required to use each instrument; and 3) available data on their measurement properties, as described by COSMIN recommendations [36]. After discussion, a single instrument was selected for every core outcome and participants were asked to vote for 1) a strong recommendation; 2) an interim recommendation along with research agenda, a research agenda without a recommendation; or 3) an alternative recommendation or the need for additional data to make an informed decision. Due to the more technical nature of this assignment, only two patients with COPD and a representative of the European Lung Foundation (ELF), with previous experience in COPD research, joined the consensus meeting, and therefore, the voting was not stratified by stakeholder group. Pre-specified voting thresholds are described in the supplementary material.

Feedback was sought by all participants of the consensus meetings to explore whether they felt they were offered the opportunity to share their views and that they were able to cast well-informed votes.

Changes from the prospectively registered protocol are summarised and justified in appendix 3 (supplementary material).

Results

The core outcome set development process is summarised in figure 1.

Delphi survey

The first round of the Delphi survey was available online between 2 May and 27 June 2020, and the second round between 21 July and 30 October. Of 1201 individuals who started a registration at the Delphi survey website, 1063 (88.5%) from 88 countries in Africa, the Americas, Asia, Europe and Oceania

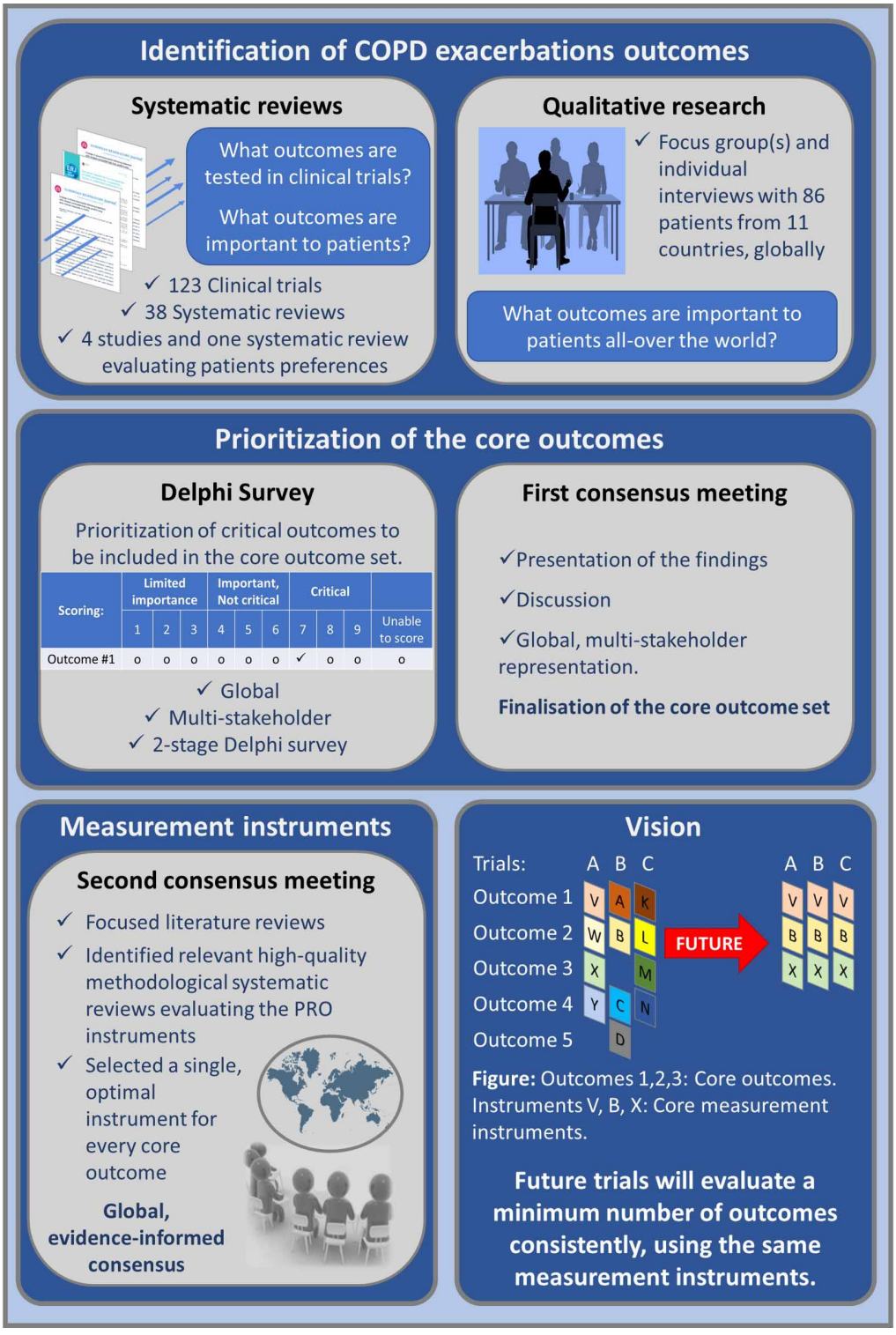

FIGURE 1 Study flowchart summarising the main steps of the core outcome set development process. PRO: patient-reported outcomes.

(figure 2) completed the first round of the survey and comprised our study population. These included 256 (24.1%) patients or patient representatives, 488 (45.9%) health professionals and 319 (30.0%) researchers. Baseline characteristics of the participants are described in tables 1–3. Six unique, additional outcomes were proposed by the respondents during the first round of the Delphi survey and were introduced in the second round (table 4).

Among all participants, 896 (84.3%) also completed the second survey round. Visual inspection of the distribution of first-round participant average outcome rating did not reveal differences between those who did or did not complete the second round of the survey. After the second round of the survey, 15 and 29 outcomes met the thresholds for inclusion in and exclusion from the core outcome set, respectively, while the ratings of nine outcomes were inconclusive. These nine outcomes were further considered during the first consensus meeting. The results of the Delphi survey are presented in detail in appendix 4 (supplementary material) and summarised in table 4. Only a minority of the participants (3.1%) reported relevant conflicts of interest and the exclusion of their responses did not alter the survey results.

Visualisation of the responses of participants from 1) low or lower-middle, 2) upper-middle and 3) high income countries did not reveal any difference in the ratings among these groups. Moreover, for every outcome, the average (median) ratings of each of these groups were very similar (maximum difference=1).

Consensus meetings

The first consensus meeting was attended by a global panel including 17 patients or patient representatives, 22 health professionals and/or clinical researchers with relevant expertise and two methodologists with expertise in core outcomes development (appendix 8, supplementary material). The methodologists did not vote in the polls, but provided methodological input during the discussion. Nine outcomes with inconclusive ratings in the Delphi survey were discussed in the consensus meeting and three of them were prioritised for inclusion in the core outcome set (table 4).

The second meeting was attended by a global panel involving two patients and a patient representative (ELF), 21 health professionals and/or clinical researchers with relevant expertise and one methodologist with expertise in core outcomes development (appendix 8, supplementary material). The structure of the core outcome set was finalised (box 1). Permanent deterioration in lung function was originally prioritised as a core outcome in the Delphi survey. However, during the consensus process, it became clear that this is a measure of the disease progression outcome, and therefore it was reclassified. For each of the core outcomes, a single, optimal measurement instrument was prioritised and recommended (table 5). Strong recommendations were issued for only four of the core outcomes, while for the remaining outcomes an interim instrument was recommended, along with a call for relevant methodological research (appendix 7, supplementary material).

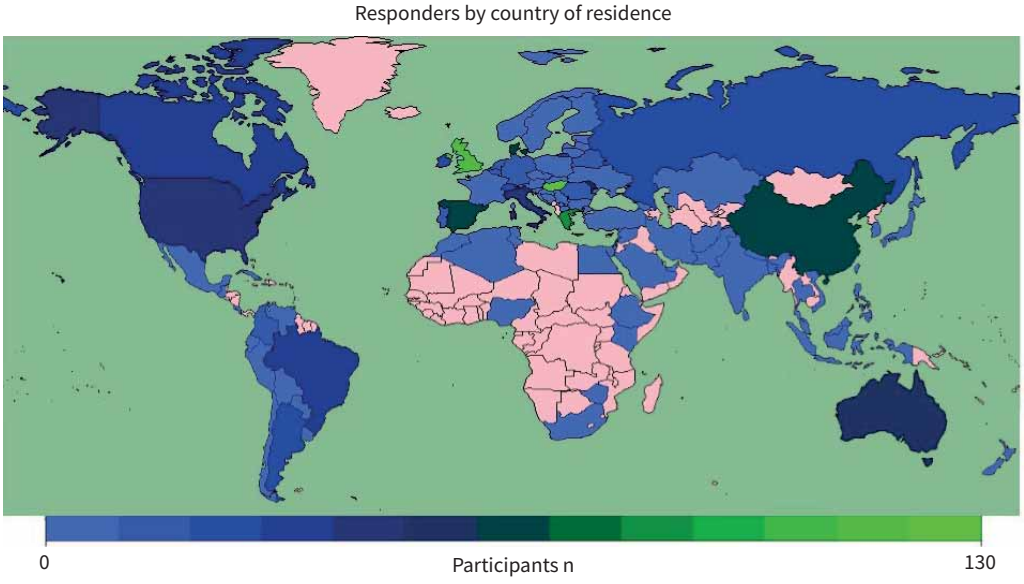

FIGURE 2 Geographic distribution of the Delphi survey participants. The colour of each country represents the number of participants. No responses were received from pink-shaded areas.

TABLE 1 Baseline characteristics of the Delphi survey participants

	Patients and representatives	Health professionals	Researchers
Study participants	256 Patients 229 Caregivers 22 Representatives 5	488 Doctors 399 Nurses 53 Physiotherapists 17 Other health professionals 19	319 Doctors 230 Nurses 13 Physiotherapists 34 Other health professionals 7 Others[¶] 35
Completed second round	197 (77.0)	398 (81.6)	291 (91.2)
Declared potential conflicts of interest	3 (1.2)	13 (2.7)	17 (5.3)
Age (years)			
21–30	4 (1.6)	74 (15.2)	31 (9.7)
31–40	10 (3.9)	132 (27.0)	91 (28.5)
41–50	17 (6.6)	109 (22.3)	82 (25.8)
51–60	56 (21.9)	97 (19.9)	64 (20.1)
61–70	93 (36.3)	62 (12.7)	45 (14.1)
71–80	66 (25.8)	12 (2.5)	6 (1.9)
81–90	9 (3.5)	2 (0.4)	0 (0.0)
>90	1 (0.4)	0 (0.0)	0 (0.0)
Female	112 (43.8)	277 (56.8)	140 (43.9)
Continent			
Africa	1 (0.4)	6 (1.2)	12 (3.8)
Americas	44 (17.2)	78 (16.0)	51 (16.0)
Asia	14 (5.5)	68 (13.9)	32 (10.0)
Europe	175 (68.4)	325 (66.6)	201 (63.0)
Oceania	22 (8.6)	11 (2.3)	23 (7.2)
Economy[#]			
Low	0 (0.0)	1 (0.2)	3 (0.9)
Lower middle	12 (4.7)	59 (12.1)	19 (6.0)
Upper middle	20 (7.8)	125 (25.6)	57 (17.9)
High	170 (66.4)	246 (50.4)	175 (54.9)
Conducting research	2 (0.8)	187 (38.3)	283 (88.7)
Designing research studies	0 (0.0)	0 (0.0)	319 (100)
Predominantly working on research	0 (0.0)	21 (4.3)	59 (18.5)
Development of guidelines	0 (0.0)	95 (19.5)	161 (50.5)

Data are presented as n or n (% of the participants in the corresponding stakeholder group). [#]: economy of the participants' country, according to the World Bank classification 2021. [¶]: researchers and not health professionals; policy makers; regulators.

Feedback was collected from all consensus meeting participants. All participants felt that their views were heard, and the consensus was well-informed.

Considerations around the selection of outcome measurement instruments

The recommended outcome measurement instruments and relevant research recommendations are summarised in table 5 and appendices 5–7 (supplementary material). Next, we summarise pertinent additional data and discussion points considered by the panel about some of the measurement instruments. A more detailed version of this section, focusing on all instruments, is available in appendix 6 (supplementary material).

Death from a COPD exacerbation

Death from COPD exacerbation is rarely evaluated in exacerbation trials. COPD exacerbations are often complicated by events such as ventricular arrhythmia, massive pulmonary embolism, acute myocardial infarction or pneumonia [37]. As a result, the determination of the cause of death during an exacerbation is complex and often inconsistent across different centres and countries. For this reason, the panel opted for a pragmatic approach based on the documented primary cause registered in the death certificate. If this is

TABLE 2 Additional baseline characteristics of patients with COPD who completed the Delphi survey

Highest level of education	
Primary education	23 (10.0)
Secondary education	111 (48.5)
University education	82 (35.8)
Not reported	13 (5.7)
Employment status	
Currently studying	1 (0.4)
Currently working	45 (19.7)
Currently unemployed	13 (5.7)
Early retirement	45 (19.7)
Retired	117 (51.1)
Not reported	8 (3.5)
Years since COPD diagnosis	
Up to 5	66 (28.8)
6–10	68 (29.7)
11–15	43 (18.8)
16–20	28 (12.2)
>20	15 (6.6)
Not reported	9 (3.9)
Exacerbation history	
Any exacerbation	
None	55 (24.0)
1	49 (21.4)
2	36 (15.7)
3	31 (13.5)
4	12 (5.2)
>4	41 (17.9)
Not reported	5 (2.2)
Severe (hospitalised) exacerbation	
None	163 (71.2)
1	34 (14.8)
2	18 (7.9)
3	6 (2.6)
4	2 (0.9)
>4	2 (0.9)
Not reported	4 (1.7)
Previous NIV use or ICU admission	
Yes	43 (18.8)
No	182 (79.5)
Not reported	4 (1.7)

Data are presented as n (%). NIV: noninvasive ventilation; ICU: intensive care unit.

COPD exacerbation or an event considered to be an immediate complication of the exacerbation, then the death should be attributed to the exacerbation. It was recognised that ideally the cause of death should be confirmed by a well-informed and blinded adjudication committee; however, this may not always be feasible.

Treatment success

Treatment success is more frequently defined as cure of the exacerbation and more specifically as the "complete resolution of all signs and symptoms of the exacerbation" [23]. However, the recovery period of an exacerbation varies significantly and may be very prolonged. Large observational studies have shown wide variability in the duration of exacerbation recovery, revealing that 25% of patients still experience symptoms associated with the exacerbation 25 or even 35 days after the onset of the exacerbation [38, 39]. Longer periods may be required until patients recover their previous exercise capacity or activities of daily living (ADL) levels [40, 41]. Moreover, exacerbations accelerate disease progression; therefore, the clinical condition after recovery from an exacerbation may be characterised by a greater symptomatic burden, compared to the previous baseline [42]. As a result, this definition of cure was considered problematic. For this reason, a more pragmatic, yet still suboptimal interim instrument was recommended by the panel: treatment success is defined as sufficient improvement of the signs and symptoms of the exacerbation, such that no additional systemic treatments (antibiotics or systemic corticosteroids) are prescribed. While

TABLE 3 Additional baseline characteristics of expert respondents (health professionals and researchers) of the Delphi survey

	Doctors	Nurses	Physiotherapists	Other health professionals	Researchers and not health professionals
Study participants	629	66	51	26	30
Completed second round	522	63	50	23	27
Declared potential conflicts of interest	20 (3.2)	1 (1.5)	0 (0.0)	5 (19.2)	4 (13.3)
Primary employment setting					
Primary care	60 (9.5)	5 (7.6)	5 (9.8)	4 (15.4)	0 (0.0)
Secondary hospital	121 (19.2)	14 (21.2)	2 (3.9)	0 (0.0)	0 (0.0)
Tertiary/university hospital	348 (55.3)	17 (25.8)	30 (58.8)	9 (34.6)	2 (6.7)
Clinical trials, methodology or epidemiology unit	1 (0.2)	3 (4.5)	0 (0.0)	1 (3.8)	1 (3.3)
Health technology assessment or guidelines development organisation	3 (0.5)	0 (0.0)	0 (0.0)	1 (3.8)	2 (6.7)
Governmental organisation	2 (0.3)	0 (0.0)	1 (2.0)	0 (0.0)	1 (3.3)
Research funding organisation/charity	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
Patients' organisation	0 (0.0)	0 (0.0)	1 (2.0)	1 (3.8)	0 (0.0)
Pharmaceutical industry	4 (0.6)	0 (0.0)	0 (0.0)	4 (15.4)	0 (0.0)
Other	26 (4.1)	3 (4.5)	7 (13.7)	1 (3.8)	7 (23.3)
Not reported	63 (10.0)	24 (36.4)	4 (7.8)	5 (19.2)	16 (53.3)
COPD patients assessed during the previous year					
None	16 (2.5)	4 (6.1)	6 (11.8)	5 (19.2)	5 (16.7)
1–250	283 (45.0)	25 (37.9)	29 (56.9)	15 (57.7)	2 (6.7)
251–500	154 (24.5)	8 (12.1)	10 (19.6)	0 (0.0)	0 (0.0)
501–750	58 (9.2)	3 (4.5)	4 (7.8)	1 (3.8)	0 (0.0)
751–1000	30 (4.8)	1 (1.5)	1 (2.0)	0(0.0)	0 (0.0)
>1000	35 (5.6)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Not reported	53 (8.4)	24 (36.4)	1 (2.0)	5 (19.2)	23 (76.7)
Research activity					
Involved in conducting research	369 (58.7)	29 (43.9)	40 (78.4)	16 (61.5)	13 (43.3)
Involved in designing research	230 (36.6)	13 (19.7)	34 (66.7)	9 (34.6)	11 (36.7)
Devote >50% of their working time to research	45 (7.2)	11 (16.7)	11 (21.6)	6 (23.1)	7 (23.3)
Involved in developing guidelines	210 (33.4)	18 (27.3)	17 (33.3)	5 (19.2)	5 (16.7)

Data are presented as n or n (%).

still subjective, the decision of the clinician to prescribe additional systemic treatments better reflects daily clinical practice and it is often used in trials to determine treatment success or failure.

Need for higher level of care

This broad category encompasses 1) the need for hospital admission, and 2) the need for admission to the intensive care unit (ICU), for the presenting exacerbation. These outcomes are frequently evaluated in clinical trials. However, the indications for hospital or ICU admission vary across different centres and countries.

Hospital at home and telemonitoring options introduce heterogeneity in the criteria for hospital admission and length of stay [43]. This outcome is also impacted by nonclinical factors, such as social reasons for admission, discharge planning delays [44], the availability of hospital beds or travel distance. As a result, the panel recommends that the need for hospital admission should be defined pragmatically as a clinical need to admit a patient to the hospital, or to offer equivalent intensification of the monitoring or care, that may be provided in other settings (including the patients' home). Admissions for nonmedical (*e.g.* social) reasons should be reported separately. Appreciating the heterogeneity in the design of health services, the panel recommends that trialists should prospectively and transparently define in detail the reasons for a need for hospital admission in the context of each trial.

Indications for ICU admission also vary. Characteristically, while in most centres noninvasive ventilation (NIV) is now delivered in a respiratory ward or a high-dependency unit, in some centres it is still delivered in the ICU [45]. In addition, the availability of ICU beds may impact the decision to admit, and the duration of ICU stay. Conversely, patients with COPD with poor functional status and underlying multimorbidity are often not offered an ICU admission or invasive mechanical ventilation, due to futility [46]. The criteria used to support such decisions vary across centres and countries, according to local

TABLE 4 Summary of the selection process of the core outcomes from the longlist

COPD exacerbation outcomes considered	Delphi survey results			Consensus meeting	
	Patients and patient representatives	Health professionals	Researchers	Patients and patient representatives	Health professionals and researchers
Death outcomes					
Death from COPD exacerbation	81.8	94.5	96.9		
Death from any cause	68.5	74.8	84.0	100	100
Clinical and physiological outcomes					
Anxiety	35.5	27.0	28.3		
Breathlessness	79.3	93.3	94.9		
Chest discomfort	15.8	5.8	8.2		
Fatigue	54.2	46.3	44.7		
Cough	49.3	54.3	53.6		
Coughing up blood (haemoptysis)	62.1	58.3	46.8		
Production of dark-coloured sputum	56.7	58.5	53.6		
Sputum amount	38.4	42.0	35.5		
Sputum thickness (ease of expectoration)	40.4	41.8	29.0		
Wheeze	39.4	46.8	35.2		
Appetite	24.6	17.5	14.0		
Change in weight	33.5	25.8	23.9		
Respiratory muscle strength	65.5	58.8	47.8		
Low mood/depression	41.9	35.5	40.6		
Sleep quality	51.7	38.3	35.5		
Early-morning symptoms	36.5	32.0	25.6		
Night-time symptoms	45.8	50.3	41.3		
Treatment success (or failure)	80.3	87.8	89.1		
Worsening of symptoms after the initial treatment	71.9	78.5	77.1		
Disease progression	83.7	88.8	86.7		
Future exacerbations	75.9	89.3	90.4		
Lung function during and immediately after the exacerbation	71.4	54.3	43.0	7.7	11.1
Permanent deterioration in lung function	87.7	88.5	82.3		
Levels of oxygen and carbon dioxide in the blood (arterial blood gases)	76.4	80.3	75.4		
Development of pneumonia	76.4	86.8	83.6		
Development of resistant bacteria	73.4	80.8	70.6		
Damage of lung cells and lung tissue	81.3	71.5	57.3	38.5	22.2
Infection by bacteria (bugs) or viruses	72.4	68.0	64.8	92.9	68.4
Inflammation in the lungs/airways	73.4	61.5	49.1	50.0	27.8
Adverse event outcomes					
Adverse events of treatments	60.6	58.3	65.9		
Serious adverse events from treatments	76.8	89.5	93.5		
Development and/or progression of other diseases (*e.g.* heart attack)	67.5	69.5	69.6		
Resource use outcomes					
Need for hospital admission for the presenting exacerbation	69.0	84.6	90.8	100	100
Length of hospital stay for the exacerbation	45.3	62.3	68.3		
Future hospital admissions	52.2	70.5	76.5	71.4	77.8
Need for NIV use for the exacerbation	64.0	83.5	81.9	61.5	78.6
Length of NIV use for the exacerbation	58.1	60.25	57.0		
Need for admission to the ICU for the exacerbation	71.9	86.8	88.7		
Length of stay in the ICU for the exacerbation	63.1	72.8	71.0	38.5	50
Need for additional medications to achieve symptom control	64.5	59.5	57.3		
Need for long-term administration of supplemental oxygen after the exacerbation	58.6	62.8	66.9		
Need for long-term use of NIV after the exacerbation	55.7	69.5	65.5		

Continued

TABLE 4 Continued

COPD exacerbation outcomes considered	Delphi survey results			Consensus meeting	
	Patients and patient representatives	Health professionals	Researchers	Patients and patient representatives	Health professionals and researchers
Life-impact outcomes					
Ability to exercise	57.6	51.0	60.4		
Physical strength	48.8	38.3	35.5		
Walking distance	57.6	67.3	68.3		
Activities of daily living	70.4	82.5	84.6		
Health-related quality of life	75.4	82.5	87.7		
Social engagement/isolation	54.2	50.5	50.5		
Treatment adherence	72.4	83.8	84.6		
Impact on family members and caregivers	56.7	50.3	47.4		
Impact on sexual function	36.0	36.3	37.5		

Sources of outcomes
- Methodological systematic reviews
- Qualitative interviews
- Delphi survey (round 1)

Outcome selection results
- Included
- Inconclusive
- Excluded

Data are presented %. Percentages refer to the proportion of participants who consider a particular outcome critical. NIV: noninvasive ventilation; ICU: intensive care unit.

policies and availability of resources. Acknowledging that the main, consistent indication for ICU admission in this group of patients is the need for invasive mechanical ventilation, the panel recommended that trials should record the need for invasive mechanical ventilation, defined as 1) persistent or deteriorating respiratory acidosis, despite optimised medical treatment and delivery of NIV; 2) persistent or deteriorating respiratory acidosis despite optimised medical treatment and a contraindication to the use of NIV, for example due to upper airway obstruction, facial burns or severe facial deformities, where fitting a mask is impossible; or 3) respiratory arrest or peri-arrest situations, unless there is a rapid recovery from manual ventilation or provision of NIV [46]. The decision to focus on the need for invasive mechanical ventilation rather than the receipt of ventilation was based on the earlier observation that often, while these criteria are fulfilled, patients are not offered invasive ventilation, due to futility.

Levels of oxygen and carbon dioxide in the blood (arterial blood gases)

This was considered a setting- and intervention-specific outcome. Firstly, it may not be feasible to be assessed in studies recruiting in an outpatient clinic. The panel agreed that the value of measuring blood levels of oxygen and carbon dioxide in this setting may be limited.

Breathlessness

The most frequently used validated scales for measuring breathlessness in trials focusing on the management of COPD exacerbations were the Borg scales (original or modified version) and the modified Medical Research Council (mMRC) scale, while this symptom was also frequently quantified as part of the COPD Assessment Test (CAT) [23]. More specifically, mMRC does not directly assess breathlessness, as it is a measure of activity limitation due to breathlessness. Use of mMRC during an exacerbation was considered by the panel to be less sensitive, since most patients with moderate or severe exacerbations would cluster in grade 4 (“too breathless to leave the house or breathless when dressing or undressing”), thus limiting the discriminant validity of the scale in this context. CAT is a multidimensional health status tool measuring several symptoms, and therefore does not provide a focus on breathlessness [47]. The modified Borg scale is easy to complete, and broadly used in clinical practice and research. Clinically validated translations are available in many languages. Its measurement properties have been thoroughly and positively assessed [48] (appendix 6.7, supplementary material). As a result, the modified Borg scale is recommended for evaluating breathlessness. It should be measured at approximately the same time every day. It can be self-completed.

Health-related quality of life

CAT is the most frequently used validated tool for assessing health-related quality of life in trials on the management of exacerbations, followed by the St George’s Respiratory Questionnaire (SGRQ) and the

BOX 1 Core outcome set for clinical trials evaluating the management of COPD exacerbations. Detailed descriptions of the outcomes are available in the text and appendix 6 (supplementary material)

- 1) Death
  - a) Death from any cause
  - b) Death from a COPD exacerbation
- 2) Treatment success
- 3) Need for higher level of care
  - a) Need for hospital admission for the presenting exacerbation
  - b) Need for admission to the intensive care unit for the exacerbation
- 4) Levels of oxygen and carbon dioxide in the blood (arterial blood gases)
- 5) Patient-reported outcomes
  - a) Breathlessness
  - b) Health-related quality of life
  - c) Activities of daily living
  - d) Worsening of symptoms after the initial treatment
- 6) Future impact
  - a) Disease progression
  - b) Future exacerbations
  - c) Future hospital admissions
- 7) Safety
  - a) Serious adverse events from treatments
  - b) Development of resistant bacteria
  - c) Development of pneumonia
- 8) Treatment adherence

Chronic COPD Questionnaire [23]. A systematic review using the COSMIN methodology for evaluating the measurement properties of 23 instruments used to assess quality of life in COPD recommended the use of CAT, Chronic Respiratory Questionnaire, SGRQ or the Living with Chronic Obstructive Pulmonary Disease Questionnaire [49]. While these tools have similar measurement properties (appendix 6.8, supplementary material), CAT can be completed within 1–3 min, while the other tools are more complex and time consuming. Given that CAT is already the most frequently used tool for evaluating health-related quality of life, it was recommended by the panel. A comparison with a baseline estimate of the health-related quality of life prior to the exacerbation would be preferable, but in larger randomised studies, balance in the baseline characteristics of participants in the study groups will usually suffice.

Activities of daily living

This outcome is rarely evaluated in exacerbation trials [23]. ADL are classified as basic and instrumental [50]. Basic ADL are simple activities that are essential for independent life, such as self-care (showering, dressing or grooming) and basic mobility, while instrumental ADL encapsulate more complex activities, requiring higher functioning, such as preparing meals, home maintenance, shopping, handling finances and travelling alone [51]. Instrumental ADL are less relevant during an exacerbation, especially during severe exacerbations, while patients are admitted in the hospital and may not be able to undertake such complex activities; however, they are pertinent to quantify the overall impact of an exacerbation on a patient's ADL. For this reason, the panel decided to recommend a tool focusing on basic ADL, to be evaluated during the exacerbation and a second tool, assessing both basic and instrumental ADL for longer-term follow-up.

The psychometric properties of instruments used to quantify ADL in patients with COPD have been evaluated in two methodological systematic reviews [51, 52]. Five of the identified instruments focused on basic ADL, of which the Katz Activities of Daily Living Scale, the Barthel index and the motor subscale of the functional independence measure were not disease specific and included domains that are less relevant to COPD patients (*e.g.* control of bladder and bowels). While the Glittre index is disease specific, it focuses on exercise capacity and includes a simple exercise component, which many patients may find challenging to complete during an exacerbation. Finally, the Capacity of Daily Living During the Morning (CDLM) Questionnaire [53] is a simple, disease-specific questionnaire, with measurement properties adequately evaluated with favourable findings (appendix 6.9, supplementary material). For this reason, the CDLM tool was recommended for quantifying basic ADL during an exacerbation.

The identified methodological reviews revealed eight disease-specific tools assessing a combination of instrumental and basic ADL [51, 52]. Responsiveness to change in a patient's clinical condition, a crucial characteristic required for evaluating the impact of exacerbation on ADL, has only been confirmed for

TABLE 5 Outcome measurement instrument recommendations

Death from any cause	Death from any cause during study period. Record date of death.
Death from COPD exacerbation	Consider the immediate cause of death as documented in the death summary. In cases of death due to an immediate complication of an exacerbation, such as a ventricular arrhythmia, massive pulmonary embolism or myocardial infarction, the exacerbation should be considered the cause of death. Ideally, cause of death will need to be confirmed by a blinded adjudication committee. However, this may not always be feasible.
Treatment success	Treatment success defined as sufficient improvement of the signs and symptoms of the exacerbation that no additional systemic treatments (antibiotics or systemic corticosteroids) are required.
Need for hospital admission for the presenting exacerbation	A clinical need to admit a patient to the hospital, or equivalent intensification of the monitoring or care that may be provided in other settings (including patient's home). Admissions for social reasons should be reported separately. For evaluation of this outcome, investigators should record whether a patient required admission at any time point and whether they still required hospital admission at a specific follow-up time point.
Need for admission to the ICU for the presenting exacerbation	Need for ICU admission should be evaluated on the basis of the need for invasive mechanical ventilation, defined as: 1) persistent or deteriorating respiratory acidosis despite optimised medical treatment and delivery of NIV; 2) persistent or deteriorating respiratory acidosis despite optimised medical treatment and a contraindication for the use of NIV, for example due to severe facial deformity where fitting a mask is impossible, upper airway obstruction, or facial burns; 3) respiratory arrest or peri-arrest situations unless there is a rapid recovery from manual ventilation or provision of NIV. For evaluation of this outcome, investigators should record whether a patient required admission at any time point and whether they still require ICU admission at a specific follow-up time point.
Levels of oxygen and carbon dioxide in the blood (arterial blood gases)	A setting- and intervention-specific outcome. A baseline and at least one follow-up measurement are required with a clear indication of whether or not the patient was receiving oxygen at the time of the measurement, and if yes, how much. It may not be feasible for studies evaluating outpatients.
Breathlessness	Breathlessness should be evaluated using the modified Borg scale. It should be measured at approximately the same time every day. It can be self-completed.
Health-related quality of life	The COPD Assessment Test should be used for assessing health-related quality of life.
Activities of daily living	The Capacity of Daily Living During the Morning Questionnaire should be used for evaluating basic activities of daily living during the exacerbation. The Manchester Respiratory Activities of Daily Living Questionnaire should be used for evaluating basic and instrumental activities of daily living, during recovery (long-term impact of the exacerbation).
Worsening of symptoms after the initial treatment	The modified Borg scale and the COPD Assessment Test should be used to detect symptom worsening after the initial treatment.
Disease progression	Permanent deterioration in lung function should be used to evaluate the impact of exacerbations on disease progression. Two pulmonary function tests during stable clinical condition are needed: one within 6 months prior to the index exacerbation, and one within 2–6 months afterwards. Change from baseline in FEV_1, FVC and FEV_1/FVC ratio should be noted. The number of exacerbations experienced between the two measurements should be noted. Ideally, only the index exacerbation should be included between the two measurements. Disease progression as a core outcome is only relevant for longer-term studies that recruit participants during stable disease state, in anticipation of an exacerbation.
Future exacerbations	Future exacerbations, noting whether they are moderate or severe, after treatment success is confirmed.
Future hospital admissions	Future hospital admissions for any medical reason, or equivalent intensification of the monitoring or care that may be provided in other settings, after treatment success is confirmed.
Serious adverse events from treatments	Following the definition of the International Council for Harmonisation. A serious adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment, that fulfils any of the following: 1) results in death; 2) is life threatening; 3) requires inpatient hospitalisation or prolongation of existing hospitalisation; 4) results in persistent or significant disability/incapacity; 5) is a congenital anomaly or birth defect. Suspected unexpected serious adverse reactions should also be reported.
Development of resistant bacteria	Trials evaluating antimicrobials, antimicrobial stewardship strategies, novel immune modifiers or other interventions that may affect bacterial resistance should evaluate bacterial resistance to the administered antibiotics in spontaneous sputum. As a minimum, resistance should be evaluated at baseline and within a week after treatment completion. Sputum induction may provide additional information. However, in each study, researchers should consider the balance between the added value compared to the risk, participants' discomfort and required resources.
Development of pneumonia	Pneumonia confirmed by the presence of new consolidation upon chest radiography or other imaging modalities of the chest, in the presence of consistent clinical signs and symptoms. When possible, chest imaging should be acquired at baseline, to assess for the presence of pneumonia. This may not be possible for trials recruiting patients outside the hospital setting. Follow-up chest imaging should be driven by clinical need.
Treatment adherence	An intervention-specific outcome. Methods for assessing treatment adherence should be reported clearly.
■ Strong recommendation	■ Interim recommendation, with research agenda

ICU: intensive care unit; NIV: noninvasive ventilation; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

three of these tools: the Manchester Respiratory Activities of Daily Living Questionnaire (MRADL) [54], the COPD Activity Rating Scale (CARS) [55], and the 11-item Pulmonary Functional Status Scale (PFSS-11) [56]. While all three tools were considered valid options, the performance characteristics of the MRADL questionnaire were more thoroughly validated compared to CARS, while it was also considered simpler to complete, compared to the PFSS-11 tool (appendix 6.9, supplementary material). For promoting consistency, the panel recommends that the MRADL questionnaire be used to evaluate both basic and instrumental ADL at recovery from COPD exacerbations. A comparison with a baseline estimate of the ADL prior to the exacerbation would be beneficial and could potentially be captured retrospectively during recruitment. Recall bias is anticipated to be limited, since in most cases, the duration of the acute event at recruitment would rarely exceed a week and the questions refer to some of the most critical activities of daily living.

Disease progression

This outcome was suggested by patients during the qualitative research studies that preceded the Delphi survey. Acute exacerbations are known to accelerate disease progression in patients with COPD [42, 57, 58]. Several parameters have been used as potential measures of disease progression, including symptom burden, health status, exercise capacity, blood biomarkers, pulmonary function decline or radiologic progression revealed in computed tomography of the chest [58–62].

There was agreement within the panel that evaluation of disease progression as an outcome in exacerbation trials is only meaningful as change from baseline; therefore, a baseline measurement is required. To achieve that, participants would have to be recruited while the disease is stable, in anticipation of developing an exacerbation. However, such a study design requires significantly more resources and prolonged follow-up periods or a patient database with recent measurement taken during periods of clinical stability.

Not surprisingly, disease progression is only rarely evaluated as an outcome in exacerbation trials using objective tests [23]. Change from baseline in pulmonary function was only assessed in two of the trials included in the methodological systematic review, while imaging was not used in any of the studies as an estimate of disease progression. Symptoms and quality of life are evaluated frequently, but not as change from baseline (see the respective outcomes).

Change in forced expiratory volume in 1 s (FEV_1) over time is the most established instrument for evaluating COPD progression in clinical trials and observational studies evaluating the management of disease longitudinally, and for this reason, the panel recommends that it should also be used for evaluating the impact of exacerbations on disease progression. Acknowledging the limitations of this study design, the panel recommends that this outcome only be considered core for long-term studies where baseline values can be captured. Acknowledging the limitations of this study design, the panel recommends that this outcome only be considered core for long-term studies where baseline values can be captured.

Development of resistant bacteria

Antimicrobial resistance is often explored as part of a composite microbiological response outcome in trials involving antibiotics as interventions [23]. Bacterial growth and resistance are usually evaluated in spontaneous sputum, while in the absence of sputum bacterial eradication is presumed and is not further assessed. The panel adopts this approach and recommends that trials evaluating antimicrobials, antimicrobial stewardship strategies, novel immune modifiers or other interventions that may affect bacterial resistance should test bacterial resistance in spontaneous sputum. As a minimum, resistance should be explored at baseline and within a week after completion of the treatment. Sputum induction may provide additional information when spontaneous sputum is not available. However, in each study, researchers should consider the balance between the added value of sputum induction, compared to the risk, participant's discomfort and required resources.

Development of pneumonia

Development of pneumonia as a safety outcome is often evaluated in exacerbation trials [23]. Methodology is consistent and was adopted by this task force. Pneumonia should be confirmed by the presence of new consolidation in the chest radiograph or other imaging modalities of the chest, in the presence of consistent clinical signs and symptoms. When possible, chest imaging should be acquired at baseline, to assess for the presence of pneumonia. However, this may not be possible for trials recruiting patients outside the hospital setting. Follow-up chest imaging should be driven by clinical need.

Discussion

Based on a rigorous methodology, recommended by the COMET initiative, this task force developed a core outcome set for clinical trials assessing pharmacological and nonpharmacological interventions in COPD exacerbations. In addition, it recommended a single optimal measurement instrument for evaluating each core outcome and prioritised methodological research for further optimising some of these instruments in the future. This work was informed by systematic reviews, qualitative research involving 86 patients from 11 countries globally, an extensive, multi-stakeholder two-stage Delphi survey that was completed by 1063 participants from 88 countries and two multi-stakeholder consensus meetings with global representation. Uptake of the core outcome set by clinical trials and other clinical research studies is a critical measure of success and for this reason we have developed a dissemination strategy that is summarised in appendix 9.4 (supplementary material).

A key objective of the panel was to develop a pragmatic core outcome set, that would not require excessive resource commitment and would be feasible to be evaluated in all clinical trials, to promote implementation. While the final core outcome set includes more outcomes than some of the other sets, most of the selected outcomes are simple to assess, routinely collected, and do not require excessive resources. Moreover, when possible, the panel favoured the selection of simple and pragmatic measurement instruments, taking into consideration the time and resources required for capturing them. Recognising that disease progression can only be evaluated in trials of a longer-term and resource intensive design, the panel recommended that this outcome should only be assessed in this subgroup of trials. However, the importance of disease progression as an outcome should not be underestimated, and trialists are encouraged to consider appropriate study designs to capture it.

Several of the prioritised outcomes are currently only evaluated infrequently in relevant clinical trials [23]. Moreover, variability was observed in the instruments used to measure many of the core outcomes. These observations confirm that this work was indeed needed and can improve the consistency, quality and comparability of clinical trials on the management of exacerbations. While the panel was able to recommend one optimal instrument for consistently evaluating each of the core outcomes, most of these were considered interim recommendations, paired with a research agenda. Due to the variability in the instruments used in trials by now, adequate validation and information on the measurement properties of the instruments in the context of exacerbation trials to support strong recommendations was lacking. However, the recommendations of instruments were assessed based on currently available evidence, including data on the frequency that each instrument is used in exacerbation trials, but also previously conducted rigorous systematic reviews evaluating the measurement properties of all recommended patient reported outcomes [48, 49, 51, 52]. Still, trialists are encouraged to embed in their trials methodological research studies that could facilitate further optimisation of the measurement instruments. Similar challenges with the selection of outcomes and measurement instruments to be used have been identified in trials assessing the management of other acute respiratory events, including pneumonia, acute bronchitis, and the coronavirus disease 2019 [63–65]. Crosstalk among these fields could be beneficial.

COPD exacerbations represent an acute condition that can be successfully managed. Therefore, the timing of outcomes evaluation is a crucial parameter that should be optimised and standardised. This is especially so for the precise time when the overall treatment outcome (treatment success) is assessed. However, our methodological systematic review did not conclude on the optimal measurement time point due to significant clinical and methodological heterogeneity of the included studies [23]. Consequently, further data are needed to inform the optimal time point for evaluating treatment success, and our panel was not able to produce informed recommendations. Moreover, the duration of follow-up is trial specific, and the panel opted not to recommend a minimum duration of follow-up. However, to promote consistency and comparability, it is suggested that longer-term outcomes should be evaluated at 3 and 6 months from recruitment if the selected follow-up duration includes one or both time points. Moreover, it is suggested that the outcomes should be evaluated at specific time points, rather than at discharge or at symptom relief, since such “mobile” time points might introduce bias.

While this core outcome set and measurement instruments were developed for clinical trials in COPD exacerbations, it would be important to be captured also in observational studies as this could facilitate the validation and optimisation of the measurement instruments recommended for each outcome. While this is the first formal core outcome set for COPD exacerbation trials, COPD exacerbation outcomes have been prioritised by two other initiatives. The eo-Drive trial group (Eosinophil-driven Corticotherapy for Patients Hospitalized for COPD Exacerbation; NCT04234360) prioritised outcomes for their clinical trial [66] and CICERO (Collaboration in COPD Exacerbations ERS clinical research collaboration) developed standards for clinical assessment, management and follow-up of hospitalised exacerbations [67]. While this core

outcome set is broader than the outputs of the previous initiatives, as described in appendix 9.1 (supplementary material), all previously prioritised outcomes are included in our core outcome set and that could further promote consistency.

A potential limitation of this work is that it did not fully follow the methodology proposed by the COSMIN recommendations for selecting the recommended outcome instruments. COSMIN recommends *de novo* conduct of methodological systematic reviews to evaluate the measurement properties of all available instruments that could be used to assess an outcome, and is particularly relevant for patient-reported outcomes. While it was not feasible to complete these as part of an ERS task force, we identified relevant high-quality methodological systematic reviews, evaluating the available instruments for all patient-reported outcomes that were included in the core outcome set, which were used to inform our recommendations. Despite our best efforts, the Delphi survey was somewhat limited by the lack of respondents from low-income countries. Lack of access or engagement represent a recognised problem, limiting the participation of people from low-income countries to such online surveys [68]. Given the wide geographic distribution and multi-stakeholder involvement of our sample, and the similar responses across lower-middle, upper-middle and high income countries, we do not believe that significantly limits the generalisability of our findings. The prospectively published, transparent protocol represent a major strength of this study. Unfortunately, we had to deviate from the protocol on two occasions; these deviations are described and justified in detail in appendices 3.6 and 9.3 (supplementary material).

In summary, this task force developed a core outcome set for trials in acute exacerbations of COPD and recommended an optimal instrument for measuring each of the core outcomes, aiming to improve the consistency, quality and comparability of future relevant clinical trials.

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References

1 Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. *Lancet* 2007; 370: 786–796.

2 Singh D, Agusti A, Anzueto A, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. *Eur Respir J* 2019; 53: 1900164.

3 Mathioudakis AG, Janssens W, Sivapalan P, *et al.* Acute exacerbations of chronic obstructive pulmonary disease: in search of diagnostic biomarkers and treatable traits. *Thorax* 2020; 75: 520–527.

4 Hastie AT, Martinez FJ, Curtis JL, *et al.* Association of sputum and blood eosinophil concentrations with clinical measures of COPD severity: an analysis of the SPIROMICS cohort. *Lancet Respir Med* 2017; 5: 956–967.
5 Gayle A, Dickinson S, Morris K, *et al.* What is the impact of GOLD 2017 recommendations in primary care? – a descriptive study of patient classifications, treatment burden and costs. *Int J Chron Obstruct Pulmon Dis* 2018; 13: 3485–3492.
6 Rothnie KJ, Müllerova H, Smeeth L, *et al.* Natural history of chronic obstructive pulmonary disease exacerbations in a general practice-based population with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2018; 198: 464–471.
7 Kardos P, Vogelmeier C, Worth H, *et al.* A two-year evaluation of the 'real life' impact of COPD on patients in Germany: the DACCORD observational study. *Respir Med* 2017; 124: 57–64.
8 Wedzicha JA, Miravitlles M, Hurst JR, *et al.* Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J* 2017; 49: 1600791.
9 Han MK, Quibrera PM, Carretta EE, *et al.* Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort. *Lancet Respir Med* 2017; 5: 619–626.
10 Müllerová H, Shukla A, Hawkins A, *et al.* Risk factors for acute exacerbations of COPD in a primary care population: a retrospective observational cohort study. *BMJ Open* 2014; 4: e006171.
11 Wedzicha JA, Calverley PMA, Albert RK, *et al.* Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J* 2017; 50: 1602265.
12 Dobler CC, Morrow AS, Beuschel B, *et al.* Pharmacologic therapies in patients with exacerbation of chronic obstructive pulmonary disease: a systematic review with meta-analysis. *Ann Intern Med* 2020; 172: 413–422.
13 Dobler CC, Morrow AS, Farah MH, *et al.* Nonpharmacologic therapies in patients with exacerbation of chronic obstructive pulmonary disease: a systematic review with meta-analysis. *Mayo Clin Proc* 2020; 95: 1169–1183.
14 McDonald VM, Osadnik CR, Gibson PG. Treatable traits in acute exacerbations of chronic airway diseases. *Chron Respir Dis* 2019; 16: 1479973119867954.
15 Kefala AM, Fortescue R, Alimani GS, *et al.* Prevalence and clinical implications of respiratory viruses in stable chronic obstructive pulmonary disease (COPD) and exacerbations: a systematic review and meta-analysis protocol. *BMJ Open* 2020; 10: e035640.
16 Papi A, Bellettato CM, Braccioni F, *et al.* Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med* 2006; 173: 1114–1121.
17 Bafadhel M, McKenna S, Terry S, *et al.* Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med* 2011; 184: 662–671.
18 Sivapalan P, Lapperre TS, Janner J, *et al.* Eosinophil-guided corticosteroid therapy in patients admitted to hospital with COPD exacerbation (CORTICO-COP): a multicentre, randomised, controlled, open-label, non-inferiority trial. *Lancet Respir Med* 2019; 7: 699–709.
19 Mathioudakis AG, Chatzimavridou-Grigoriadou V, Corlateanu A, *et al.* Procalcitonin to guide antibiotic administration in COPD exacerbations: a meta-analysis. *Eur Respir Rev* 2017; 26: 160073.
20 Butler CC, Gillespie D, White P, *et al.* C-reactive protein testing to guide antibiotic prescribing for COPD exacerbations. *N Engl J Med* 2019; 381: 111–120.
21 Agusti A, Faner R, Celli B, *et al.* Precision medicine in COPD exacerbations. *Lancet Respir Med* 2018; 6: 657–659.
22 Mathioudakis AG, Sivapalan P, Papi A, *et al.* The DisEntangling Chronic Obstructive pulmonary Disease Exacerbations clinical trials NETwork: DECODE-NET: rationale and vision. *Eur Respir J* 2020; 56: 2000627.
23 Mathioudakis AG, Moberg M, Janner J, *et al.* Outcomes reported on the management of COPD exacerbations: a systematic survey of randomised controlled trials. *ERJ Open Res* 2019; 5: 00072-02019.
24 Mathioudakis AG, Janner J, Moberg M, *et al.* A systematic evaluation of the diagnostic criteria for COPD and exacerbations used in randomised controlled trials on the management of COPD exacerbations. *ERJ Open Res* 2019; 5: 00136-02019.
25 Vollenweider DJ, Frei A, Steurer-Stey CA, *et al.* Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2018; 10: CD010257.
26 Walters JA, Tan DJ, White CJ, *et al.* Different durations of corticosteroid therapy for exacerbations of chronic obstructive pulmonary disease. *Emergencias* 2020; 32: 363–364.
27 Williamson PR, Altman DG, Bagley H, *et al.* The COMET Handbook: version 1.0. *Trials* 2017; 18: Suppl. 3, 280.
28 't Hoen LA, Groen J, Scheepe JR, *et al.* A quality assessment of patient-reported outcome measures for sexual function in neurologic patients using the consensus-based standards for the selection of health measurement instruments checklist: a systematic review. *Eur Urol Focus* 2017; 3: 444–456.
29 Mathioudakis AG, Abroug F, Agusti A, *et al.* Core outcome set for the management of acute exacerbations of chronic obstructive pulmonary disease. The COS-AECOPD ERS task force study protocol. *ERJ Open Res* 2020; 6: 00193-2020.
30 Kirkham JJ, Davis K, Altman DG, *et al.* Core outcome Set – STAndards for development: the COS-STAD recommendations. *PLoS Med* 2017; 14: e1002447.

31 Kirkham JJ, Gorst S, Altman DG, *et al.* Core Outcome Set – STAndards for Reporting: the COS-STAR statement. *PLoS Med* 2016; 13: e1002148.
32 Zhang Y, Morgan RL, Alonso-Coello P, *et al.* A systematic review of how patients value COPD outcomes. *Eur Respir J* 2018; 52: 1800222.
33 Kouijzer M, Brusse-Keizer M, Bode C. COPD-related fatigue: impact on daily life and treatment opportunities from the patient's perspective. *Respir Med* 2018; 141: 47–51.
34 Rosa F, Bagnasco A, Ghirotto L, *et al.* Experiences of older people following an acute exacerbation of chronic obstructive pulmonary disease: a phenomenological study. *J Clin Nurs* 2018; 27: e1110–e1119.
35 Kessler R, Ståhl E, Vogelmeier C, *et al.* Patient understanding, detection, and experience of COPD exacerbations: an observational, interview-based study. *Chest* 2006; 130: 133–142.
36 Mokkink LB, Terwee CB, Patrick DL, *et al.* The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Qual Life Res* 2010; 19: 539–549.
37 Zvezdin B, Milutinov S, Kojicic M, *et al.* A postmortem analysis of major causes of early death in patients hospitalized with COPD exacerbation. *Chest* 2009; 136: 376–380.
38 Seemungal TA, Donaldson GC, Bhowmik A, *et al.* Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 161: 1608–1613.
39 Aaron SD, Donaldson GC, Whitmore GA, *et al.* Time course and pattern of COPD exacerbation onset. *Thorax* 2012; 67: 238–243.
40 McAuley HJC, Harvey-Dunstan TC, Craner M, *et al.* Longitudinal changes to quadriceps thickness demonstrate acute sarcopenia following admission to hospital for an exacerbation of chronic respiratory disease. *Thorax* 2021; 76: 726–728.
41 Spruit MA, Gosselink R, Troosters T, *et al.* Muscle force during an acute exacerbation in hospitalised patients with COPD and its relationship with CXCL8 and IGF-I. *Thorax* 2003; 58: 752–756.
42 Anzueto A. Impact of exacerbations on COPD. *Eur Respir Rev* 2010; 19: 113–118.
43 Jeppesen E, Brurberg KG, Vist GE, *et al.* Hospital at home for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012; 5: CD003573.
44 Bai AD, Dai C, Srivastava S, *et al.* Risk factors, costs and complications of delayed hospital discharge from internal medicine wards at a Canadian academic medical centre: retrospective cohort study. *BMC Health Serv Res* 2019; 19: 935.
45 Trethewey SP, Edgar RG, Turner AM, *et al.* Ward-based non-invasive ventilation in acute exacerbations of COPD: a narrative review of current practice and outcomes in the UK. *Healthcare* 2018; 6: 145.
46 Davidson AC, Banham S, Elliott M, *et al.* BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. *Thorax* 2016; 71: Suppl. 2, ii1–i35.
47 Jones PW, Harding G, Berry P, *et al.* Development and first validation of the COPD Assessment Test. *Eur Respir J* 2009; 34: 648–654.
48 Dorman S, Byrne A, Edwards A. Which measurement scales should we use to measure breathlessness in palliative care? A systematic review. *Palliat Med* 2007; 21: 177–191.
49 Weldam SW, Schuurmans MJ, Liu R, *et al.* Evaluation of quality of life instruments for use in COPD care and research: a systematic review. *Int J Nurs Stud* 2013; 50: 688–707.
50 World Health Organization. International Classification of Functioning, Disability and Health (ICF). 2018. www.who.int/standards/classifications/international-classification-of-functioning-disability-and-health/
51 Janaudis-Ferreira T, Beauchamp MK, Robles PG, *et al.* Measurement of activities of daily living in patients with COPD: a systematic review. *Chest* 2014; 145: 253–271.
52 Liu Y, Li H, Ding N, *et al.* Functional status assessment of patients with COPD: a systematic review of performance-based measures and patient-reported measures. *Medicine* 2016; 95: e3672.
53 Partridge MR, Miravitlles M, Ståhl E, *et al.* Development and validation of the Capacity of Daily Living During the Morning questionnaire and the Global Chest Symptoms questionnaire in COPD. *Eur Respir J* 2010; 36: 96–104.
54 Yohannes AM, Roomi J, Winn S, *et al.* The Manchester Respiratory Activities of Daily Living questionnaire: development, reliability, validity, and responsiveness to pulmonary rehabilitation. *J Am Geriatr Soc* 2000; 48: 1496–1500.
55 Morimoto M, Takai K, Nakajima K, *et al.* Development of the chronic obstructive pulmonary disease activity rating scale: reliability, validity and factorial structure. *Nurs Health Sci* 2003; 5: 23–30.
56 Chen YJ, Narsavage GL, Culp SL, *et al.* The development and psychometric analysis of the short-form Pulmonary Functional Status Scale (PFSS-11). *Res Nurs Health* 2010; 33: 477–485.
57 Anzueto A, Leimer I, Kesten S. Impact of frequency of COPD exacerbations on pulmonary function, health status and clinical outcomes. *Int J Chron Obstruct Pulmon Dis* 2009; 4: 245–251.
58 Kerkhof M, Voorham J, Dorinsky P, *et al.* Association between COPD exacerbations and lung function decline during maintenance therapy. *Thorax* 2020; 75: 744–753.

59 Decramer M, Gosselink R, Rutten-Van Mölken M, *et al.* Assessment of progression of COPD: report of a workshop held in Leuven, 11–12 March 2004. *Thorax* 2005; 60: 335–342.

60 Jones PW, Agusti AG. Outcomes and markers in the assessment of chronic obstructive pulmonary disease. *Eur Respir J* 2006; 27: 822–832.

61 Shaw JG, Vaughan A, Dent AG, *et al.* Biomarkers of progression of chronic obstructive pulmonary disease (COPD). *J Thorac Dis* 2014; 6: 1532–1547.

62 Ash SY, San José Estépar R, Fain SB, *et al.* Relationship between emphysema progression at CT and mortality in ever-smokers: results from the COPDGene and ECLIPSE cohorts. *Radiology* 2021; 299: 222–231.

63 Weiss E, Zahar JR, Alder J, *et al.* Elaboration of consensus clinical endpoints to evaluate antimicrobial treatment efficacy in future hospital-acquired/ventilator-associated bacterial pneumonia clinical trials. *Clin Infect Dis* 2019; 69: 1912–1918.

64 Mathioudakis AG, Fally M, Hashad R, *et al.* Outcomes evaluated in controlled clinical trials on the management of COVID-19: a methodological systematic review. *Life* 2020; 10: 350.

65 Mathioudakis AG, Fally M, Hashad R, *et al.* COVID-19 clinical trials: unraveling a methodological Gordian knot. *Am J Respir Crit Care Med* 2020; 202: 635–637.

66 Suehs CM, Zysman M, Chenivesse C, *et al.* Prioritising outcomes for evaluating eosinophil-guided corticosteroid therapy among patients with acute COPD exacerbations requiring hospitalisation: a Delphi consensus study. *BMJ Open* 2020; 10: e035811.

67 Ramakrishnan S, Janssens W, Burgel PR, *et al.* Standardisation of clinical assessment, management and follow-up of acute hospitalised exacerbation of COPD: a Europe-wide consensus. *Int J Chron Obstruct Pulmon Dis* 2021; 16: 321–332.

68 Thakur N, Lovinsky-Desir S, Appell D, *et al.* Enhancing recruitment and retention of minority populations for clinical research in pulmonary, critical care, and sleep medicine: an official American Thoracic Society research statement. *Am J Respir Crit Care Med* 2021; 204: e26–e50.