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Review

Use of the Evaluating Respiratory Symptoms™ in COPD as an Outcome Measure in Clinical Trials: A Rapid Systematic Review

Donald M. Bushnell, MA[1] Rozanne Wilson, PhD[1] Florian S. Gutzwiller, MD, MPH[2] Nancy K. Leidy, PhD[1]
Carolina Hache, PhD[2] Chau Thach, PhD[2] Claus F. Vogelmeier, MD[3]

Abstract

Rationale: Patients with chronic obstructive pulmonary disease (COPD) struggle with respiratory symptoms that impair their daily activities and quality of life. Understanding a treatment's ability to relieve symptoms requires precise assessment. The Evaluating Respiratory Symptoms in COPD (E-RS™:COPD) was developed to quantify respiratory symptoms in clinical trials. This review study aimed to better understand how trials use this patient-reported outcome measure as an endpoint, as well as its responsiveness and performance relative to other outcome measures.

Objectives: To summarize the use of the E-RS:COPD in pharmacological trials since its qualification by regulatory authorities.

Methods: A rapid systematic literature review, using key biomedical databases to identify English language full-text publications of randomized controlled trials (RCTs) that included the E-RS:COPD as an endpoint (2010-2020), was conducted. Two investigators independently screened the publications and extracted data.

Measurements and Main Results: Of 219 screened records, 28 full-text publications were included, and data from 17 reporting 20 unique double-blind RCTs were synthesized. The E-RS:COPD was positioned as a primary or secondary endpoint in 6 publications (35%), and served as an exploratory or additional endpoint in 11 (65%). Statistically significant E-RS:COPD treatment effects versus placebo/comparator were found in 13 of the 14 publications reporting symptom results. E-RS:COPD effects corresponded well with other outcome measures (e.g., St George's Respiratory Questionnaire [SGRQ] and forced expiratory volume in 1 second [FEV_1]). Two publications reported the number of responders.

Conclusions: E-RS:COPD is sensitive to treatment effects in clinical trials testing drug therapies. Presentation of trial results should include responder analyses to facilitate interpretation and application of results.

Abbreviations: chronic obstructive pulmonary disease, **COPD**; Evaluating Respiratory Symptoms™ in Chronic Obstructive Pulmonary Disease, **E-RS™:COPD**; randomized controlled trials, **RCTs**; St George's Respiratory Questionnaire, **SGRQ**; forced expiratory volume in 1 second, **FEV_1**; patient-reported outcome, **PRO**; Food and Drug Administration, **FDA**; EXAcerbations of COPD Tool, **EXACT**; European Medicines Agency, **EMA**; population, intervention, comparator, and setting, **PICOS**; standard deviation, **SD**; long-acting muscarinic antagonists, **LAMAs**; long-acting beta2-agonists, **LABAs**; phosphodiesterase-4, **PDE4**; inhaled corticosteroid, **ICS**; CXC chemokine receptor 2, **CXCR2**; Transition Dyspnea Index, **TDI**; least squares, **LS**; minimal clinically important difference, **MCID**

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1 Evidera, Seattle, Washington, United States
2 Novartis Pharma AG, Basel, Switzerland.
3 Pulmonary and Critical Care Medicine, Department of Medicine, University Medical Centre Giessen and Marburg, Philipps-Universität Marburg, Germany and Member of the German Centre for Lung Research (DZL), Marburg, Germany

Address correspondence to:

Donald Bushnell, MA
Evidera
615 2nd Ave., Suite 500
Seattle, WA 98104
Email: Don.Bushnell@evidera.com

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Introduction

Although respiratory symptoms during stable (non-exacerbating) states are a burden to patients with chronic obstructive pulmonary disease (COPD) and a primary reason for clinic visits,[1] relatively little is known about how this outcome is affected by treatments. Precise measurement of respiratory symptoms is important for testing bronchodilators, and even more so for testing new treatments that provide symptomatic relief with benefits more directly associated with symptomatic relief than airflow limitation. The Evaluating Respiratory Symptoms™ in Chronic Obstructive Pulmonary Disease (E-RS™:COPD) is a patient-reported outcome (PRO) measure developed to quantify the severity of respiratory symptoms and test the effects of treatment in clinical trials of stable COPD.

Development of the E-RS:COPD was consistent with standards in the field and United States Food and Drug Administration (FDA) PRO guidance.[2] The total score represents overall respiratory symptom severity, with 3 sub-scales capturing breathlessness (5 items), cough and sputum (3 items), and chest symptoms (3 items). The 11 items comprising this instrument are part of an existing measure, the 14-item EXAcerbations of COPD Tool (EXACT).[3] Content validity of the E-RS:COPD was addressed through primary and secondary analyses of qualitative data.[4] Quantitative, secondary analyses of observational and clinical trial data showed the E-RS:COPD to be reliable with total and subscale scores possessing high levels of internal consistency and reproducibility.[4,5] Validity was supported by consistent relationships between the E-RS:COPD and measures of health status (St George's Respiratory Questionnaire [SGRQ]), pulmonary function (forced expiratory volume in 1 second [FEV_1]% predicted), and symptom questionnaires (SGRQ Symptoms, modified Medical Research Council dyspnea status) and known-groups analyses, including smoking status and rescue medication use.[4,5] Tests of E-RS:COPD responsiveness were conducted in data from 3 Phase 2 clinical trials.[5] Because these trials did not show significant treatment effects in the primary or secondary endpoints, data were stratified into sub-groups experiencing improvement/no improvement from baseline to week 12 using published responder definitions for 4 criterion variables, including the SGRQ (>4 point change) and 6-minute walk test (>26 meters). Results showed E-RS:COPD scores were sensitive to change. Criterion- and distribution-based methods were used to estimate responder thresholds for interpretation (total score ≥2-unit decrease (improvement); subscales: breathlessness score ≥1-unit; cough and sputum and chest symptom ≥0.7-unit).[5]

Detailed reports on the psychometric properties of the E-RS:COPD were provided to regulatory health authorities during a multi-year, multi-review process culminating in the qualification of the instrument by the European Medicines Agency (EMA)[6] in 2015 and the FDA[7] in 2016 as an exploratory endpoint in drug development trials. However, little is known about how the E-RS:COPD has been used as an endpoint in clinical trials and how the E-RS:COPD has performed since its qualification. Together, this information is of interest to health authorities and researchers because it will help inform its optimal use in future clinical trials. This review study aimed to identify published pharmaceutical clinical trials that have used the E-RS:COPD measure as an endpoint and summarize these trials, including trial design, endpoint position, and treatment effects, alone and relative to other endpoints.

Methods

This rapid systematic review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and employed several methods that adhere to the scientific rigor, transparency, reproducibility principles of a systematic review, including screening and extracting conducted by 2 independent reviewers, and risk of bias assessment conducted by 2 independent reviewers.[8-12] To accelerate the review process, constraints were applied to year of publication, publication type, study design, language, and number of data sources, as well as producing a structured narrative synthesis.

Search Strategy and Selection Criteria

Detailed search criteria are summarized in Table E1 (in the online data supplement). MEDLINE, Embase, and the Cochrane Central Register of Clinical Trials were searched via Ovid for full-text publications published between January 1, 2010 and October 31, 2020 (Table E2 in the online data supplement). The 2010 start date was selected based on the initial availability of the measure to sponsors for exploratory use in their trials before publication of the E-RS:COPD, qualification, and widespread availability. To identify ongoing trials, Embase was searched for conference abstracts published between January 1, 2019 and October 31, 2020 (Table E3 in the online data supplement).

Screening of records, assessment for risk of bias, data extraction, and quality control was conducted by 2 independent reviewers using Covidence software (Veritas Health Innovation, Melbourne, Australia),[13] recommended by the Cochrane Effective Practice and Organization of Care.[14] After duplicates were removed, titles and abstracts were screened by 2 trained independent reviewers, using the pre-defined screening tool (see Table E4 in the online data supplement), and classified as include, exclude, or unsure. Next, full texts of records were assessed for study eligibility using the study's pre-defined eligibility criteria (Table E5 in the online data supplement) by the same independent reviewers. Any discrepancies were resolved by consensus, with disputes resolved by a third investigator (first author: DMB).

Data Extraction

Two independent reviewers extracted key data elements within the population, intervention, comparator, and setting (PICOS) framework from all published full-text publications and assessed each publication's risk of bias using the criteria outlined by the Cochrane Risk of Bias tool[15,16] and guidance from the Cochrane Effective Practice and Organization of Care group.[17] Data extraction and quality assessment were conducted using the Covidence software. The PICOS framework and the objectives of this review were used to organize the data extraction tool. A full list of the detailed data extracted is provided in Table E6 in the online data supplement. Discrepancies were resolved by a consensus discussion, with disputes resolved by a third investigator (first author: DMB).

Synthesis

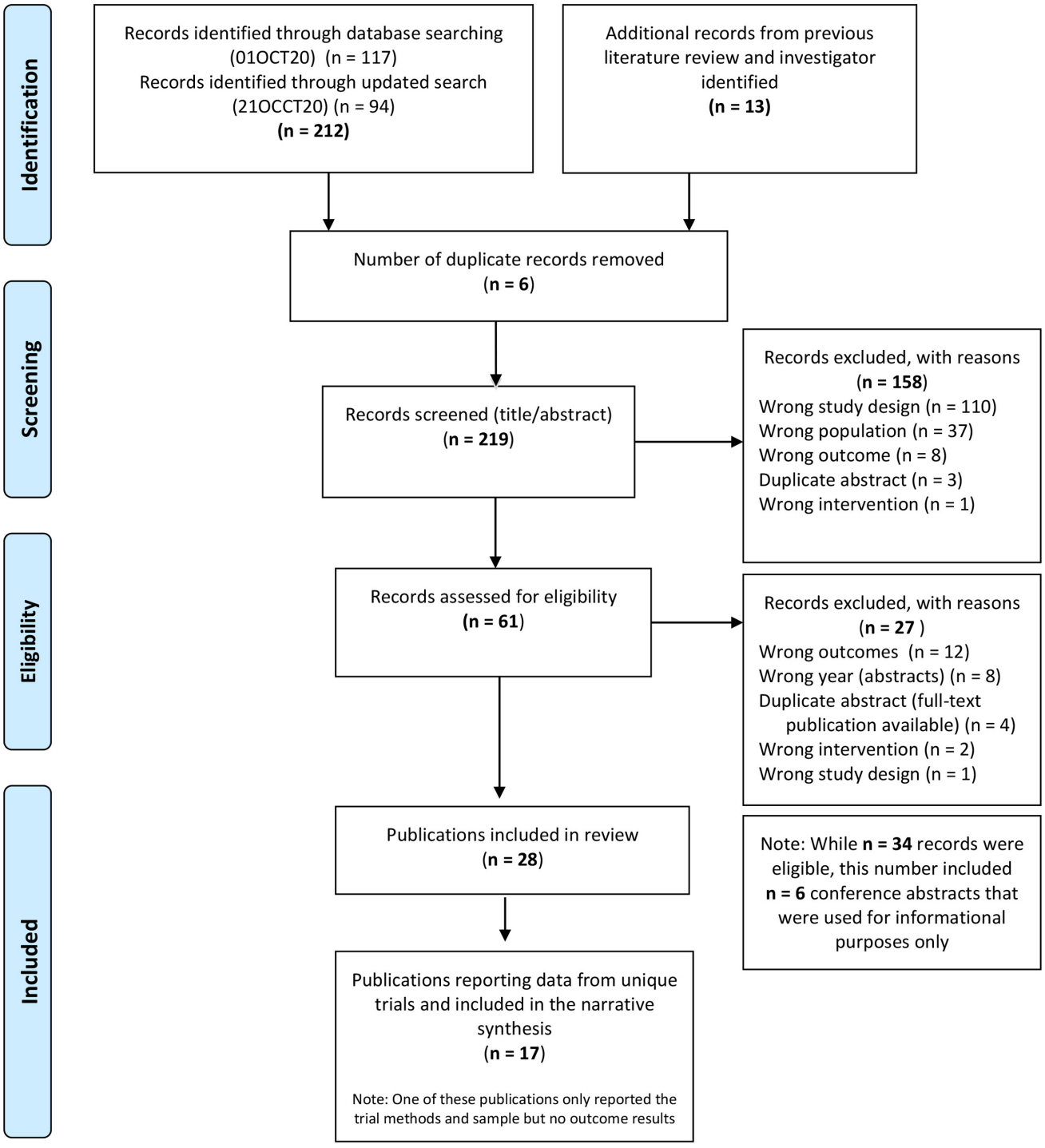
Descriptive statistics were used to summarize the key data elements extracted from all publications included in the review. To avoid trial duplication, publications that reported data from unique clinical trials were included in the narrative synthesis. Publications were classified by E-RS:COPD endpoint positioning (i.e., primary, secondary, exploratory), by the reported primary outcome measure, and by the main treatment intervention drug class. Within this classification framework, treatment effects for the E-RS:COPD and other relevant outcome measures were examined, with a focus on publications that included the E:RS:COPD as a primary or secondary endpoint. Correspondence between treatment effects observed with the E-RS:COPD and other outcomes were summarized. Finally, publications that reported a responder analysis were identified and summarized.

Results

Publication Selection

The literature search identified a total of 225 records (Figure 1). After the removal of duplicates (n=6), 219 titles and abstracts were screened for relevance, with 61 full-text publications screened for study eligibility. Figure 1 details the identification, screening process, and eligibility evaluation, as well as reasons for exclusion at each stage. Of the records screened for eligibility, 34 met the inclusion

Figure 1. Flow Diagram of the Identification, Screening, and Evaluation Process Used to Identify Clinical Trials That Used the Evaluating Respiratory Symptoms in COPD Tool to Assess Respiratory Symptoms in COPD Patients



criteria (28-full text publications; 6 conference abstracts). Conference abstracts were eligible in this rapid review but only for the purpose of identifying recent or ongoing trials including the E-RS:COPD. Therefore, 28 full-text publications were included in the review.

Overview of Included Publications

All 28 publications reported results from double-blind randomized controlled trials (RCTs):

- Seventeen publications reported data from 20 unique trials (3 publications included data from multiple trials).
- Five publications reported different findings from trials previously identified as unique.
- Six publications reported findings from pooled data that included 2 or more of the unique trials.

Overall, 12 publications (43%) reported main trial findings, 6 publications (21%) reported additional pre-specified trial findings, and 10 publications (36%) reported post-hoc or pooled analysis of trial data. Of the 17 publications reporting unique trial data, 1 was a design paper[18] with data limited to sample characteristics only. Because PICOS data elements were available, this paper is included in the narrative synthesis, with the sample size dropping to 16 when outcomes data are presented. Additional results for the 28 full-text publications are available in the online data supplement (Table E7 and Figure E1).

Risk of Bias: Of the 28 full-text publications included in this review, 4 publications were rated as having a low risk of bias across all 7 domains on the Cochrane Risk of Bias tool (14%). In the remaining 24 publications (86%), the majority of domains were rated as low risk: random sequence generation (86%), blinding of participants (89%), incomplete outcome (96%), selective reporting (89%), and other sources of bias (89%). The allocation of concealment and blinding of assessment outcomes domains were mostly rated as unsure risk of bias (75%; 57%, respectively).

Publications Included in the Narrative Synthesis (n=17)

Overall Characteristics: To avoid trial duplication, publications reporting data from unique trials[18-34] were included in the narrative synthesis (n=17). Trial characteristics are summarized in Tables 1-5. Most were multi-center international (n=10, 59%), phase 3 (n=10, 59%; Table 2) trials. Sample sizes ranged from 269 to 2431, with half (53%) including over 1000 participants. Study participants averaged 63.8 years of age (average range: 57 to 66 years) and were current or former smokers (Table 3) with moderate-to-severe (53%) or moderate-to-very-severe (24%) airflow limitation.

Treatment interventions were categorized as bronchodilator therapy (i.e., long-acting muscarinic antagonists [LAMAs]; long-acting beta2-agonists [LABAs]; phosphodiesterase-4 [PDE4] inhibitors), with or without inhaled corticosteroids (ICSs), and non-bronchodilator therapy (neutrophil elastase inhibitor; CXC chemokine receptor 2 [CXCR2] antagonist). Most publications included a bronchodilator therapy without ICSs (n=9/17, 53%) as the main treatment of interest, followed by LAMAs/LABAs (n=5, 29%; Table 4). Aclidinium bromide alone (n=3), or in combination with formoterol (n=2)/formoterol fumarate (n=1), was the most frequently investigated drug therapy, while only 2 non-bronchodilator drug therapies were investigated (AZD9668; Danirixin).

In addition to the E-RS:COPD, 11 different PRO measures were identified, with the majority of publications including 2 or more PRO measures (n=14, 82%; Table 5). Many publications included other PROs as a secondary endpoint (n=10, 59%).

Figure 2 visualizes the correspondence between the E-RS:COPD treatment effects (significant/non-significant) and other trial outcomes (PROs, FEV_1, number of exacerbations, rescue medications). Overall, statistically significant E-RS:COPD treatment effects corresponded with significant treatment effects in 8 other outcomes, including FEV_1 (59%), SGRQ (53%), and Transition Dyspnea Index (TDI) (35%; see upper right quadrant of Figure 2). Similarly, in instances when there were no E-RS:COPD treatment effects (non-significant), there were no treatment effects with other outcome measures. There were no divergent cases, i.e., non-significant E-RS:COPD effects with significant effects observed in other outcome measures (see upper left quadrant). There was also a clear pattern of correspondence between E-RS:COPD total and SGRQ total mean score changes from baseline to follow-up (treatment periods varied) (Figure 3).

E-RS:COPD as Primary or Secondary Endpoint in Unique Trials (n=6)

Characteristics: Six publications described trials that positioned the E-RS:COPD as a primary (n=2)

Table 1. Characteristics of Publications Reporting Use of the Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease Tool in Unique Clinical Trials[a]

First Author, Year	Clinical Trial Number, Trial Name, Funding Source	Trial Design Trail Phase Blinding Number of Treatment Groups	Setting Number of Sites Location	Total Number of Randomized Trial Participants	Severity of Airflow Limitation	Treatment Period (weeks)	Treatment Intervention Drug Class	Study Primary/Co-Primary Outcome Measure	Primary Outcome Reported Treatment Effects (yes/no)	E-RS:COPD Reported Treatment Effects (yes/no)
E-RS:COPD as the primary endpoint (n = 2)										
Lazaar 2020[21]	NCT03034967 Not reported GlaxoSmithKline	RCT: parallel-group Phase 2b Double-blind 5 groups	Multi-center 64 sites Multi-country: 9 countries (location not reported)	614	Moderate to severe	24 weeks	CXCR2 in addition to standard of care	E-RS: COPD (dose-response) vs. placebo Safety vs. placebo)	No	See primary outcome treatment effects
Smith 2019[22]	NCT02375724 Not reported AstraZeneca and Berlin Chemie	RCT: parallel-group Phase 4 Double-blind 1 group	Multi-center 30 sites Multi-country: 5 European countries (location not reported)	269	Moderate	8 weeks	LAMA	E-RS: COPD	Yes (total score)	See primary outcome treatment effects
E-RS:COPD as a secondary endpoint (n = 4)										
Ferguson 2018[19]	NCT02497001 KRONOS AstraZeneca	RCT: parallel-group Phase 3 Double-blind 4 groups	Multi-center 215 sites Multi-continental: Canada, China, Japan, and the United States	1902	Moderate to very severe	24 weeks	ICS/LAMA/LABA	FEV_1	Yes	Yes (not all groups)
Lee 2017[23]	NCT02164539 Not reported GlaxoSmithKline	RCT: parallel-group Phase 2 Double-blind 6 groups	Multi-center 55 sites Multi-continental: Argentina, Germany, Poland, Romania, Russia, Ukraine, and the United States	338	Not reported	6 weeks	ICS/LAMA	FEV_1	Yes	Yes (total score and all domains)
Papi 2017[24]	EudraCT 2012–004162–17 Not reported Mundipharma	RCT: parallel-group Phase 3 Double-blind 3 groups	Multi-center 223 sites Multi-continental: Bulgaria, Czech Republic, Germany, Hungary, Latvia, Lithuania, Republic of Macedonia, Poland, Romania, Russian Federation, Slovakia, South Africa, South Korea, Spain, Ukraine, and the United Kingdom	1765	Moderate to severe	52 weeks	ICS/LABA	No exacerbations	No (trend towards lower moderate-severe exacerbation rates)	Yes (total score)
Singh 2020[20]	NCT03443414; EudraCT 2016–005205-40 Not reported Verona	RCT: parallel-group Phase 2b Double-blind 4 groups	Multi-center 47 sites Multi-country: Bulgaria, Czech Republic, Germany, Poland, Romania, and the United Kingdom	405	Moderate to severe	4 weeks	PDE3 and PDE4 inhibitors	FEV_1	Yes	Yes (total score)
E-RS:COPD as an Exploratory Endpoint/Post Hoc Endpoint (n = 11)										
Beier 2013[25]	NCT01462929 Not reported Almirall and Forest Laboratories	RCT Phase 3b Double-blind 2 groups	Multi-center 41 sites Multi-country: Czech Republic, Germany, Hungary, and Poland	414	Moderate to severe	6 weeks	LAMA	FEV_1	Yes	Yes (significant improvement in total score)
D'Urzo	NCT01437397	RCT	Multi-center	1692	Moderate	24	LAMA/	FEV_1	Yes	Yes

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2014[26]	AUGMENT COPD Not Reported	Phase 3 Double-blind 4 groups	222 sites Multi-continental: North America, Australia, and New Zealand		to severe	weeks	LABA			
Kerwin 2017[27]	NCT02347761; NCT02347774 GOLDEN 3; GOLDEN 4 Sunovion	RCT Phase 2 (all) GOLDEN 3 and GOLDEN 4: Double-blind 4 groups (all)	Multi-center Not reported Single-country: United States	GOLDEN 3: 653 GOLDEN 4: 641 (1294 across, all trials)	Moderate to very severe	12 weeks	LAMA	FEV_1	Yes	No (overall, LS mean difference relative to placebo not significant)
Kerwin 2018[31]	NCT02347761; NCT02347774; NCT02276222 GOLDEN 3; GOLDEN 4; GOLDEN 5 Sunovion	RCT Phase 3 (all) GOLDEN 3 and GOLDEN 4: Double-blind; GOLDEN 5: open-label 2 groups (all)	Multi-center Not reported Single-country: United States	2379	Moderate to very severe	GOLDEN 3/ GOLDEN 4: 12 weeks GOLDEN 5: 48 weeks	LAMA/ LABA	FEV_1	Yes	Yes (12-week placebo-controlled studies only)
Maltais 2019[28]	NCT03034915 Not reported GlaxoSmithKline	RCT: parallel-group Phase 4 Double-blind 3 groups	Multi-center 213 sites Multi-continental: Germany, United States, Argentina, Sweden, Canada, Italy, South Africa, Netherlands, Spain, Australia, France, and Mexico	2431	Moderate to severe	24 weeks	LAMA/ LABA	FEV_1	Yes	Yes (total score)
McGarvey 2016[32]	NCT00891462; NCT01001494; NCT01462929 ACCORD COPD 1; ATTAIN; Not reported Almirall and Forest Laboratories	RCT Phase 3 (ACCORD COPD 1 & ATTAIN); Phase 3b (active-comparator study) Double-blind (all) 4 groups	Multi-center Not reported Single-country: United States	ACCORD COPD 1: 375 ATTAIN: 542 Active-comparator: 414 (1331 across all trials)	Moderate to severe	NCT00891462: 12 weeks NCT01001494: 24 weeks NCT01462929: 6 weeks	LAMA	Not specified	Not applicable	Yes (total score and cough and sputum domain)
Murray 2018[33]	NCT00949975; NCT01023516 Not reported AstraZeneca	RCT Phase 2 Double-blind 2 groups	Multi-center Not reported Single-country: United States	340	All severity	12 weeks for both trials	Neutrophil elastase inhibitor	Exacerbation recovery	Not applicable (no treatment effects reported)	Yes
Naya 2018[34]	NCT02345161 FULFIL GlaxoSmithKline	RCT: parallel-group Phase 3 Double-blind 4 groups (ITT and EXT)	Multi-center Not reported Not reported	ITT population: 1810 EXT subpopulation: 430	Severe to very severe	24 weeks (ITT pop) 52 weeks (EXT subset population)	ICS/ LAMA/ LABA	CID	Yes (significantly reduced risk of CID in patients with COPD	Not reported
Rennard 2016[18]	NCT01443845 Not reported AstraZeneca and Forest Laboratories	RCT: parallel-group Phase 4 Double-blind 1 group	Multi-center Not reported Multi-country: 17 countries (location not	2354	Moderate to severe	52 weeks	PDE4 inhibitor added to ICS/ LABA	No exacerbations	Not reported	Not reported (sample results only)

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			reported)							
Sethi 2019[29]	NCT02796677 AMPLIFY AstraZeneca	RCT: parallel-group Phase 3 Double-blind 4 groups	Multi-center Not reported Multi-continental: Bulgaria, Czech Republic, Germany, Hungary, Israel, Poland, Russia, Spain, Ukraine, United Kingdom, and the United States	1594	Moderate to very severe	24 weeks	LAMA/ LABA	FEV_1	Yes	Not reported
Singh 2014[30]	NCT01462942 ACLIFORM-COPD Almirall and Forest Laboratories	RCT: parallel-group Phase 3 Double-blind 4 groups	Multi-center 193 sites Multi-continental: 22 countries Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, the Netherlands, Poland, Romania, Russia, Slovakia, Spain, Sweden, Ukraine, United Kingdom, South Africa, and South Korea	1729	Moderate to severe	24 weeks	LAMA/ LABA	FEV_1	Yes	Yes

[a]N=17

E-RS=Evaluating Respiratory Symptoms tool; RCT=randomized controlled trial; CXCR=CXC chemokine receptor 2 antagonist; LAMA=long-acting muscarinic antagonist; ICS=inhaled corticosteroid; LABA=long-acting beta2-agonist; FEV_1=forced expiratory volume in 1 second; PDE3=phosphodiesterase-3; PDE4=phosphodiesterase-4; LS=least square; ITT=intention to treat; EXT =extension; CID=clinically important difference

or a secondary (n=4) endpoint (Table 6).[19-24] These trials involved samples of 269 (1 treatment group) to 1902 (4 treatment groups) patients with moderate-to-severe COPD (Table 1), testing a bronchodilator therapy (n=5) with 1 trial testing a non-bronchodilator therapy (CXCR2).[21] Treatment duration ranged from 4 to 52 weeks. FEV_1 served as the primary endpoint in 3 and exacerbation frequency in 1. For the 2 trials using the E-RS:COPD as a primary endpoint, 1 reported change from baseline in total score over 8 weeks[22] while the second (co-primary with safety) reported change from baseline in total and subscale scores at 6 months.[21]

Treatment Effects: Four publications reported mean baseline E-RS:COPD total scores, with all participants entering the studies at a similar symptom severity level (mean=11.68, SD=0.50; range: 9.7 [6.06]–13.6 [6.77]; Table 6). Four publications reported E-RS:COPD total score least square (LS) mean change from baseline to follow-up,[19,20,22,23] while 1 publication reported subscale LS mean change from baseline to follow-up.[23] Two of these publications reported a 2-point or greater total score improvement (i.e., decrease in scores) across treatment groups (range: ~2.0 points to ~2.4 points as estimated from figure data).[20,22] Ferguson and colleagues[19] reported LS mean total score change for each treatment group, with the mean change scores ranging from 0.7 to 1.1 points.

Four of the 6 publications reported a significant primary endpoint treatment effect (FEV_1 [n=3]; E-RS:COPD [n=1]), while 2 publications[21,24] reported a trend towards a primary endpoint improvement without statistical significance (decrease in respiratory symptom scores [E-RS:COPD] lower exacerbation rate) (Table 6). The publication that included the E-RS:COPD as the primary endpoint[21] and investigated a non-bronchodilator therapy, reported a trend toward improvement in respiratory symptoms, but no significant difference between E-RS:COPD LS mean total score change (or subscales) versus placebo.

Three of the 4 publications with the E-RS:COPD as a secondary endpoint presented trials testing bronchodilator therapies,[20,23,24] and each of these

Table 2. Summary of Characteristics and Study Design of Included Publications Reporting Data from Unique Clinical Trials[a]

Characteristic	Number of Publications	Percentage of Publications
Year of Publication	3	18%
2013–2015	9	53%
2016–2018	5	29%
2019–2020	17	100%
Clinical Trial Design[b]: RCT	17	100%
Trial Setting: multi-center		
Trial Phase[c]		
2	4	24%
3	10	59%
5	3	18%
Blinding		
Double-blind	17	100%
Open-label[d]	1	6%

Percentages were rounded in this table; thus, the sum of the individual percentages does not always add up to 100%.

[a](N=17)
[b]Eleven publications (n=11/17, 65%) reported parallel-group RCTs study design.
[c]For the phase 2 trials, 2 publications reported on phase 2b trials; for the phase 3 trials, 2 publications reported on phase 3b trials
[d]One publication reported pooled data from 3 clinical trials, 2 of which were double-blind trials, and one was an open-label trial[31]

RCT=randomized controlled trial

reported statistically significant E-RS:COPD total score treatment effects (i.e., improvement, or decrease in scores) versus placebo (n=2) or treatment comparator (n=2; Table 6). Ferguson and colleagues[19] reported statistically significant E-RS:COPD total score change for 1 treatment group versus comparator (p=0.043) with no significant treatment effects for the other treatment groups (p=0.479; p=0.492).

In terms of the E-RS:COPD subscales, 3 publications[22-24] (n=3) reported statistically significant breathlessness subscale treatment effects, 2 publications reported statistically significant cough and sputum treatment effects,[22,23] and 1 publication[23] reported statistically significant chest symptom treatment effects (Table 6).

Correspondence Between Trial Primary Endpoint Treatment Effects and E-RS:COPD Treatment Effects: As noted, the 4 articles presenting the E-RS:COPD as a secondary endpoint (i.e., change from baseline in respiratory symptoms) reported statistically significant E-RS:COPD treatment effects. In each case, significant improvements were observed in the primary outcome measure, specifically, lung function[19,20,23] and exacerbation frequency.[24] Ferguson and colleagues[19] reported a primary endpoint treatment effect of improved lung function with a corresponding respiratory symptom improvement for 1 treatment group (not all). Lazaar and colleagues[21] found corresponding non-significant treatment effects among the co-primary endpoints: change from baseline in dose-response on respiratory symptom severity (E-RS:COPD) and safety (adverse events, 12-lead electrocardiogram, clinical laboratory, and hematological evaluations).

Responder Analysis: Three of the 6 publications that included the E-RS:COPD as a primary or secondary endpoint referenced the interpretation guidelines (proposed responder definition or clinically meaningful score change threshold)[21-23] (Table 6) for symptomatic improvement proposed by Leidy and colleagues[5]:

- E-RS:COPD total score ≥2.0-point reduction (scale range: 0–40)
- E-RS:COPD breathlessness subscale score ≥1.0-point reduction (scale range: 0–17)
- E-RS:COPD cough and sputum subscale score ≥0.70-point reduction (scale range 0–11)
- E-RS:COPD chest symptoms subscale score ≥0.70-point (scale range: 0–12)

Lee and colleagues[23] reported that the mean total score changes of 2 treatment groups exceeded 2 points (-2.6 points; -2.5 points) and reported results for exceeding thresholds for the subscales of breathlessness (≥1.0 point), cough and sputum (≥0.70 points), and chest symptoms (≥0.70 points). Singh and colleagues[20] also reported group differences versus placebo for all 4 ensifentrine doses at week 4 that were near or greater than the E-RS:COPD total score 2-point change.

Only 1 of 3 publications referencing interpretation reported the percentage of E-RS:COPD responders, indicating that 49% (treatment) to 67% (placebo) were non-responders.[21]

E-RS:COPD as an Exploratory Endpoint in Unique Trials (n=11)

The E-RS:COPD tool was included as an exploratory or post hoc endpoint in 11 publications reporting

Table 3. Summary of Patient Baseline Characteristics of Included Publications Reporting Data from Unique Clinical Trials[a]

Characteristic	Number of Publications (n=17)	Percentage of Publications (n=17)
Geographic Location[b]		
North America (United States and Canada)	9	53%
Europe	8	47%
Asia	3	18%
Africa	2	12%
South America	2	12%
Oceania	2	12%
Not Reported	3	18%
Single-country	4	24%
Multi-country-Single Continent	3	18%
Multi-country-Multi-continent	7	41%
Multi-country (location not reported)	3	18%
Sample Size[c]		
250–500	6	35%
501–1000	2	12%
1001–2000	6	35%
>2000	3	18%
Age Category		
Adult (18–64)	15	88%
Older Adults (≥65 years)	2	12%
Age (mean and SD)	63.8 (8.38)[d]	-
Race		
White	14	82%
Black	8	47%
Native American, American Indian or Alaska Native, and Native Hawaiian or Other Pacific Islander	6	35%
Asian	7	41%
Other	7	41%
Not Reported	3	18%
Females, %		
26%–50%	17	100%
Smoking Status		
Current/Former	16	94%
Smoking History (packs/per year)	8	47%
Not Reported	0	0%
Severity of Airflow Limitation of COPD		
Moderate	1	6%
Moderate to Severe	9	53%
Moderate to Very Severe	4	24%
Mild to Very Severe	1	29%
Severe to Very Severe	1	6%
Not Reported	1	6%
Severity of COPD (GOLD criteria)		
Gold 2–3: moderate to severe COPD	4	24%
Gold 1–4: mild to very severe COPD	1	6%
Not Reported	12	71%
History of Exacerbation[e] (Publications including history in past 12 months)	11	65%
COPD Description		
Chronic Bronchitis	1	6%
Emphysema	8	47%
Both/Either	1	6%
Not Reported	7	41%

Percentages were rounded in this table; thus, the sum of the individual percentages does not always add up to 100%.

[a](N=17)
[b]Not mutually exclusive categories, studies may include participants from more than one category
[c]Two studies[27,32] reported data from multiple trials (not pooled data); the authors categorized the sample based on the average sample size of the individual trials and not across all trials because the data were not pooled.
[d]Standard deviation for 2 trials are not reported, total standard deviation across all studies was calculated based on n=18 unique trials.
[e]While the inclusion criteria listed a history of exacerbations in 6 studies, 11 publications reported history of exacerbation in the past 12 months when summarizing participant baseline characteristics.

SD=standard deviation; COPD=chronic obstructive pulmonary disease; GOLD=Global initiative for obstructive Lung Disease

unique trial data (Table 1).[18-34] Given that the main focus of this synthesis was on publications that included the E-RS:COPD as a primary or secondary endpoint, we limit the reporting of the exploratory results to the responsiveness of the E-RS:COPD.

E-RS:COPD total score LS mean change from baseline to follow-up was reported in 9 publications, with LS mean score changes ranging from -0.69

Table 4. Summary of Main Treatment Interventions and Outcomes Evaluated in Publications Reporting Data from Unique Clinical Trials[a]

Drug Class and Name for Main Treatment Intervention[b]	Number of Publications (n=17)	Percentage of Publications (n=17)
Bronchodilator Therapy With or WSithout ICS		
Anticholinergics: LAMA	***4***	***24%***
Aclidinium Bromide	3	18%
Glycopyrrolate	1	6%
Combination: Anticholinergic and LABA in a Single Device (LAMA/LABA)	***5***	***29%***
Aclidinium Bromide/Formoterol Fixed Dose Combination	2	12%
Aclidinium Bromide/Formoterol Fumarate	1	6%
Umeclidinium/Vilanterol	1	6%
Glycopyrrolate /Background LABA Not Specified[c]	1	6%
Combination: Corticosteroid in Single Device plus LABAs (ICS/LABA)	***1***	***6%***
Formoterol /Fluticasone	1	6%
Combination: Corticosteroid in Single Device Plus LAMA (ICS/LAMA)	***1***	***6%***
Formoterol Fumarate/Umeclidinium	1	6%
Triple Combination in Single Device (ICS/LAMA/LABA)	***2***	***12%***
Formoterol Fumarate/Umeclidinium/Vilanterol	1	6%
Budesonide/Glycopyrrolate/Formoterol Fumarate	1	6%
PDE4 Inhibitors	***2***	***12%***
RPL554	1	6%
Roflumilast (added to ICS/LABA)	1	6%
Non-Bronchodilator Therapy		
Neutrophil Elastase Inhibitor	***1***	***6%***
AZD9668	1	6%
CXC Chemokine Receptor 2 Antagonist	***1***	***6%***
Danirixin	1	6%
Number Treatment Groups		
1	2	12%
2	3	18%
3	2	12%
4	8	47%
5	1	6%
6	1	6%
Number of Timepoint Assessments (baseline to follow-up)		
Single Assessment	6	35%
Multiple Assessment	11	65%
Run in Period (weeks)		
0–2 weeks	8	47%
3–4 weeks	7	41%
Not Applicable	2	12%
Treatment Duration (weeks)		
0–5 weeks	1	6%
6–12 weeks	5	29%
13–24 weeks	8	47%
25–48 weeks	1	6%
49–72 weeks	2	12%

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Follow-up Duration (weeks)		
0–2 weeks	7	41%
3–4 weeks	1	6%
Not Applicable	9	53%

Percentages were rounded in this table; thus, the sum of the individual percentages does not always add up to 100%.

[a](N=17)
[b]Based on main treatment intervention reported in publications (n=17)
[c]One publication[31] was categorized as a LABA/LAMA because the goal of the post hoc analysis was to examine the effect of background LABA therapy on efficacy and safety of glycopyrrolate.

ICS=inhaled corticosteroid; LAMA=long-acting muscarinic antagonist; LABA=long-acting beta2-agonist

points to -3.14 among investigational bronchodilator therapies. Of these publications, 4 reported total score LS mean change from baseline to follow-up among treatment groups that were ≥ a 2-point decrease (improved respiratory symptoms).[20,26,32,34] One study[28] reported breathlessness LS mean score changes ranging from -0.22 to -0.67 across groups, cough and sputum LS mean score change of -0.32 to -0.45 across groups, and chest symptoms LS mean score changes of -0.15 to -0.39 across groups.

Of the 11 publications, 8 (7 bronchodilator and 1 non-bronchodilator) reported E-RS:COPD total score treatment effects, all statistically significant (Table 1) and demonstrating correspondence with the primary endpoint treatment effects. One publication reported a decline in total score (improved symptoms) from baseline to follow-up versus placebo that was less than 2 points and did not reach statistical significance.[31] Only 1 publication reported treatment effects on E-RS:COPD subscale scores for both aclidinium and tiotropium.[25]

Three publications[28,32,33] referenced the guidelines for symptomatic improvement[5] proposed by Leidy et al [5,28,32,33] in 2014. One reported the number of responders, with the percentage of E-RS:COPD total score responders 36% among the treatment group versus 27% among each of the active comparators.[28]

Discussion

To our knowledge, this review study is the first to systematically examine and summarize the existing publications that reported on the use of the E-RS:COPD as a symptom outcome measure in pharmaceutical trials since its qualification. While the E-RS:COPD has been qualified by the FDA and EMA as an exploratory endpoint in drug development trials, several sponsors have elected to use it as a primary or secondary endpoint. Overall, the literature confirms that the E-RS:COPD is responsive to change, as shown by its ability to detect symptomatic improvements over time, and between treatment groups.

Most publications reported on trials investigating bronchodilator therapies with ICSs (e.g., LAMAs and/or LABAs with ICS). This finding was expected, as the combination of widening the airways, via a bronchodilator, and the anti-inflammatory actions of an ICS are more likely to provide symptomatic relief than a single bronchodilator therapy. One publication that included the E-RS:COPD as a primary endpoint reported results from a non-bronchodilator drug therapy, danirixin, that was administered in addition to standard of care inhaled medications.[21] While this study (as well as a previous phase 2 study examining danirixin that was not included in this review because it was published as a letter to the editor[35]), highlighted a positive trend in respiratory symptom improvements, no significant treatment effects have been reported as a result of this drug therapy. Further, Lazaar and colleagues[21] reported a large unexpected placebo effect. The authors attributed this finding to an observed study effect during the 7-day run-in period before treatment, which may have contributed to the lack of treatment effects observed in this clinical trial. Thus, future trials may benefit from a prolonged run-in period to mitigate the potential for a placebo treatment effect.

Statistically significant treatment effects for the E-RS:COPD were consistent with other treatment effects, including FEV_1, SGRQ, and TDI. While lung function, typically measured by spirometry, is the most common endpoint in COPD drug trials, it is well known that associations are weak between airflow limitation (FEV_1) and PROs, including symptoms and health status.[36-38] Further, research investigating COPD treatments is evolving, with an increased interest in new treatments focusing

Table 5. Summary of Other Patient-Reported Outcome Measures Used in Included Publications Reporting Data from Unique Clinical Trials[a]

Characteristic	Number of Publications	Percentage of Trials (%)
Number of PROs used in Addition to the E-RS:COPD		
1 PRO	3	18%
2 PROs	7	41%
3 or More PROs	7	41%
Other PROs Outcome		
Secondary Endpoint	10	59%
Exploratory Endpoint	3	18%
Post Hoc Analysis Study Endpoints	2	12%
Not Applicable	2	12%
Publication's PRO Use Goal(s)		
Symptom Monitoring	2	12%
Health-related Quality of Life	2	12%
Symptoms and Health-related Quality of Life	13	76%
Other PRO Measures Used Across Unique Clinical Trials		
SGRQ	11	65%
BDI-TDI	6	35%
Daytime Symptoms (early morning/daytime)	5	29%
Nighttime Symptoms	5	29%
EXACT-PRO	4	24%
CAT	3	18%
Other (List all)		
Cough Severity VAS	1	6%
Medical Research Council Dyspnea Scale	1	6%
Patient's Global Assessment of Change	1	6%
Leicester Cough Questionnaire	1	6%
CPPAC	1	6%

Percentages were rounded in this table; thus, the sum of the individual percentages does not always add up to 100%.

[a](N=17)

PRO=patient-reported outcome; E-RS=Evaluating Respiratory Symptoms; SGRQ=St George's Respiratory Questionnaire; BDI-TDI=Baseline Dyspnea Indexes -Transition Dyspnea Indexes; EXACT-PRO=the EXAcerbations of Chronic pulmonary disease Tool; CAT=COPD Assessment Tool; VAS=visual analog scale; CPPAC=Clinic Visit PROactive Physical Activity in COPD

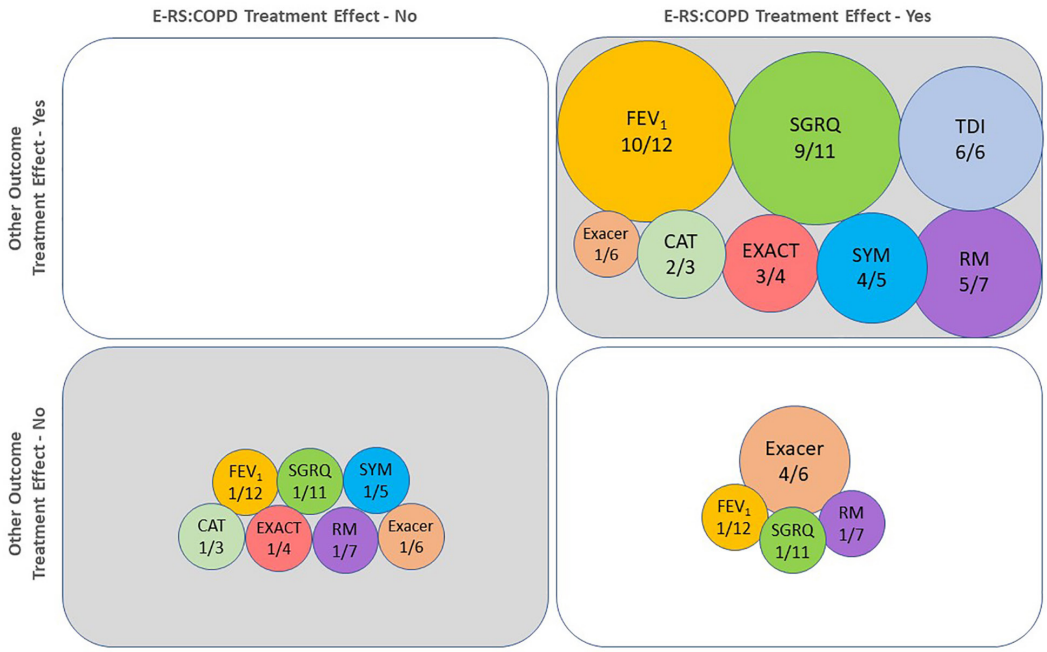
on symptom relief, thus, highlighting the need to include a patient-reported symptom outcome measure as a key or primary endpoint. Symptom-specific measures complement pulmonary function and health status measures to provide a comprehensive evaluation of the effects of treatment on how patients feel and function. Given the essential role of symptomatic distress in the lives of patients with COPD, understanding the effects of various treatments on these symptoms could drive actionable treatment goals in the clinical setting.

This review highlights a gap in the approach used to identify clinically relevant effects in pharmacological interventions. Specifically, a limited number of publications discussed the interpretation of results, and fewer still provided responder analyses, which is a preferred method for determining and communicating clinical relevance. Use or reference to the proposed interpretation guidelines[5] was inconsistent. None of the papers discussed retesting the proposed guidelines in the trial. Trial samples and study designs were generally consistent with the E-RS:COPD context of use and the data underlying the proposed interpretation guidelines. This review included studies with participants who were clinically stable with moderate-to-severe airflow limitation. Complementary baseline E-RS:COPD scores were approximately 9 to 14 points, also suggesting moderate symptomatology.[5] Although it is reasonable to assume the proposed E-RS:COPD interpretation guidelines would apply to these reviewed studies, investigators should include confirmation in their research plan and make adjustments as needed.

This rapid review highlights that several publications that included the E-RS:COPD as primary or secondary endpoints appeared to follow minimal reporting standards for inclusion of PROs within clinical trials. However, it is evident there is a need for further guidance on how to include and report clinically meaningful treatment effects within clinical trials using instruments such as the E-RS:COPD. Such standards,[39,40] in conjunction with the FDA guidance on PROs,[2] should be reported consistently to provide the necessary information to make informed decisions when evaluating new drug therapies.

Future trials testing new COPD drug treatments that aim to provide symptomatic relief should

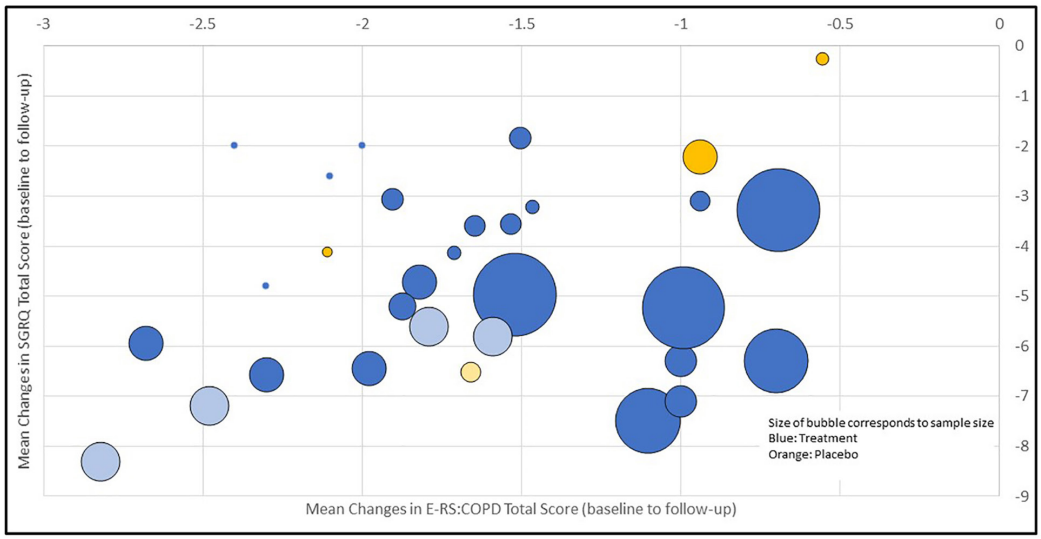
Figure 2. Distribution of Evaluating Respiratory Symptoms in COPD Tool Treatment Effects and Other Outcome Measure Treatment Effects Within Each Included Publication



The denominator for each bubble is based on the number of publications that include and report treatment effects for both the E-RS:COPD and the other outcome measures. The bubble size is based on the numerator reported in the figure.

E-RS: COPD=Evaluating Respiratory Symptoms in COPD Tool; FEV1=forced expiratory volume in 1 second; SGRQ=St George's Respiratory Questionnaire; TDI=Transition Dyspnea Index; Exacer=exacerbations; CAT=COPD Assessment Test; EXACT=EXACT-PRO; SYM= early morning (n=4)/daytime (n=1) COPD symptoms of COPD and nighttime symptoms of COPD; RM=rescue medications

Figure 3. Correspondence Between the Evaluating Respiratory-Symptoms in COPD Tool and the St George's Respiratory Questionnaire Score Change[a]



[a]baseline to follow-up

This plot includes data from 8 of the 17 publications that reported baseline to follow-up mean score changes for both the E-RS:COPD and the SGRQ. Each bubble (n= 31) represents a treatment group (including placebo) reported within the 8 publications. The bubble size is based on the sample number of each treatment group.

SGRQ=St George's Respiratory Questionnaire; E-RS:COPD=Evaluating Respiratory Symptoms in COPD

Table 6. Key Findings from Publications Using the E-RS:COPD as a Primary or Secondary Outcome Measure[a]

Trial Number Author, Year (N=6)	Treatment Duration	Sample	Treatment Groups	Treatment Intervention Drug Class	E-RS:COPD Endpoint Positioning and Significance	Key Results
NCT03034967 Lazaar 2020[21]	24 weeks	N=614 Moderate-to-severe airflow limitation[b] **E-RS:COPD baseline total score:** Group 1: DNX5mg= 12.73 (6.232) Group 2: DNX10mg= 11.53 (6.288) Group 3: DNX25mg= 11.70 (6.724) Group 4: DNX35mg= 12.08 (5.804) Group 5: DNX50mg= 11.43 (5.219) Control Group: Placebo= 12.01 (6.299)	Danirixin hydrobromide salt tablets (DNX) Group 1: 5mg Group 2: 10mg Group 3: 25mg Group 4: 35mg Group 5: 50mg Group 6: Placebo	CXC chemokine receptor 2 antagonist	Co-Primary: E-RS:COPD (dose-response) vs. placebo Co-primary: Safety vs. placebo	**E-RS:COPD total score LS mean change from baseline for follow-up:** Group 1-4 : Not reported Control Group: Placebo=-2.11 **E-RS:COPD total score LS mean change vs. placebo or comparator:** No significant difference between mean score change (total score and subscales) vs. placebo. Across all treatment groups, total score and subscale scores at month 6 across showed a trend toward decreased scores (improvement in respiratory symptoms), with trends higher than placebo **E-RS:COPD responder analysis:** Definition: (clinically meaningful score change) total score: ≥2 points; breathlessness: 1 point; cough and sputum: 0.7 points; chest symptoms: 0.7 point Percentage of responders: 49%–67% of all patients were non-responders at 6 months
NCT02375724 Smith 2019[22]	8 weeks	N=269 Moderate airflow limitation, symptomatic **E-RS:COPD baseline score:** Total score: Group 1: 12.5 Control Group: Not reported Cough and sputum sub-scale: Group 1: 3.7 Control Group: Not reported Breathlessness sub-scale: Group 1: 6.0 Control Group: Not reported Chest symptoms sub-scale: Group 1: 2.9 Control Group: Not reported	Aclidinium Group 1: 400mcg Group 2: Placebo	LAMA	Primary: ERS:COPD total score at 8 weeks[c] Secondary: E-RS:COPD cough and sputum score at 8 weeks[c] Exploratory: E-RS:COPD total score and all sub-scale scores at 4 and 8 weeks	**E-RS:COPD total score LS mean change from baseline for follow-up:** Week 4: ~ -1.4 (treatment improvement); ~ -0.5 Placebo improvement Week 8: ~ -2.0 ; ~ -0.9 **E-RS:COPD LS mean change vs. placebo/ comparator: treatment-placebo differences:** Aclidinium 400mcg significantly improved a range of daily symptoms, including cough, in symptomatic patients with moderate COPD compared with placebo: Total score: [c]Week 4: -0.9 (0.4); $p<.05$ [c]Week 8: -1.1 (0.6); $p<.05$ Breathlessness sub-scale: [c]Week 4: -0.6 (0.2); $p<.05$ [c]Week 8: -0.6 (0.3); $p<.05$ Cough and sputum sub-scale: Week 4: -0.1 (0.1); not significant [c]Week 8: -0.3 (0.2); $p<.05$ Chest symptoms sub-scale: Week 4: -0.2 (0.1); non-significant Week 8: -0.2 (0.2); non-significant **E-RS:COPD Responder analysis:** Definition: (MCID) total score: 2 points; breathlessness: 1 point; cough and sputum: 0.7; chest symptoms: 0.7 Percentage of responders: not reported
NCT02497001 Ferguson 2018[19]	24 weeks	N=1902 Moderate-to-very severe airflow limitation **E-RS:COPD baseline total score:** Group 1-4: Not reported Control Group:	BGF MDI GFF MDI BUD/FORM DPI Group 1: BGF MDI 320/18/ 9.6mcg	ICS/ LAMA/ LABA	Secondary: E-RS:COPD total scorec (Primary: FEV_1[c])	**FEV_1:** [c]AUC_{0-4} versus BFF MDI (lLS mean difference 104mL, 95% CI 77 to 131; $p<0{\cdot}0001$) [c]AUC_{0-4} versus BUD/FORM DPI (91mL, 64 to 117; $p<0{\cdot}0001$) **E-RS:COPD total score LS mean change from baseline**

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		Not applicable	Group 2: GFF MDI 18/9.6mcg Group 3: BFF MDI 320/9.6mcg Group 4: Open-label BUD/FORM DPI 400/12mcg			Group 1: GF MDI: -1.1 (0.13) Group 2: GGF MDI: -0.7 (0.14) Group 3: BGF MDI: -1.0 (0.19) Group 4: BUD/FOR: -1.0 (0.19) Control Group: Not applicable **E-RS:COPD total score LS mean change for BGF MDI vs comparators [n, LSM (SE); LSM 95% CI):** Group 1: BGF MDI 320/18/9.6mcg: n=638; –1.5 (0.13); NA [c]Group 2: GFF MDI 18/9.6mcg: n=621; –0.7 (0.14); –0.38 (–0.74 to –0.01);*p*=0.043 Group 3: BFF MDI 320/9.6mcg: n=313; –1.0 (0.19); –0.16 (–0.61 to 0.28);*p*=0.479 Group 4: Open-label BUD/FORM DPI 400/12mcg: n=313; –1.0 (0.19); –0.16 (–0.60 to 0.29);*p*=0.4923 **E-RS:COPD responder analysis:** not reported
NCT02164539 Lee 2017[23]	6 weeks	N=338 Airflow limitation not reported **E-RS:COPD baseline total score:** Group 1: FF100mcg= 10.8 (5.50) Group 2: FF/UMEC100/15.6mcg: 11.9 (5.12) Group 3: FF/UMEC100/62.5mcg: 9.7 (6.06) Group 4: FF/UMEC100/125mcg: 10.7 (6.47) FF/UMEC100/250mcg: 9.8 (5.39) FF/VI100/25mcg: 11.7 (5.46)	FF FF/UMEC FF/VI Group 1: FF 100mcg Group 2:FF/UMEC 100/15.6mcg Group 3:FF/UMEC 100/62.5mcg Group 4:FF/UMEC 100/125mcg Group 5:FF/UMEC 100/250mcg Group 6:FF/VI 100/25mcg	ICS/LAMA	Secondary: E-RS:COPD total score[c] (Primary: FEV_1[c])	**Trough FEV_1:** FF/UMEC 62.5 (0.140L [*p*=0.019]) and 125mcg (0.120L [*p*=0.039]), **PEF:** All FF/UMEC doses vs. FF (*p*≤0.05) **E-RS:COPD LS mean change from baseline to follow-up:** Total score: Group 1: FF 100mcg=0.5 (0.54) Group 2–4: Not reported Breathlessness: Group 1: FF 100mcg=0.1 (0.26) Group 2–4: Not reported Cough and Sputum: Group 1: FF 100mcg=0.1 (0.19) Group 2–4: Not reported Chest symptoms: Group 1: FF 100mcg=0.3 (0.18) Group 2–4: Not reported **E-RS:COPD LS mean change (95% CI) vs comparator (ITT population last 7 days of Phase A: week 4)** [c]Total score: Group 1: FF 100mcg: n=39; 0.5 (0.54) Group 2: FF/UMEC 100/15.6mcg: n=42; 3.1 (-4.6 -1.7); *p*≤0.001 Group 3: FF/UMEC 100/62.5mcg: n=39; 3.0 (-4.5, -1.6); *p*≤0.001 Group 4: FF/UMEC 100/125mcg: n=43; 2.0 (-3.4, -0.6); *p*≤0.01 Group 5: FF/UMEC 100/250mcg: n=81; 2.0 (-3.2, -0.7); *p*≤0.01 Group 6: (FF/VI 100/25mcg: n=83; 1.7 (-2.9, -0.4); *p*≤0.01 [c]Breathlessness Group 1: FF 100mcg: n=39; 0.1 (0.26) Group 2: FF/UMEC 100/15.6mcg: n=42; -1.1 (-1.8, -0.4); *p*≤0.01 Group 3: FF/UMEC 100/62.5mcg: n=39; -1.2 (-1.9, -0.5); *p*≤0.01 Group 4: FF/UMEC 100/125mcg: n=43; -0.6 (-1.2, 0.1); non-significant Group 5: FF/UMEC 100/250mcg: n=81; -0.9 (-1.5, -0.3); *p*≤0.01 Group 6: (FF/VI 100/25mcg: n=83; -0.7 (-1.3, 0.0); *p*≤0.05 [c]Cough and sputum Group 1: FF 100mcg: n=39; 0.1 (0.19) Group 2: FF/UMEC 100/15.6mcg: n=42; - 0.8

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						(-1.3, -0.3); $p \leq 0.001$ Group 3: FF/UMEC 100/62.5mcg: n=39; -0.7 (-1.2, -0.2); $p \leq 0.01$ Group 4: FF/UMEC 100/125mcg: n=43; -0.6 (-1.1, -0.1); $p \leq 0.05$ Group 5: FF/UMEC 100/250mcg: n=81; -0.4 (-0.9, 0.0); non-significant Group 6: (FF/VI 100/25mcg: n=83; -0.4 (-0.9, 0.0); non-significant [c]Chest symptoms Group 1: FF 100mcg: n=39; 0.3 (0.18) Group 2: FF/UMEC 100/15.6mcg: n=42; - 1.1 (-1.6, -0.7); $p \leq 0.001$ Group 3: FF/UMEC 100/62.5mcg: n=39; -1.2 (-1.7, -0.7); $p \leq 0.001$ Group 4: FF/UMEC 100/125mcg: n=43; -0.8 (-1.3, -0.4); $p \leq 0.001$ Group 5: FF/UMEC 100/250mcg: n=81; -0.7 (-1.3, -0.4); $p \leq 0.01$ Group 6: (FF/VI 100/25mcg: n=83; -0.6 (-1.0, -0.2); $p \leq 0.01$ **MCID:** LS mean change (ITT population) from baseline in E-RS:COPD total score was greatest for FF/UMEC 15.6mcg and 62.5mcg, with both reaching the MCID (-2.6 and -2.5 points, respectively). Similar results were found for the E-RS:COPD subscales of breathlessness, cough and sputum, and chest symptom. **E-RS:COPD responder analysis:** Definition: (MCID) total score: ≥2 point decrease; breathlessness: ≥1 point decrease; cough and sputum: ≥0.7 decrease; chest symptoms: ≥0.7 decrease Percentage of responders: not reported
EudraCT 2012–004162–17 Papi 2017[24]	52 weeks	N=1765 Moderate-to-severe airflow limitation ≥2 exacerbations preceding year **E-RS:COPD baseline total score:** Group 1–3: Not reported	FP/FORM FORM Group 1: FP/FORM 500/20mcg BID Group 2: FP/FORM 250/10mcg BID Group 3: FORM 12mcg BID	ICS/LABA	Secondary: E-RS:COPD total score[c] (Primary: Exacerbation Frequency)	**Exacerbations:** FP/FORM 500/20µg versus FORM (RR: 0.79; P=0.084). **E-RS total score LS mean change from baseline to follow-up:** Group 1–3: Not reported [c]**E-RS:COPD total score LS mean change across treatment groups** Group 1: FP/FORM 500/20µg vs FORM -0.47 units [P=0.039] Group 2: 250/10µg versus FORM -0.52 units [P=0.021] [c]**E-RS:COPD breathlessness subscale** Group 1: FP/FORM 500/20µg vs FORM -0.22 units [P=0.066] Group 2: 250/10µg versus FORM -0.27 units [P=0.024] **MCID:** not reported **E-RS:COPD responder analysis:** not reported
NCT03443414; EudraCT 2016–005205-40 Singh 2020[20]	4 weeks	N=405 Moderate to severe airflow limitation **E-RS:COPD baseline total score:** Group 1: 0.75mg= 13.6 (6.77) Group 2: 1.5mg= 12.3 (6.05) Group 3: 3mg= 12.0 (6.03) Group 4: 6mg= 12.2 (6.29)	Ensifentrine Group 1: 0.75mg Group 2: 1.5mg Group 3: 3mg Group 4: 6mg Group 5: Placebo	PDE 3 and 4 inhibitors	Secondary: E-RS:COPD total score[c] (Primary: FEV_1[c])	**Peak FEV_1: Week 4, LS mean difference vs placebo (all p<0.0001):** Group 1: 0.75mcg=146mL (95% CI 75, 216) Group 2: 1.5mcg=153mL (95% CI 83, 222) Group 3: 3mcg = 200mL (95% CI 131, 270) Group 4: 6mcg =139 mL (95% CI 69, 210) **E-RS:COPD total score LS mean change from baseline to week 4:** Group 1: 0.75mcg: ~ -2.3 TX IMP Group 2: 1.5mcg: ~ -2.4 TX IMP Group 3: 3mcg: ~ -2.0 TX IMP Group 4: 6mcg: ~ -2.1 TX IMP Placebo: 1.19 IMP

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	Group 5: Placebo= 11.5 (6.23)			**E-RS:COPD total score LS mean change vs placebo:** [c]Week 1: Group 1: 0.75mcg =p<.05 Group 2: 1.5mcg =p<.01 Group 3: 3mcg =p<.05 Group 4: 6mcg= p<.05 [c]Week 2: Group 1: 0.75mcg =p<.05 Group 2: 1.5mcg =p<.01 Group 3: 3mcg =p<.01 Group 4: 6mcg=p<.05 [c]Week 3: All treatment groups-placebo: p<.01 [c]Week 4: All treatment groups-placebo: p<.01 **MCID:** not reported **E-RS:COPD responder analysis:** not reported

[a]N=6
[b]As defined in the trial's inclusion criteria for airflow limitation.
[c]Significant treatment effects reported

E-RS:COPD=Evaluating Respiratory Symptoms in COPD; MCID=minimal clinically important difference; BGF=budesonide/glycopyrrolate/formoterol fumarate; MDI=metered-dose inhaler; GFF=glycopyrrolate/formoterol fumarate; BUD/FORM DPI=budesonide/formoterol fumarate dry-powder inhaler; BFF=budesonide/formoterol fumarate; ICS=inhaled corticosteroid; LAMA=long-acting muscarinic antagonist; LABA=long-acting beta agonist; FEV_1=forced expiratory volume in 1 second; AUC=area under the curve; LS=least square; CI=confidence interval; FF=fluticasone furoate; UMEC=umeclidinium; VI=vilanterol; ITT=intention to treat; FP=fluticasone propionate; TX=treatment; IMP=improvement

enroll patients with moderate-to-severe respiratory symptoms and target those with the greatest unmet need to increase the likelihood of detecting a clinically meaningful effect. Further, in addition to being a valid, reliable, and responsive tool for measuring respiratory symptoms in patients living with moderate-to-severe COPD, the E-RS:COPD may be a useful PRO measure of respiratory symptoms in other populations. For example, a recent post-hoc examination of the psychometric properties and responsiveness of this tool was done among adults living with chronic airflow obstruction and a reversible component known as asthma-COPD overlap (ACO), with results indicating the E-RS:COPD was a suitable measure in this group of ACO patients.[41] Also, Bacci and colleagues assessed the E-RS:COPD in an idiopathic pulmonary fibrosis population and found that its items applied to their respiratory symptom experience.[42] Again, these new context of uses would need to be tested for validity and reliability, and examine potential new scoring algorithms.

Limitations of this Research

Results should be considered in light of this review's limitations. While the goal of this rapid review was to produce synthesized knowledge on the use of the E-RS:COPD to support decision making in a timely manner, it is important to acknowledge that the applied constraints may have led to the exclusion of relevant E-RS:COPD data. Specifically, this search only included papers published in English, did not include grey literature, and was limited to 3 databases that may have excluded trials published in non-English countries, or remain unpublished. Results and conclusions are based on information that appeared in the publication itself, with some publications including a comprehensive reporting of E-RS:COPD results (e.g., mean change from baseline to follow-up, responder definitions, treatment effects, responder analysis) and others including fewer of these elements.

Conclusions

Findings from this review demonstrate that the E-RS:COPD has been used in 20 RCTs testing the efficacy of treatment in patients living with moderate-to-severe COPD. Statistically significant E-RS:COPD treatment effects moved in the same direction as the main outcomes. Presentation of trial results should include responder analyses to facilitate interpretation and application of results.

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Author Contributions:

All authors contributed to the conception and design of the review. RW executed the literature search. All authors analyzed and interpreted the data. DMB and RW contributed equally as co-first authors and all authors participated in the development and critical review of the manuscripts. DMB had full access to all the data and final responsibility for the decision to submit for publication. All authors provided final approval for publication submission and are accountable for the accuracy and integrity of this work.

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Declaration of Interest

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