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

Donald M. Bushnell, MA¹ Rozanne Wilson, PhD¹ Florian S. Gutzwiller, MD, MPH² Nancy K. Leidy, PhD¹ Carolina Hache, PhD² Chau Thach, PhD² Claus F. Vogelmeier, MD³

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 [FEV₁]). 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, FEV₁; patient-reported outcome, PRO; Food and Drug Administration, FDA; EXAcerbations of COPD Tool, EXACT; European Medicines Agency, EMA; population, intervention, comparator, and setting, PICO; standard deviation, SD; long-acting muscarinic antagonists, LAMAs; long-acting beta2-agonists, LABAs; phosphodiesteerase-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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Donald Bushnell, MA
Evidera, Seattle, Washington, United States

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

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, 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. 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). Content validity of the E-RS:COPD was addressed through primary and secondary analyses of qualitative data. 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. 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 [FEV1]% predicted), and symptom questionnaires (SGRQ Symptoms, modified Medical Research Council dyspnea status) and known-groups analyses, including smoking status and rescue medication use. Tests of E-RS:COPD responsiveness were conducted in data from 3 Phase 2 clinical trials. Because these trials did not show significant treatment effects in the primary or secondary endpoints, data were stratified into subgroups 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).

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) in 2015 and the FDA 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 criteria.
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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 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 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, FEV1, number of exacerbations, rescue medications). Overall, statistically significant E-RS:COPD treatment effects corresponded with significant treatment effects in 8 other outcomes, including FEV1 (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

| First Author, Year | Clinical Trial Number, Trial Name, Funding Source | Trial Design Trial 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 202021 | 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 | CXR/2 in addition to standard of care | E-RS: COPD (dose response) vs placebo Safety vs placebo | No | See primary outcome treatment effects |
| Smith 201922 | NCT02375274 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 201819 | NCT02497001 KRONOS AstraZeneca | RCT: parallel-group Phase 3 Double-blind 4 groups | Multi-center 215 sites Multi-continent: Canada, China, Japan, and the United States | 1902 | Moderate to very severe | 24 weeks | ICS/ LAMA/ LABA | FEV1 | Yes | Yes (not all groups) |
| Lee 201723 | NCT02164539 Not reported GlaxoSmithKline | RCT: parallel-group Phase 2 Double-blind 6 groups | Multi-center 55 sites Multi-continent: Argentina, Germany, Poland, Romania, Russia, Ukraine, and the United States | 338 | Not reported | 6 weeks | ICS/ LAMA | FEV1 | Yes | Yes (total score and all domains) |
| Papi 201724 | EudraCT 2012-004162-17 Not reported Mundipharma | RCT: parallel-group Phase 3 Double-blind 3 groups | Multi-center 223 sites Multi-continent: 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 202020 | NCT02443414; 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 | FEV1 | Yes | Yes (total score) |
| **E-RS:COPD as an Exploratory Endpoint/Post Hoc Endpoint (n = 11)** | | | | | | | | | | | | |
| Beier 201325 | NCT01462929 Not reported Almirall and Forest Laboratories | RCT | Multi-center 41 sites Multi-country: Czech Republic, Germany, Hungary, and Poland | 414 | Moderate to severe | 6 weeks | LAMA | FEV1 | Yes | Yes (significant improvement in total score) |
| D’Urzo | NCT01437397 | RCT | Multi-center | 1692 | Moderate | 24 weeks | LAMA/ LABA | FEV1 | Yes | Yes |

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| Year | Study | Design | Phase | Country/Setting | Follow-up | Treatment | Response | Outcome | Notes |
|------|-------|--------|-------|----------------|-----------|-----------|----------|---------|-------|
| 2014<sup>26</sup> | 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<sup>27</sup> | NCT02347761; NCT02347774 | GOLDEN 3; GOLDEN 4 | 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<sub>1</sub> | Yes | No (overall, LS mean difference relative to placebo not significant) |
| Kerwin 2018<sup>31</sup> | NCT02347761; NCT02347774; NCT02276222 | GOLDEN 3; GOLDEN 4; GOLDEN 5 | 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<sub>1</sub> | Yes | Yes (12-week placebo-controlled studies only) |
| Maltais 2019<sup>38</sup> | NCT03034915 | Not reported | GlaxoSmithKline | RCT: parallel-group | Phase 4 | Double-blind 3 groups | 2431 | Moderate to severe | 24 weeks | LAMA/ LABA | FEV<sub>1</sub> | Yes | Yes (total score) |
| McGarvey 2016<sup>32</sup> | 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 (no treatment effects reported) | Yes (total score and cough and sputum domain) |
| Murray 2018<sup>33</sup> | NCT00949975; NCT01023516 | Not reported | AstraZeneca | RCT | Phase 2 | Double-blind 2 groups | 340 | All severity | 12 weeks for both trials | Neutrophil elastase inhibitor | Exacerbation recovery | Not applicable (no treatment effects reported) | Yes |
| Naya 2018<sup>34</sup> | 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 sub-population: 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 |
| Remnad 2016<sup>18</sup> | 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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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. FEV1 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 weeks22 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 colleagues19 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 (FEV1 [n=3]; E-RS:COPD [n=1]), while 2 publications21,24 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 endpoint21 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...
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Table 2. Summary of Characteristics and Study Design of Included Publications Reporting Data from Unique Clinical Trials

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

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

- 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 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 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.

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 effects. In each case, significant improvements were observed in the primary outcome measure, specifically, lung function and exacerbation frequency. Ferguson and colleagues 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 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) for symptomatic improvement proposed by Leidy and colleagues:

- 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)

- 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
unique trial data (Table 1). 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

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

<sup>a</sup> (N=17)

<sup>b</sup> Not mutually exclusive categories, studies may include participants from more than one category

<sup>c</sup> Two studies<sup>27,33</sup> 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.

<sup>d</sup> Standard deviation for 2 trials are not reported, total standard deviation across all studies was calculated based on n=18 unique trials.

<sup>e</sup> 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.
# Table 4. Summary of Main Treatment Interventions and Outcomes Evaluated in Publications Reporting Data from Unique Clinical Trials

| Drug Class and Name for Main Treatment Intervention | Number of Publications (n=17) | Percentage of Publications (n=17) |
|-----------------------------------------------------|------------------------------|----------------------------------|
| **Bronchodilator Therapy With or Without ICS**       |                              |                                  |
| **Anticholinergics: LAMA**                           |                              |                                  |
| Acilinium Bromide                                    | 4                            | 24%                              |
| Glycopyrrolate                                       | 3                            | 18%                              |
| **Combination: Anticholinergic and LABA in a Single Device (LAMA/LABA)** | 5                            | 29%                              |
| Acilinium Bromide/Formoterol Fixed Dose Combination | 2                            | 12%                              |
| Acilinium Bromide/Formoterol Fumarate               | 1                            | 6%                               |
| Umeclidinium/Vilanterol                              | 1                            | 6%                               |
| Glycopyrrolate/Background LABA Not Specified         | 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%                               |
| **CXCR 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) | 6                            | 35%                              |
| Single Assessment                                    | 11                           | 65%                              |
| Multiple Assessment                                  |                              |                                  |
| **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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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 study28 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 publications28,32,33 referenced the guidelines for symptomatic improvement5 proposed by Leidy et al5,28,32,33 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 editor35), 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 colleagues21 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 FEV1, 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 (FEV1) and PROs, including symptoms and health status.36-38 Further, research investigating COPD treatments is evolving, with an increased interest in new treatments focusing
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 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. 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, in conjunction with the FDA guidance on PROs, 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

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

| Characteristic | Number of Publications 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=Assessing 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

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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

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

*baseline to follow-up
### Table 6. Key Findings from Publications Using the E-RS:COPD as a Primary or Secondary Outcome Measure

| Trial Number | Treatment Duration | Sample | Treatment Groups | Treatment Intervention Drug Class | Treat- E-RS: COPD Endpoint Positioning and Significance | Key Results |
|--------------|--------------------|--------|------------------|-----------------------------------|----------------------------------------------------------|-------------|
| NCT03034967 | 24 weeks           | N=614  | Danirixin hydrobromide salt tablets (DNX) | CXC chemokine receptor 2 antagonist | Co-primary: E-RS:COPD total score LS mean change from baseline for follow-up: | E-RS:COPD total score LS mean change from baseline for follow-up: |
| Lazar 2020   |                    |        | Group 1: DNX5mg=12.73 (6.232) | Group 1: 5mg | Group 1: Placebo | Group 1: 5mg vs. placebo |
|              |                    |        | Group 2: DNX10mg=11.53 (6.288) | Group 2: 10mg | Group 2: Placebo | Co-primary: Safety vs. placebo |
|              |                    |        | Group 3: DNX25mg=11.70 (6.724) | Group 3: 25mg | | |
|              |                    |        | Group 4: DNX35mg=12.08 (5.804) | Group 4: 35mg | | |
|              |                    |        | Group 5: DNX50mg=11.43 (5.219) | Group 5: 50mg | | |
|              |                    |        | Control Group: Placebo=12.01 (6.299) | Group 6: Placebo | | |
| NCT02375724 | 8 weeks            | N=269  | Acildinium Group 1: 400mcg | LAMA Primary: ERS:COPD total score at 8 weeks | E-RS:COPD total score LS mean change from baseline for follow-up: |
| Smith 2019   |                    |        | Group 2: Placebo | | | E-RS:COPD total score LS mean change vs. placebo/ comparator: treatment-placebo differences: |
|              |                    |        | Group 3: 12.5 | Group 1: Placebo | | Acildinium 400mcg significantly improved a range of daily symptoms, including cough, in | |
|              |                    |        | Control Group: Not reported | | | | |
|              |                    |        | Cough and sputum sub-scale: | | | | |
|              |                    |        | Group 1: 3.7 | | | | |
|              |                    |        | Control Group: Not reported | | | | |
| NCT02497001 | 24 weeks           | N=1902 | BGF MDI Group 1: BGF MDI 320/18/9.6mcg | ICS/ LAMA/ LABA | Secondary: E-RS:COPD total score: (Primary: FEV1) | E-RS:COPD total score LS mean change from baseline | |
| Ferguson 2018|                    |        | Not reported | | | | |

*continued on next page*
| NCT02164539 | Lee 2017 | 6 weeks | N=338 | Airflow limitation not reported | E-RS:COPD baseline total score: | FF | FF/UMECC | FF/Vi | ICS/ LAMA | Secondary: E-RS:COPD total score C (Primary: FEV1 1) | E-RS:COPD responder analysis: not reported |
|-------------|---------|---------|-------|--------------------------------|-------------------------------|----|----------|-------|---------|-------------------------------------|-------------------------------------|
|             |         |         |       |                                | Group 1: FF100mcg= 10.8 (5.50) | Group 2: 250mcg= 11.7 (5.46) | FF/UMECC | 100mcg | FF/VI | Group 1: FF 100mcg<br>Group 2: 250mcg<br>Group 3: 500mcg<br>Group 4: 750mcg<br>Group 5: 1000mcg<br>Group 6: 1500mcg<br>Group 7: 2000mcg<br>Group 8: 2500mcg<br>Group 9: 3000mcg<br>Group 10: 3500mcg<br>Group 11: 4000mcg<br>Group 12: 4500mcg<br>Group 13: 5000mcg<br>Group 14: 5500mcg<br>Group 15: 6000mcg<br>Group 16: 6500mcg<br>Group 17: 7000mcg<br>Group 18: 7500mcg<br>Group 19: 8000mcg<br>Group 20: 8500mcg<br>Group 21: 9000mcg<br>Group 22: 9500mcg<br>Group 23: 10000mcg<br>Group 24: 10500mcg<br>Group 25: 11000mcg<br>Group 26: 11500mcg<br>Group 27: 12000mcg<br>Group 28: 12500mcg<br>Group 29: 13000mcg<br>Group 30: 13500mcg<br>Group 31: 14000mcg<br>Group 32: 14500mcg<br>Group 33: 15000mcg<br>Group 34: 15500mcg<br>Group 35: 16000mcg<br>Group 36: 16500mcg<br>Group 37: 17000mcg<br>Group 38: 17500mcg<br>Group 39: 18000mcg<br>Group 40: 18500mcg<br>Group 41: 19000mcg<br>Group 42: 19500mcg<br>Group 43: 20000mcg<br>Group 44: 20500mcg<br>Group 45: 21000mcg<br>Group 46: 21500mcg<br>Group 47: 22000mcg<br>Group 48: 22500mcg<br>Group 49: 23000mcg<br>Group 50: 23500mcg<br>Group 51: 24000mcg<br>Group 52: 24500mcg<br>Group 53: 25000mcg<br>Group 54: 25500mcg<br>Group 55: 26000mcg<br>Group 56: 26500mcg<br>Group 57: 27000mcg<br>Group 58: 27500mcg<br>Group 59: 28000mcg<br>Group 60: 28500mcg<br>Group 61: 29000mcg<br>Group 62: 29500mcg<br>Group 63: 30000mcg<br>Group 64: 30500mcg<br>Group 65: 31000mcg<br>Group 66: 31500mcg<br>Group 67: 32000mcg<br>Group 68: 32500mcg<br>Group 69: 33000mcg<br>Group 70: 33500mcg<br>Group 71: 34000mcg<br>Group 72: 34500mcg<br>Group 73: 35000mcg<br>Group 74: 35500mcg<br>Group 75: 36000mcg<br>Group 76: 36500mcg<br>Group 77: 37000mcg<br>Group 78: 37500mcg<br>Group 79: 38000mcg<br>Group 80: 38500mcg<br>Group 81: 39000mcg<br>Group 82: 39500mcg<br>Group 83: 40000mcg<br>Group 84: 40500mcg<br>Group 85: 41000mcg<br>Group 86: 41500mcg<br>Group 87: 42000mcg<br>Group 88: 42500mcg<br>Group 89: 43000mcg<br>Group 90: 43500mcg<br>Group 91: 44000mcg<br>Group 92: 44500mcg<br>Group 93: 45000mcg<br>Group 94: 45500mcg<br>Group 95: 46000mcg<br>Group 96: 46500mcg<br>Group 97: 47000mcg<br>Group 98: 47500mcg<br>Group 99: 48000mcg<br>Group 100: 48500mcg<br>Group 101: 49000mcg<br>Group 102: 49500mcg

**E-RS:COPD total score LS mean change for BFG MDI vs comparators [n, LSM (SE); LSM 95% CI]**

| Group 1: BFG MDI: 320/9.6mcg n=638; -1.5 (0.13); NA |
| Group 2: GFF MDI: -0.7 (0.14) |
| Group 3: GFF MDI: -1.0 (0.19) |
| Group 4: BUD/PO: -1.0 (0.19) |

Control Group: Not applicable

**E-RS:COPD responder analysis:** not reported

**E-RS:COPD responder analysis:** not reported

**E-RS:COPD responder analysis:** not reported

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### Responsiveness of the E-RS:COPD in Clinical Trials

| Study | N (weeks) | Baseline Score | Treatment | Secondary Score | Esr score | Exacerbations | MCID: LS mean change from baseline to follow-up: |
|-------|-----------|----------------|-----------|----------------|-----------|---------------|-----------------------------------------------|
| EudraCT 2012-004162-17 | 52 weeks | Moderate-severity airflow limitation ≥2 exacerbations preceding year | E-RS:COPD total score: Group 1–3: Not reported | FP/FORM FORM | E-RS:COPD total score<sup>c</sup> (Primary: Exacerbation Frequency) | FP/FORM 500/20µg versus FORM (RR: 0.79; P=0.084) | *E-RS:COPD total score LS mean change across treatment groups |
| Papi 2017<sup>24</sup> | 4 weeks | Moderate-severity airflow limitation | Enalapril | PDE-3 and 4 inhibitors | E-RS:COPD total score<sup>c</sup> (Primary: FEV<sub>1</sub>) | Peak FEV<sub>1</sub>: Week 4, LS mean difference vs placebo (all p<0.0001): |
| NCT03443414; EudraCT 2016-005205-40 | 4 weeks | Moderate-severity airflow limitation | Enalapril | PDE-3 and 4 inhibitors | E-RS:COPD total score<sup>c</sup> (Primary: FEV<sub>1</sub>) | Peak FEV<sub>1</sub>: Week 4, LS mean difference vs placebo (all p<0.0001): |

<sup>1</sup>Chest symptoms

<sup>2</sup>MCID: LS mean change (ITT population) from baseline in E-RS:COPD total score was greatest for FF/UMEC 13.5mcg 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 symptoms.

**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

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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.\textsuperscript{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.\textsuperscript{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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