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## ORIGINAL ARTICLE

# Measuring respiratory symptoms in clinical trials of COPD: reliability and validity of a daily diary

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## ABSTRACT

**Background** Although respiratory symptoms are characteristic features of COPD, there is no standardised method for quantifying their severity in stable disease.

**Objective** To evaluate the EXACT-Respiratory Symptom (E-RS) measure, a daily diary comprising 11 of the 14 items in the Exacerbations of Chronic Pulmonary Disease Tool (EXACT).

**Methods** Qualitative: patient focus group and interviews to address content validity. Quantitative: secondary data analyses to test reliability and validity.

**Results** Qualitative: n=84; mean (SD) age 65 (10) years, FEV<sub>1</sub> 1.2(0.4) L; 44% male. Subject descriptions of their respiratory symptoms were consistent with E-RS content and structure. Quantitative: n=188; mean (SD) age 66 (10) years, FEV<sub>1</sub> 1.2(0.5) L; 50% male. Factor analysis (FA) showed 3 subscales: RS-Breathlessness, RS-Cough & Sputum, and RS-Chest Symptoms; second-order FA supported a general factor and total score. Reliability (total and subscales): 0.88, 0.86, 0.73, 0.81; 2-day test-retest ICC: 0.90, 0.86, 0.87, 0.82, respectively. Validity: Total scores correlated significantly ( $p < 0.0001$ ) with SGRQ Total ( $r=0.75$ ), Symptoms ( $r=0.66$ ), Activity ( $r=0.57$ ), Impact ( $r=0.70$ ) scores; subscale correlations were also significant ( $r=0.26$ ,  $p < 0.05$  (RS-Chest Symptoms with Activity) to  $r=0.69$ ,  $p < 0.0001$  (RS-Cough & Sputum with Symptoms). RS-Breathlessness correlated with rescue medication use ( $r=0.32$ ,  $p < 0.0001$ ), clinician-reported mMRC ( $r=0.33$ ,  $p < 0.0001$ ), and FEV<sub>1</sub>% predicted ( $r=-0.17$ ,  $p < 0.05$ ). E-RS scores differentiated groups based on chronic bronchitis diagnosis ( $p < 0.01$ – $0.001$ ), smoking status ( $p < 0.05$ – $0.001$ ), and rescue medication use ( $p < 0.05$ – $0.0001$ ).

**Conclusions** Results suggest the RS-Total is a reliable and valid instrument for evaluating respiratory symptom severity in stable COPD. Further study of sensitivity to change is warranted.

## INTRODUCTION

COPD is a progressive disease characterised by persistent airflow limitation with varying degrees of airway wall narrowing, inflammation and emphysema. Respiratory symptoms, including breathlessness, cough and sputum production, are characteristic features of the disease and have significant adverse effects on patient functioning and quality of life.<sup>1–4</sup> Although spirometric measures are useful for diagnosis and evaluating change in lung function, they do not capture symptom severity or variability; weak correlations between lung function and symptoms show they cannot be used

## Key messages

## What is the key question?

- Is there a standardised, reliable and valid diary to evaluate daily respiratory symptoms in clinical studies of stable COPD?

## What is the bottom line?

- Yes, the E-RS.

## Why read on?

- This paper presents methods and results of two studies showing that RS-Total and subscale scores (RS-Breathlessness, RS-Cough & Sputum, RS-Chest Symptoms) have content validity and are reliable and valid in stable patients with COPD.

as proxies for one another.<sup>5–9</sup> Because respiratory symptoms are patient-experienced, it is important to measure this outcome directly, through a patient-reported outcome (PRO) instrument.

To date, there is no standardised method for evaluating respiratory symptoms of stable COPD with a documented development programme consistent with good research practices<sup>10–11</sup> and the Food and Drug Administration (FDA) PRO Guidance.<sup>12</sup> Dyspnoea is the most frequently assessed symptom, often measured with the Baseline/Transition Dyspnea Index,<sup>13</sup> or modified Medical Research Council Dyspnea Scale (mMRC). Health-status measures with symptom components include the St George's Respiratory Questionnaire (SGRQ),<sup>14</sup> Chronic Respiratory Disease Questionnaire,<sup>15</sup> Clinical COPD Questionnaire,<sup>16</sup> and COPD Assessment Test.<sup>17</sup> These questionnaires are completed by subjects intermittently using varied recall periods (eg, since the last visit, past month, previous week, or now).

An alternative to periodic symptom assessment is a patient-completed diary, capturing symptoms each day. This approach is necessary for studies examining the temporal and dynamic nature of respiratory symptoms, including their relationship to other variables such as activity, stress, environmental conditions and rescue medication use. In clinical trials, diaries can be used to evaluate time to symptomatic improvement and/or magnitude and persistence of change over the treatment period. Regulatory agencies have expressed interest

in electronic daily symptom assessments in pharmaceutical trials, with their reduced recall bias and technology enabled compliance monitoring.<sup>12–18</sup> One diary, the Breathlessness, Cough and Sputum Scale, has shown evidence of reliability, validity and responsiveness.<sup>19–20</sup> However, it is limited to three items, and its development was not based on qualitative data from the target population, raising concerns about content validity.<sup>10–12</sup>

The Exacerbations of Chronic Pulmonary Disease Tool (EXACT)-Respiratory Symptoms (RS) (E-RS) was designed to meet the need for a standardised respiratory symptom diary with a development history consistent with good research practices and FDA PRO requirements. The E-RS uses 11 respiratory symptom items from the 14-item EXACT,<sup>21–24</sup> offering efficiencies for investigators and subjects by permitting two validated uses for one diary: (1) assessment of COPD exacerbations using the EXACT total score<sup>21–24</sup>; (2) quantification of respiratory symptoms in stable COPD using RS-Total and subscale scores.

This paper describes the methods and results of research to assess content validity, reliability and validity of the E-RS in patients with stable COPD.

## MATERIALS AND METHODS

The research was conducted in two phases. Phase I addressed content validity through qualitative research methods. Phase II tested score reliability and validity using an existing dataset.<sup>23</sup> All data were gathered in accordance with the amended Declaration of Helsinki, with study protocols approved by an independent institutional review board (IRB) and all participants providing written informed consent prior to data collection (Essex IRB, ID# A2-3864, A2-3864B; Ethical Review Committee, ID# 472-05-09).

In each phase, study participants were recruited from pulmonary and primary care clinics across the USA using inclusion criteria similar to those used in pharmaceutical trials: >40 years of age; diagnosis of stable COPD; emphysema or chronic bronchitis; and ≥10 pack-year smoking history. Exclusion criteria: medical diagnosis of asthma without postbronchodilator airway obstruction; acute congestive heart failure or unstable angina, bronchiectasis, lung cancer, or tuberculosis; or treatment for respiratory infection or pneumonia within the past 60 days. Phase-specific inclusion/exclusion criteria and methods are described below. Following enrolment and consent, each site provided clinical information related to the participant's diagnosis, pulmonary function and clinician rating of disease severity.

### Phase I: qualitative: content validity

A two-step process was used to assess and document the extent to which the items comprising the E-RS adequately and accurately reflect respiratory symptoms of COPD in a stable state. Methods are outlined below, with details provided in the online supplementary appendix.

#### Stage 1: secondary analyses of existing qualitative data

Qualitative analyses were performed on data gathered during the development of the EXACT,<sup>21</sup> that is, data from focus groups and interviews with patients with COPD and a history of a clinic visit or hospitalisation for exacerbation in the previous 6 months (n=63). The purpose of the original study was to characterise COPD exacerbations from the patient's perspective. The data included participant descriptions of the nature and severity of symptoms during a stable state presented as part of their characterisations of COPD and/or to facilitate descriptions of exacerbations, that is, relative to their stable state.

#### Stage 2: new focus groups

Additional focus groups were conducted in a new sample of clinically stable patients (n=21), that is, exacerbation-free for 12 months. The purpose of Stage 2 was to determine if there were new insights or information related to respiratory symptoms in stable COPD not discussed by patients with an exacerbation history and to ensure that saturation had been reached.

Each focus group was led by an experienced study team member using a semistructured discussion guide to elicit information on patient perspectives of respiratory symptoms. To characterise the sample, participants completed the mMRC Dyspnea Scale,<sup>25</sup> the SGRQ for COPD (SGRQ-C),<sup>26</sup> and a sociodemographic questionnaire.

#### Analyses

Descriptive statistics were used to characterise the sample. Atlas.ti 5.0 facilitated thematic analyses of the qualitative data. For each stage of analysis, symptomatic themes were summarised in a saturation grid and mapped to the respiratory symptom items in the EXACT to determine the extent to which this subset of items, named the E-RS, would adequately capture respiratory symptoms in stable disease. Patient understanding of instructions, items, and response categories was addressed using cognitive interviewing methodology during EXACT development.<sup>21</sup>

### Phase II: quantitative: score reliability and validity

Secondary analyses were performed on a subset of data from a previously published prospective observational study used to develop the EXACT.<sup>23</sup> Specifically, data from the stable control sample (n=188) were used. These patients had no history of treatment for exacerbation in the preceding 60 days and were considered clinically stable on enrolment. Subjects were recruited through clinical sites in over 20 states across the USA.

#### Measures

All participants completed the SGRQ-C and sociodemographic forms during the enrolment clinic visit; site staff provided clinician ratings of patient dyspnoea (mMRC) and disease severity, and results of the most recent stable-state spirometry. Each subject completed an eDiary for the ensuing 7 days that included EXACT candidate items, rescue medication use and global ratings of change.<sup>23</sup>

#### Statistical analyses

Analyses were prespecified in a statistical analysis plan completed following Phase I. Because the intent was to evaluate the performance properties of the E-RS as a daily diary, analyses were conducted with data from Day 1, the same day clinic data were gathered, unless otherwise specified. Item-level analyses included measures of central tendency, floor and ceiling effects, item-total correlations, item response frequencies and interitem correlations. Confirmatory (CFA), exploratory (EFA), and second-order factor analyses were performed to evaluate the structure of the measure and develop the scoring algorithms.

Internal consistency was assessed using Cronbach's  $\alpha$ , with a target value of greater than 0.70, to make the instrument suitable for use in clinical trials.<sup>27</sup> Two-day test-retest reliability was evaluated for consecutive days (Days 1–2; 2–3; 3–4, etc.), with data from patients reporting no change in lung condition on the daily global assessment question, and Days 1 and 7 in all

subjects, with the latter assuming symptomatic stability across these two observations (no confirmatory global assessment). Intraclass correlation coefficients (ICC), paired *t* tests and effect sizes were computed.

Validity was examined by correlating E-RS scores with SGRQ total and domain scores, rescue medication use, clinician rating of dyspnoea on the mMRC, and forced expiratory volume in 1 s (FEV<sub>1</sub>) % predicted. Known-groups validity was tested using Student *t* test, comparing E-RS scores of those with and without a medical diagnosis of chronic bronchitis (clinician-reported), current and former smokers (self-report), and those using no rescue medication versus three or more puffs (Day 1; self-report). Scores were also compared across clinician-rated disease severity, hypothesising weak relationships given the multidimensional nature of the clinician's assessment. To take this into account, analyses were performed with and without controlling for age, comorbidity status ( $\leq 1$  or  $\geq 2$ ) and FEV<sub>1</sub>.

Statistical analyses were performed using SAS statistical software V.9.1 (Cary, North Carolina, USA).

## RESULTS

### Samples

Sample demographic and clinical characteristics by phase and stage are shown in table 1.

### Phase I: content validity

Qualitative analyses identified three categories of respiratory symptoms patients experience when stable: breathlessness, cough and sputum, and chest symptoms. Representative quotations for each symptom category and the interrelationship/co-occurrence of symptoms and the saturation grid are provided in online supplementary appendix tables S1 and S2.

Participants spoke of being 'breathless', 'short of breath', and having difficulty breathing, with severity levels that varied day to day. Cough and sputum were generally discussed together; most patients were unable to make it through the day without coughing. Sputum was characterised in terms of quantity and thickness. Most participants cited difficulty coughing up sputum or phlegm. Chest symptoms included congestion, tightness and discomfort, which also varied day to day. Participants often presented their respiratory symptom descriptions as inter-related experiences, describing how they related to and affected one another.

Content of the final instrument, in the context of the 14-item EXACT, is shown in online supplementary appendix table S3.

### Phase II: reliability and validity

Item and factor analyses and scoring algorithm

Participants used the full range of response options, with no missing data and minimal floor and ceiling effects. The CFA

**Table 1** Sample demographic and clinical characteristics by phase

Characteristic	Phase I: content validity		Phase II: score reliability & validity
	Stage 1: secondary analysis of EXACT qualitative data* (n=63)	Stage 2: new focus group† (n=21)	(n=188)
Age mean (SD)	65.2 (10.4)	67.8 (8.7)	65.8 (9.7)
Male (%)	28 (44.4)	14 (66.7)	91 (48.4)
Smoking status, n (%)			
Current	20 (31.7)	9 (42.9)	58 (30.9)
Former	42 (66.7)	12 (57.1)	130 (69.1)
Duration of disease in years, mean (SD)	7.9 (6.2)	8.9 (7.3)	7.5 (7.0)
FEV <sub>1</sub>	1.16 (0.4)	1.3 (0.5)	1.3 (0.6)
FEV <sub>1</sub> % predicted, mean (SD)	45.8 (16.1)	47.9 (16.6)	51.2 (19.6)
mMRC dyspnoea score, n (%)			
0 None	1 (1.6)	5 (23.8)	15 (8.0)
1 Hurrying uphill	8 (12.7)	8 (38.1)	62 (33.0)
2 Walks slower on level	18 (28.6)	3 (14.3)	56 (29.8)
3 Stops after walking	27 (42.9)	4 (19.0)	49 (26.1)
4 Too breathless	6 (9.5)	1 (4.8)	6 (3.2)
Missing	3 (4.8)	0 (0.0)	0 (0.0)
SGRQ total‡	56.3 (18.6)	48.0 (16.0)	50.8 (19.9)
Symptoms	64.3 (23.3)	62.0 (23.1)	60.8 (21.2)
Activity	72.6 (19.7)	61.0 (21.0)	69.7 (23.5)
Impact	45.7 (21.3)	35.8 (16.4)	36.8 (22.3)
Patient-reported comorbidity, n (%)§			
Hypertension	21 (33.3)	10 (47.6)	73 (38.8)
Diabetes	12 (19.0)	4 (19.0)	24 (12.8)
Heart disease	10 (15.9)	1 (4.8)	35 (18.6)
Chronic sinusitis	5 (7.9)	2 (9.5)	13 (6.9)
Other	16 (25.4)	4 (19.0)	12 (6.4)

\*Three focus groups, twenty-five 1:1 interviews, two 2:1 interviews among stable COPD patients.

†Four new focus groups.

‡Phase I, Stage 1: n=54–61; Phase II: n=181–188.

§Not mutually exclusive.

EXACT, Exacerbations of Chronic Pulmonary Disease Tool; FEV<sub>1</sub>, forced expiratory volume in 1 s; GOLD, Global Initiative on Obstructive Lung Disease; mMRC, modified Medical Research Council; SGRQ, St. George's Respiratory Questionnaire.

**Table 2** Exploratory factor analysis: promax factor loading\*

Item number	Factor 3	Factor 2	Factor 1
RS-Breathlessness			
Q7—Breathless today	<b>0.777</b>	0.040	0.056
Q8—Describe how breathless	<b>0.747</b>	0.122	−0.170
Q9—Short of breath—personal care	<b>0.749</b>	0.103	−0.053
Q10—Short of breath—indoor	<b>0.750</b>	−0.079	0.081
Q11—Short of breath—outdoor	<b>0.644</b>	−0.154	0.196
RS-Cough & Sputum			
Q2—How often cough	0.017	<b>0.717</b>	0.156
Q3—How much mucus when cough	0.004	<b>0.850</b>	−0.082
Q4—Difficulty bringing up mucus	0.071	<b>0.447</b>	0.284
RS-Chest Symptoms			
Q1—Chest feel congested	0.006	0.290	<b>0.575</b>
Q5—Have chest discomfort	−0.029	−0.043	<b>0.876</b>
Q6—Chest feels tight	0.113	0.069	<b>0.622</b>

n=188.

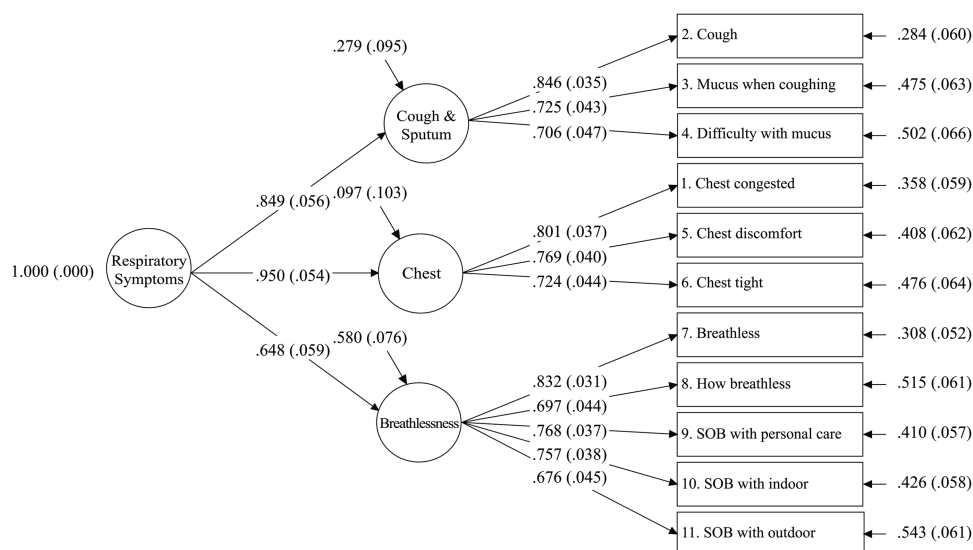
In bold: Factor 3: RS-Breathlessness; Factor 2: RS-Cough &amp; Sputum, Factor 1: RS-Chest Symptoms.

For each item, response scale scores range from 5 to 6, with higher scores reflecting greater severity.

\* $\chi^2=44.24$  (DF=25),  $p=0.010$ ; RMSEA=0.064, RMSR=0.027.

RMSEA, root mean square error of approximation; RMSR, root mean square residual; RS, respiratory symptoms.

confirmatory fit index (CFI) was 0.75, less than the 0.95 prespecified as a good fit for unidimensionality, thereby precluding the use of Rasch analysis for the total score. EFA showed a three-factor solution (table 2), indicating that three respiratory symptom subscales comprise the measure. The second-order factor model fit the data very well (CFI=0.96), with standardised coefficients between the items and respiratory symptom factors, and between the respiratory symptom factors and the general factor, all greater than 0.60 (range 0.68 to 0.85 and 0.65 to 0.95, respectively) (see figure 1). The 0.94 correlation between general factor and RS-Total scores provided further support for an empirical general factor governing the three E-RS factors.



**Figure 1** Higher-Order Factor Model for the E-RS. Confirmatory Fit Index (CFI)=0.958. Root Mean Square Error of Approximation (RMSEA)=0.073 (90% CI 0.050 to 0.096). Standardised Root Mean Square Residual (SRMR)=0.043. The E-RS is a derivative instrument, using the 11 respiratory symptom items from the 14-item EXACT. SOB, shortness of breath.

The scoring algorithms for the E-RS yield a total score and three subscale scores, with higher scores on these ordinal-level scales indicating more severe symptoms. Item-level scores range from 4 to 5 points (0 to 3 or 0 to 4), which are summed to yield total and subscale scores. E-RS scores are calculated for each day the diary is completed, and may be aggregated or summarised in a manner consistent with the study purpose and design.

Descriptive statistics, floor and ceiling effects, total and subscale intercorrelations, and sample patient-level figures for RS-Total scores over 7 days are provided in online supplementary appendix tables S4a and b and appendix figure S1.

### Reliability

Reliability parameters are presented in table 3; reproducibility estimates for Days 1 to 2 are shown, with the remaining consecutive-day analyses appearing in online supplementary appendix table S5.

### Validity

Correlations between E-RS scores and alternative assessments of respiratory symptom severity (concurrent validity), related constructs (convergent validity), and weakly related constructs (divergent validity) are provided in table 4.

RS-Total and subscale scores (RS-Breathlessness, RS-Cough & Sputum, and RS-Chest Symptoms) differentiated those with and without a diagnosis of chronic bronchitis, current and ex-smokers, and rescue medication free versus  $\geq$  three puffs (table 5). The univariate models of clinician-rated disease severity were not significant, but the multivariate models for RS-Total ( $p < 0.05$ ), RS-Breathlessness ( $p < 0.05$ ), and RS-Cough & Sputum scores ( $p < 0.01$ ) were significant (see online supplementary appendix table S6).

### DISCUSSION

Although respiratory symptoms play a key role in the diagnosis, assessment and management of patients with COPD and symptom relief is an important target of therapy, there is no standardised, reliable and valid daily diary for evaluating this



**Table 3** E-RS reliability: internal consistency and test-retest reproducibility

		Reproducibility (Day 1 and Day 2) (n=76)†					
E-RS* scale (# items)	Internal consistency (n=188)  Cronbach's $\alpha$	ICC‡	Day 1 mean (SD)	Day 2 mean (SD)	Difference (SD)	p Value§	Effect size
RS-Total Score (11)	0.88	0.90	9.62 (6.24)	9.66 (6.36)	−0.04 (2.88)	0.91	−0.01
RS-Breathlessness (5)	0.86	0.86	5.07 (3.65)	4.87 (3.63)	0.20 (1.95)	0.38	0.05
RS-Cough & Sputum (3)	0.73	0.87	2.82 (2.30)	2.88 (2.18)	−0.07 (1.15)	0.62	−0.03
RS-Chest Symptoms (3)	0.81	0.82	1.74 (1.86)	1.91 (2.07)	−0.17 (1.18)	0.21	−0.09
		Reproducibility (Day 1 and Day 7) (n=171)¶					
RS-Total Score		0.73	11.9 (6.77)	12.1 (7.22)	−0.15 (5.14)	0.70	−0.02
RS-Breathlessness		0.71	5.95 (3.75)	6.09 (4.13)	−0.15 (3.00)	0.53	−0.04
RS-Cough & Sputum		0.69	3.51 (2.28)	3.42 (1.96)	0.09 (1.67)	0.49	0.04
RS-Chest Symptoms		0.62	2.45 (2.11)	2.54 (2.27)	−0.09 (1.92)	0.52	−0.04

\*Ranges: RS-Total 0 to 40; RS-Breathlessness 0 to 17; RS-Cough & Sputum 0 to 11; RS-Chest Symptoms 0 to 12; higher scores=more severe symptoms.

†Intraclass correlation coefficient.

‡Participants reporting 'no change' between the two consecutive days.

§p value from paired t test.

¶Participants completing the diary at Day 1 and Day 7.

E-RS, Exacerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms; ICC, intraclass correlation coefficient.

outcome in natural history studies and clinical trials. This paper presents the first evidence of the validity and reliability of the E-RS to meet this need.

Phase I of this work addressed content validity.<sup>10–28</sup> Participant descriptions of their breathlessness, cough and sputum were consistent with the literature<sup>3–5–8–9–29</sup> and the content and structure of the E-RS. Of particular note were descriptions of chest symptoms (chest congestion, discomfort and tightness), a symptom set not measured with existing questionnaires.<sup>14–17–19</sup>

Participant descriptions of symptom variability suggest an unstable component to 'stable' COPD, consistent with findings reported by Kessler *et al*<sup>29</sup> in severe patients. Of the symptomatic patients participating in this pan-European observational study (70% of the 2441), most (63%) experienced symptom variability, with over half indicating variance throughout the

week (54%) or across seasons (60%). The most variable symptoms were breathlessness and chest tightness; variability in breathlessness was associated with a history of two or more exacerbations the prior year and greater adverse impact on daily activity.<sup>29</sup> These results suggest respiratory symptoms in COPD may not be as stable as previously believed,<sup>30</sup> and that further research on day-to-day variability is needed.

It is important to note that the E-RS is administered in the evening prior to bedtime with respondents rating their symptoms as they reflect back on the day. This method is efficient and less burdensome than twice-daily assessments. However, this approach may be less precise for those interested in characterising and tracking nighttime or morning symptoms, specifically.<sup>29–31</sup> Studies could be performed to evaluate the added precision of administering the E-RS twice-daily, with the corresponding adjustment in recall period, or using a separate morning diary for this purpose.

Participants described breathlessness, cough, sputum and chest congestion as co-occurring and interacting, suggesting a respiratory symptom complex in COPD that can be captured through a total score, representing the overall severity of this symptom complex, and subscale scores capturing the three types of respiratory symptoms. This was supported quantitatively in the second-order factor structure and strong interscale correlations, internal consistency reliability levels and validity metrics. This measurement structure permits step-down hypothesis testing, with respiratory symptom severity overall tested first, followed by tests for breathlessness, cough and sputum, and chest symptoms.

Internal consistency estimates for RS-Total, RS-Breathlessness, and RS-Chest Symptom scores exceeded the conservative 0.80 standard, indicating a high degree of precision with low measurement error. Score reproducibility over two consecutive days in patients reporting no change was very high. The lower estimates over a six-day interval (Day 1 and Day 7) are consistent with the known symptom variability day to day in stable patients. This finding is pertinent given regulatory authority interest in the use of daily symptom assessments<sup>12</sup> and the need for further study of symptom temporal-severity dynamics.

**Table 4** Validity: correlation with related constructs and alternative measures

Measure	n*	E-RS scale†			
		Total score	Breathlessness	Cough & Sputum	Chest Symptoms
SGRQ total	181	<b>0.75***</b>	<b>0.69***</b>	<b>0.58***</b>	<b>0.52***</b>
Symptoms	188	<b>0.66***</b>	<b>0.44***</b>	<b>0.69***</b>	<b>0.60***</b>
Activity	184	<b>0.57***</b>	<b>0.68***</b>	0.31***	0.26***
Impact	181	<b>0.70***</b>	<b>0.61***</b>	<b>0.55***</b>	<b>0.54***</b>
mMRC	188	0.33***	<b>0.38***</b>	0.24**	0.16*
Rescue medication use	188	0.32***	<b>0.34***</b>	0.26**	0.17*
FEV <sub>1</sub> % predicted	188	−0.10	−0.17*	−0.05	0.01

†Sample sizes are a function of missing item-level data.

‡Day 1, Spearman's rank-order correlation.

**Bold** coefficients identify related constructs with strongest expected value.

\*p<0.05; \*\*p<0.001; \*\*\*p<0.0001.

E-RS, Exacerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms; FEV<sub>1</sub>, forced expiratory volume in 1 s; mMRC, modified Medical Research Council; SGRQ, St George's Respiratory Questionnaire.

**Table 5** Known-groups validity: E-RS Mean (SD) scores by chronic bronchitis diagnosis, smoking status, and rescue medication use

E-RS scores*	Chronic bronchitis			Smoking status			Rescue medication use†		
	Yes (n=51)	No (n=137)	p Value‡	Current smoker (n=58)	Ex-smoker (n=130)	p Value‡	3 or more puffs (n=58)	No (n=94)	p Value‡
RS-Total	15.0 (6.2)	10.8 (6.6)	0.0001	14.8 (6.8)	10.6 (6.3)	<0.0001	14.7 (6.1)	9.9 (6.3)	<0.0001
RS-Breathlessness	7.3 (3.4)	5.4 (3.7)	0.0018	6.9 (3.7)	5.5 (3.6)	0.0183	7.6 (3.4)	4.7 (3.4)	<0.0001
RS-Cough & Sputum	4.5 (2.1)	3.1 (2.2)	0.0002	4.7 (2.0)	3.0 (2.2)	<0.0001	4.3 (2.0)	3.0 (2.3)	0.0009
RS-Chest Symptoms	3.2 (2.3)	2.2 (2.0)	0.0059	3.2 (2.4)	2.1 (1.9)	0.0012	2.9 (2.1)	2.2 (2.1)	0.0453

\*RS-Total and RS-domain score ranges are as follows with the higher values indicating greater severity of respiratory symptoms: RS-Total scores range from 0 to 40; RS-Breathlessness scores range from 0 to 17; RS-Cough & Sputum scores range from 0 to 11; and RS-Chest Symptoms scores range from 0 to 12.

†Study Day 1.

‡Student t test.

E-RS, Exacerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms.

The magnitude and pattern of correlations between health status (SGRQ), dyspnoea (mMRC), rescue medication use, and FEV<sub>1</sub> and E-RS subscales were consistent with score validity. The chronic bronchitic phenotype and current smokers were more symptomatic,<sup>32–34</sup> while subjects who reported no rescue medication use on Day 1 also reported significantly less severe symptoms, with the strongest effect observed in the RS-Breathlessness scale. Although one might speculate that the relationship between symptom severity and the clinician's global assessment of COPD severity would be stronger, the modest relationship had improved power when confounding factors were controlled. This supports the differential and complementary roles played by direct symptom assessment from the patient and the clinician's integrated assessment of the patient's COPD, with the latter including a clinical appraisal of symptoms, spirometry, physical assessment, exacerbation history, treatment history, comorbidity and general health, among other factors.

Although the dataset did not permit an evaluation of sensitivity to change, results of known-groups analyses offer preliminary insight into score interpretation. For example, the difference in RS-Total scores between symptomatic and less symptomatic patients (table 5) was approximately 4 on the 40-point scale. Effect sizes were very large (>0.60), indicating that 4 points may be substantially greater than a 'minimally clinically important difference' (MCID). Applying a commonly used distribution-based method for estimating the MCID (0.5 SD of the sample mean; online supplementary appendix table S4a), estimates would be: RS-Total: 3.35; RS-Breathlessness: 1.85; RS-Cough & Sputum: 1.15; RS-Chest Symptoms: 1.05. Until anchor-based estimates across multiple samples are available, these values should be considered preliminary since they are probably higher than the true MCID.

Although respiratory symptoms may be assessed periodically as part of existing COPD-specific health status questionnaires, there are several potential advantages of daily assessments. First, daily scores reduce recall bias and provide a prospective, daily accounting of symptom severity. Second, this approach yields information on day-to-day variability. Third, daily data offer analytical flexibility, with methods for evaluation over time determined by the study purpose. Advantages of the E-RS specifically include its embedded position within the EXACT, providing data on exacerbations and respiratory symptoms simultaneously, with no additional patient burden. The EXACT was developed as an eDiary, with short, easy-to-read questions and recommendations for formatting and reminders to enhance compliance. Compliance rates were high (94%) in this short-term validation study, and have exceeded 88% across several 3–6 month clinical trials,<sup>24</sup> suggesting eDiaries are feasible in

this patient population. Widespread smart phone access may facilitate future testing and use of eDiaries in natural history studies or clinical practice.<sup>35</sup>

An important question is the suitability of the E-RS for international studies. During the development of the parent instrument, international content and translation experts served on the advisory panel. To date, the EXACT has been translated into more than 50 languages with cognitive interviews conducted with COPD patients in the target countries to assure cultural and linguistic equivalence. Although the EXACT has performed well in international trials,<sup>24</sup> an evaluation of E-RS score reliability, validity and responsiveness in international settings is warranted.

## CONCLUSIONS

The E-RS was designed to assess daily respiratory symptoms in clinical studies of COPD. Results suggest the instrument is content valid with quantitative evidence of score reliability and validity. Further research on the performance properties of E-RS scores in new samples and its sensitivity to change, including MCID estimation and development of responder definitions, are warranted.

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**Competing interests** NK Leidy, CC Sexton, and LT Murray are employed and SM Notte was employed by Evidera (formerly United BioSource Corporation), which provides consulting and other research services to pharmaceutical, device, government and non-government organisations. As Evidera employees, they work with a variety of companies and organisations and are expressly prohibited from receiving any payment or honoraria directly from these organisations for services rendered. BU Monz was an employee of Boehringer Ingelheim at the time this research was conducted; M Goldman is an employee of AstraZeneca; and L Nelsen is an employee of Merck & Company. BI, AstraZeneca, and Merck develop and market respiratory products. PW Jones and S Sethi consult with various companies on topics related to COPD and its treatment.

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**Data sharing statement** Readers are asked to contact the first author to discuss access to data used in this study.

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## REFERENCES

- Calverley PM, Georgopoulos D. Chronic obstructive pulmonary disease: symptoms and signs. *Eur Respir Mon* 2006;38:7–23.
- Food and Drug Administration. Draft guidance for industry on chronic obstructive pulmonary disease: developing drugs for treatment; availability. *Fed Regist* 2007;72:63618.
- Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of COPD, 2011. [cited 2013 Aug]. [http://www.goldcopd.org/uploads/users/files/GOLD\\_Report\\_2011\\_Feb21.pdf](http://www.goldcopd.org/uploads/users/files/GOLD_Report_2011_Feb21.pdf)
- Viegi G, Pistelli F, Sherrill DL, et al. Definition, epidemiology and natural history of COPD. *Eur Respir J* 2007;30:993–1013.
- Kuyucu T, Guclu SZ, Saylan B, et al. A cross-sectional observational study to investigate daily symptom variability, effects of symptom on morning activities and therapeutic expectations of patients and physicians in COPD-SUNRISE study. *Tuberkuloz ve toraks* 2011;59:328–39.
- Schlecht NF, Schwartzman K, Bourbeau J. Dyspnea as clinical indicator in patients with chronic obstructive pulmonary disease. *Chron Respir Dis* 2005;2:183–91.
- Tsiligianni I, Kocks J, Tzanakis N, et al. Factors that influence disease-specific quality of life or health status in patients with COPD: a review and meta-analysis of Pearson correlations. *Prim Care Respir J* 2011;20:257–68.
- Voll-Aanerud M, Eagan TM, Plana E, et al. Respiratory symptoms in adults are related to impaired quality of life, regardless of asthma and COPD: results from the European community respiratory health survey. *Health Qual Life Outcomes* 2010;8:107.
- Wijnhoven HA, Kriegsman DM, Hesselink AE, et al. Determinants of different dimensions of disease severity in asthma and COPD: pulmonary function and health-related quality of life. *Chest* 2001;119:1034–42.
- Patrick DL, Burke LB, Gwaltney CJ, et al. Content validity—establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report: part 1—eliciting concepts for a new PRO instrument. *Value Health* 2011;14:967–77.
- Patrick DL, Burke LB, Gwaltney CJ, et al. Content validity—establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO Good Research Practices Task Force report: part 2—assessing respondent understanding. *Value Health* 2011;14:978–88.
- Food and Drug Administration. Guidance for industry on patient-reported outcome measures: use in medical product development to support labeling claims. *Fed Regist* 2009;74:65132–3.
- Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest* 1988;93:580–6.
- Jones PW, Quirk FH, Baveystock CM, et al. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;145:1321–7.
- Guyatt GH, Berman LB, Townsend M, et al. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987;42:773–8.
- van der Molen T, Willemse BW, Schokker S, et al. Development, validity and responsiveness of the Clinical COPD Questionnaire. *Health Qual Life Outcomes* 2003;1:13.
- Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD Assessment Test. *Eur Respir J* 2009;34:648–54.
- European Medicines Agency, Respiratory Drafting Group. *Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD)*. EMA/CHMP/483572/2012. London: European Medicines Agency, 2012. [cited 2013 December 19]. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2012/08/WC500130880.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/08/WC500130880.pdf)
- Leidy NK, Rennard SI, Schmier J, et al. The breathlessness, cough, and sputum scale: the development of empirically based guidelines for interpretation. *Chest* 2003;124:2182–91.
- Leidy NK, Schmier JK, Jones MK, et al. Evaluating symptoms in chronic obstructive pulmonary disease: validation of the Breathlessness, Cough and Sputum Scale. *Respir Med* 2003;97(Suppl A):S59–70.
- Leidy NK, Wilcox TK, Jones PW, et al. Development of the EXacerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT): a patient-reported outcome (PRO) measure. *Value Health* 2010;13:965–75.
- Jones PW, Chen WH, Wilcox TK, et al. Characterizing and quantifying the symptomatic features of COPD exacerbations. *Chest* 2011;139:1388–94.
- Leidy NK, Wilcox TK, Jones PW, et al. Standardizing measurement of chronic obstructive pulmonary disease exacerbations. Reliability and validity of a patient-reported diary. *Am J Respir Crit Care Med* 2011;183:323–9.
- Leidy NK, Murray LT, Jones PW, et al. Performance of the EXacerbations of Chronic Pulmonary Disease Tool (EXACT) in three randomized controlled trials of COPD. *Ann Am Thorac Soc* Published Online First: 16 Jan 2014.
- Darbee JC, Ohtake PJ. Outcome measures in cardiopulmonary physical therapy: Medical Research Council (MRC) dyspnea scale. *Cardiopul Phys Ther J* 2006;17:29–37.
- Meguro M, Barley EA, Spencer S, et al. Development and Validation of an Improved, COPD-Specific Version of the St. George Respiratory Questionnaire. *Chest* 2007;132:456–63.
- Hays RD, Anderson RT, Revicki DA. Assessing reliability and validity of measurement in clinical trials. In: Staquet MJ, Hays RD, eds. *Quality of Life Assessment in Clinical Trials: Methods and Practice*. New York: Oxford University Press, 1998:169–82.
- Rothman M, Burke L, Erickson P, et al. Use of existing patient-reported outcome (PRO) instruments and their modification: the ISPOR Good Research Practices for Evaluating and Documenting Content Validity for the Use of Existing Instruments and Their Modification PRO Task Force Report. *Value Health* 2009;12:1075–83.
- Kessler R, Partridge MR, Miravittles M, et al. Symptom variability in patients with severe COPD: a pan-European cross-sectional study. *Eur Respir J* 2011;37:264–72.
- Lopez-Campos JL, Calero C, Quintana-Gallego E. Symptom variability in COPD: a narrative review. *Int J Chron Obstruct Pulmon Dis* 2013;8:231–8.
- Partridge MR, Karlsson N, Small IR. Patient insight into the impact of chronic obstructive pulmonary disease in the morning: an internet survey. *Curr Med Res Opin* 2009;25:2043–8.
- Etter JF. Short-term change in self-reported COPD symptoms after smoking cessation in an internet sample. *Eur Respir J* 2010;35:1249–55.
- Sumner H, Woodcock A, Kolsum U, et al. Predictors of objective cough frequency in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013;187:943–9.
- de Oca MM, Halbert RJ, Lopez MV, et al. The chronic bronchitis phenotype in subjects with and without COPD: the PLATINO study. *Eur Respir J* 2012;40:28–36.
- Coons SJ, Gwaltney CJ, Hays RD, et al. Recommendations on evidence needed to support measurement equivalence between electronic and paper-based patient-reported outcome (PRO) measures: ISPOR ePRO Good Research Practices Task Force report. *Value Health* 2009;12:419–29.

**Measuring Respiratory Symptoms in Clinical Trials of COPD:  
Reliability and Validity of a Daily Diary**

**APPENDIX**

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**Running head:** E-RS: Respiratory Symptom Measurement COPD

**Keywords:** COPD, Respiratory Symptoms, Psychometric, Qualitative, Breathlessness, Cough, Sputum, Chest Symptoms

**What is the key question?** Is there a standardized, reliable, and valid diary to evaluate daily respiratory symptoms in clinical studies of stable COPD?

**What is the bottom line?** Yes, the E-RS.

**Why read on?** This paper presents methods and results of two studies showing that RS-Total and subscale scores (RS-Breathlessness, RS-Cough & Sputum, RS-Chest Symptoms) have content validity and are reliable and valid in stable patients with COPD.



## APPENDIX

### PHASE I: QUALITATIVE RESEARCH TO ADDRESS CONTENT VALIDITY

#### Methods

Qualitative research methods were used to assess and document the extent to which the items comprising the E-RS adequately and accurately reflect respiratory symptoms of COPD in a stable (non-exacerbating) health state. To accomplish this objective, 2 stages of research were undertaken.

#### *Stage 1: Secondary Analyses of Existing Qualitative Data*

Qualitative analyses were performed on data gathered during the development of the EXACT.<sup>1</sup> Specifically, data from focus groups, 2:1, and 1:1 interviews with men and women with COPD and a history of a clinic visit or hospitalisation for exacerbation in the previous 6 months (n=63) were used; data from 8 patients with a recent exacerbation (less than 10 days) were excluded. The purpose of the original study was to understand how patients with COPD describe exacerbations, including the symptomatic features, changes before and during an event, patterns of recovery, and perceptions of severity and duration. The data included participant descriptions of the nature and severity of symptoms during a stable state, presented as part of their characterizations of COPD and/or to facilitate their descriptions of exacerbations, i.e., relative to their stable disease. Subjects were recruited through pulmonary and primary care clinics in four states in four regions of the United States (US): Arizona, Florida, Maryland, and Michigan. The most recent pulmonary function values were provided by the clinical sites with distributions reviewed throughout enrolment to assure representation across varying degrees of airway

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obstruction. Protocols were approved by an appropriate institutional review board (IRB) and consent was obtained from each participant prior to any discussion of study-related materials.

Focus groups and interviews were conducted at focus group facilities or private rooms in the clinical setting and performed by 2 experienced study team members trained in qualitative research methods and the purpose and needs of the study. Semi-structured interview guides were used to facilitate focused discussion and optimize consistency. Focus groups were led by one primary staff member with the second staff member serving as an assistant, taking notes and facilitating discussion or clarity as needed. An experienced researcher observed the proceedings and offered recommendations to staff as needed during planned breaks. Groups and interviews lasted approximately 2 hours and were audio recorded and transcribed for analysis.

The software program, Atlas.ti version 5.0<sup>2</sup> was used to organize the data. For the E-RS analyses, study team members reviewed the transcripts and examined the data for specific reference to respiratory symptoms the patients identified and described in relationship to their stable (non-exacerbating) state. The respiratory symptoms included in the coding dictionary created in the development of the EXACT were used in the initial phase of analysis, with the coding modified as needed to ensure that quotes were specific to respiratory symptoms in a non-exacerbating state. Reference to exacerbation experiences were included only if they provided context for a description of stable symptoms, e.g., statements comparing and contrasting the nature and severity of respiratory symptoms in an acute versus a stable period. Two research team members independently coded the first two transcripts, followed by a post-coding comparison and reconciliation. With inter-coder agreement assured, the remaining transcripts were coded by one staff member and reviewed by a senior study investigator who refined the files as needed for

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quality and clarity. Saturation of respiratory symptoms was reached in these secondary analyses. Sample codes and quotations from these analyses are provided in Appendix Table 1.

### *Stage 2: New Focus Groups*

In addition to the Stage 1 secondary analyses, 4 new focus groups were conducted in a new sample of patients with COPD (n=21) who were considered clinically stable, i.e., no clinic visits or hospitalisations for exacerbations for a minimum of 12 months. The purpose of these focus groups was to determine if there were any new symptoms, insights, or information related to respiratory symptoms in stable COPD not discussed by patients with a recent exacerbation history (Stage 1).

An experienced, trained moderator led each group with the help of an assistant, using a semi-structured discussion guide focusing on the types and nature of respiratory symptoms and symptom experiences during non-exacerbation periods. This guide was designed to facilitate the spontaneous identification of respiratory symptoms by the study participants. Focus groups included an elicitation exercise during which the moderator asked participants to identify all of the respiratory symptoms they experience, which were recorded on a white board. When the group participants could not identify any new symptoms, each listed symptom was discussed in detail, including alternative names, descriptions of severity, stability and/or variability, and factors influencing its expression. Focus groups lasted approximately 90 minutes and were audio recorded for transcription and analysis.

Atlas.ti version 5.0<sup>2</sup> was used to organize the data. Following an initial review of the transcripts, it was determined that the Stage 1 coding dictionary could be used as the starting point for analyzing the Stage 2 data, with specific attention given to any new symptoms or symptom descriptions that

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required a new code. Two research team members independently coded the first 3 transcripts, followed by a post-coding comparison and reconciliation with a senior study investigator. Because there was agreement between the two coders, one coder completed the fourth transcript and the senior study investigator reviewed and finalized coding. Sample codes and quotations from these analyses are included in Appendix Table S1.

Saturation was defined as two new focus group discussions during which no new symptoms or symptom descriptions were introduced. The saturation grid displaying each respiratory symptom identified in the data by group and individual participant is shown in Appendix Table S2.

## Results

Representative quotations by symptom category is shown in Appendix Table S1. The respiratory symptoms, shown in Appendix Tables S1 and S2, mapped well to the 11 respiratory symptom items from the EXACT. Although several participants named “wheeze” as a symptom, there was substantial variability in how they described and characterized this symptom, ranging from a feeling of tightness or congestion (covered under existing items) to a whistling sound when they breathed through their chest congestion. Elicited descriptions of “wheeze” from patients who did not identify this symptom also varied. Because of the inconsistent interpretation of the word “wheeze” and the conceptual and symptomatic link between the diverse descriptions and existing items, the research team concluded that the E-RS retained its content validity without this nebulous term.

## PHASE II: QUANTITATIVE RESEARCH

Supplemental results from the quantitative analyses are provided in Appendix Tables S4–S6 and Appendix Figure S1.



## REFERENCES

1. Leidy NK, Wilcox TK, Jones PW, *et al.* Development of the EXAcerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT): a patient-reported outcome (PRO) measure. *Value Health* 2010;13:965–75.
2. Muhr T. *User's Manual for ATLAS.ti 5.0*. Berlin: ATLAS.ti Scientific Software Development GmbH, 2004.

**Appendix Table S1. Representative Participant Quotations by Respiratory Symptom Category**

Symptom	Quotation Description, difficulty, severity, variability
<b>Breathlessness</b>	
Short of breath or breathless	<p><i>“Breathing like a horse” (203), “feeling like I’m choking to death...like somebody’s got a pillow over your face and you’re smothering” (204), “take my breath away from me” (302), “out of breath” (306), “can’t get a breath” (202), “choking up” (207), “not breathing adequately, not getting enough oxygen” (206), “couldn’t get enough air in” (102), “can’t breathe” (101, 104), “breathing hard” (306), “gulp air trying to get air into my lungs” (102) “trouble breathing” (402).</i></p> <p><i>“Mine fluctuates so much I can have it-like talking I’m fine but walking from here to my car I’ll be short of breath and I have to be on oxygen. I don’t have a consistent-I’m up and down” (102).</i></p>
With personal care activities – washing/dressing	<p><i>“Taking a shower makes me short...I get short of breath” (102), “I cannot go into the shower before – without taking medication because once I get in the shower I’m breathing like a horse” (203) and “bending over” (202) “tying your shoes” (203).</i></p>
With indoor activities – cleaning, household work	<p><i>“But I do get really short. I get short of breath. Activity doesn’t bother me too much as long as it’s not excessive. I can do some light gardening, things around the house. Going up stairs hurts a little bit and we have stairs in our house. But surprisingly, going down hurts worse” (207) .</i></p> <p><i>“But if I go up a short-it don’t have to be long stairs, just a couple stairs and I get shortness of breath. And if I do too much of anything I get shortness of breath” (105).</i></p> <p><i>“If I do any lifting or anything I have to bend over and catch my breath” (306).</i></p> <p><i>“Lifting anything kind of heavy- -I get shortness of breath” (103).</i></p> <p><i>“Carrying bundles, groceries and all that” (203).</i></p> <p><i>Emptying the dishwasher” (102), “scrubbing my floor” (202), “sweeping the floor” (303) “vacuuming” (203, 402), and “housework” (402).</i></p>
With outdoor activities – outside the home, yard work	<p><i>When I try to walk out there, I can go maybe 50 yards and I have to stop and lean up against a post or something to catch my breath (2:1 #102); “yard work” (102, 304, 402), “gardening” (203, 205, 207) , “cutting grass” (207).</i></p>
<b>Cough &amp; Sputum</b>	
Cough	<p><i>“Well, if I get a hard cough it seems like I keep coughing, and it’s a dry cough. It seems like you want to get something up, but there’s nothing there to get up, and you cough and cough and cough. Finally, for some reason, you just quit” (302).</i></p> <p><i>“It’s a very deep and stringent cough” (2:1 #101), “I don’t have a dry cough” (FG #409), “I cough to clear my lungs” (FG #202).</i></p> <p><i>“Really hard” (202), “really, really hard” (305) and “hacking” (304) (402) “I cough all day long on and off...” (306).</i></p> <p><i>“Usually every day I have to cough.” (402) “I cough every morning” (FG #305), “I cough every day” (FG #303), “I cough every day. Every morning I get up. I cough” (FG #307).</i></p> <p><i>“...some days are really bad...and other days I don’t have a problem” (402).</i></p>

Symptom	Quotation Description, difficulty, severity, variability
Mucus (phlegm)	<p><i>"I have two different kinds of cough, and wet and dry doesn't really... There's the kind that comes with congestion" (FG #502).</i></p> <p><i>I'm coughing up something every day" (FG #303). "I cough every morning. Until I get something up..." (FG #305). "But I never cough and rarely do I cough up sputum..." (CD #308).</i></p> <p><i>"It's all clear, thick mucus that I cough up and it's not all that pleasant to describe" (304), "I bring up mucus at least once a day" (202), "six or seven times [a day]" (206).</i></p> <p><i>"It's a constant thing. It's just more or less. And less is good and more is bad" (206). "Maybe two times a week" (105).</i></p> <p><i>"I cough when I have phlegm building up in the chest and that's the way you expel it" (206).</i></p>
Difficulty bringing up mucus	<p><i>"Well, you know you need to cough up some mucus but it just don't seem to want to come up" (104).</i></p> <p><i>"Very difficult to get it to come up" (206) "you have to work at it" (202).</i></p> <p><i>"Can't seem to get anything up" (302, 305).</i></p> <p><i>"Because when I cough sometimes I'll kind of bring up some mucus and I don't want it to come up. And that sometimes causes you to-so you find yourself straining. You know it needs to come up because your body tells you need to cough it up" (105).</i></p>
<b>Chest Symptoms</b>	
Congestion	<p><i>"Congestion is how you describe it." (101); Congested, congested....I guess there must be congestion in there" (401).</i></p> <p><i>"Sticky" (202), "stopped up" (306), "fluid on the lungs" (206). "Crap in your lungs" (102).</i></p> <p><i>"A lot of congestion.... All in my chest" (402).</i></p> <p><i>Yeah, it's not extreme, but it's not just a little bit, either" (306).</i></p> <p><i>"Well, I'm always congested. Always. I'm always-but it's really bad like in the morning" (402).</i></p> <p><i>Like if you hear a gurgling sound. It's congestion in there. It needs a way to get up" (402).</i></p> <p><i>Yeah. It's just like you can't open it up. It's like using glue on your hands and you're pulling it apart and you can't-it won't open so the air can't come in because it just stays like this. And that's what I call stickiness. It's just that I don't-the phlegm is there and I just don't feel like I'm getting the breath I need" (202).</i></p> <p><i>"What does it feel like?...It feels something like a little heaviness. Feels heavy. And it might even be sometimes you take a deep breath and you might even get a little pain with it and your throat gets dry" (CD #308).</i></p>
Discomfort	<p><i>[Chest discomfort is different from congestion] because I can tell when I'm congested and I can't breathe, but the discomfort, it's just the pain in my chest from the coughing. Every time I cough my chest hurts so much" (CD #202).</i></p> <p><i>"Mine is just kind of in my chest I feel-the best way I could describe it is maybe a little heavy in there and I will cough up, I'll have some fluid that once I kind of get some of that up I kind of feel a little bit better or if I have a-take one of those little emergency squirtums and I'll feel a lot better" (304).</i></p>

Symptom	Quotation Description, difficulty, severity, variability
Tight	<p><i>"I can only explain it this way. You feel as though your air is up to here and you can't get any more than that, especially when your chest feels really tight and you have congestion, as well" (CD #302).</i></p> <p><i>"It's like something squeezing, it's a real tight heavy feeling sitting on your chest or something" (303).</i></p> <p><i>"In a vice" (302), "feel like it's trapped in here...around your throat and lungs" (306), "my rib cage is not big enough for my lungs or it feels like it's squishing my lungs...my lung wants more room" (202), "I feel my chest getting tighter, and it just burns" (104), "you feel like it's so tight that you think you're going to stop breathing" (403).</i></p> <p><i>Right here and I-like somebody just closed up the breathing pipe and my shoulders are hitting my ears. That's how much I'm going to gasp for air" (203).</i></p>
<b>Respiratory Symptoms</b>	
Inter-relationships; co-occurrence of respiratory symptoms	<p><i>"In my case sometime I'm just watching TV and just get mucus built up and you start coughing. You going to have shortness of breath and cough a lot. And I don't have to be doing anything. You know, just all of a sudden I start coughing the way he did just start coughing. Mucus coming up and then you get shortness of breath because the mucus was building up" (105).</i></p> <p><i>Well, sometimes it's very difficult to get it[mucus/phlegm] to come up. So, when that happens it makes it more difficult to breathe" (206). "When the phlegm gets in your bronchial tubes...it's hard to breathe" and "it makes you feel like you're choking. I mean, your breath is cut off because you can't get air through the phlegm" (202).</i></p> <p><i>"The tightness of the chest, some of the heavy on the chest like I guess-like I can't breathe, will never get it off if I'm coughing. I cough but if I'm coughing at night as well I can get it up but tightness of your-or heaviness of your chest seem like it go on all day" (104).</i></p> <p><i>"Well, it's an everyday thing. I get a certain amount of chest congestion everyday; you're always coughing up something. A little tightness in your chest and you feel like you've got to bring up something all the time" (306).</i></p> <p><i>"If I have a bad day it's because I'm sticky and I can't get my breath..." (402).</i></p> <p><i>"...I don't use my hand inhaler very often except for when I'm really sticky and I know I can't get a breath. I will do it just because it makes me cough and it helps loosen the phlegm" (202).</i></p> <p><i>"You feel like you have phlegm and you have shortness of breath and you have to cough. You feel some sort of pressure or tightness. It doesn't feel right. It doesn't feel smooth, like you're breathing normally" (CD #201).</i></p>



**Appendix Table S2. E-RS Focus Group Saturation Grid**

Spontaneous Concepts by Group					Concepts by Focus Group Participant (spontaneously or after prompting)																							
FG 1 (N=5)	FG 2 (N=7)	FG 3 (N=6)	FG 4 (N=3)		1	2	3	4	5	1	2	3	4	5	6	7	1	2	3	4	5	6		1	2	3		
Breathlessness																												
Breathless /short of breath	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X		
Short of breath during activities	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X				X		
Cough and Sputum																												
Cough (frequency)	X	X	X	X					X	X	X		X		X	X		X		X	X	X		X	X	X		
Sputum/mucus/phlegm	X	X	X	X			X	X	X	X	X				X			X		X	X	X		X	X	X		
Difficult bringing up sputum/mucus/phlegm	X	X	X	X	X		X	X		X	X				X			X		X	X	X		X		X		
Chest Symptoms																												
Chest congestion	X	X	X	X	X	X					X				X					X		X		X	X	X		
Chest discomfort/heavy	X	X	X		X	X		X			X				X	X			X	X		X						
Chest tightness	X	X	X	X	X	X		X		X	X				X	X		X	X		X	X		X		X		

X indicates that patients reported experiencing the symptom.

**Appendix Table S3. Content of the EXACT and EXACT-RS<sup>a</sup>**

Symptom Construct	Item-level Construct <sup>1</sup>	Item Number
<b>Breathlessness</b>		
	Breathless today <sup>2</sup>	7
	Breathless with activity <sup>3</sup>	8
	Short of breath - personal care <sup>3</sup>	9
	Short of breath - indoor activity <sup>3</sup>	10
	Short of breath - outdoor activity <sup>3</sup>	11
<b>Cough and Sputum</b>		
	Cough frequency <sup>3</sup>	2
	Mucus quantity <sup>3</sup>	3
	Difficulty with mucus <sup>2</sup>	4
<b>Chest Symptoms</b>		
	Congestion <sup>2</sup>	1
	Discomfort <sup>2</sup>	5
	Tightness <sup>2</sup>	6
<b>Additional Attributes</b>		
	Tired or weak <sup>2</sup>	12
	Sleep disturbance <sup>2</sup>	13
	Scared or worried <sup>2</sup>	14

<sup>a</sup> All 14 items are administered as a daily diary; The EXACT total score uses all 14 items with logit scoring transformed to a 0 to 100 interval-level scale; E-RS scoring uses only the respiratory symptom items, with subscales for breathlessness, cough and sputum, and chest symptoms. E-RS scores are based on summation to yield ordinal-level scales.

<sup>1</sup>. Items are worded as simple questions. Recall: “Today”. Patients are asked to complete the diary every evening before they go to bed. The formatted instrument is available through [exactpro@evidera.com](mailto:exactpro@evidera.com).

<sup>2</sup>. 5-point scale, Not at all to Extremely

<sup>3</sup>. 5-point scale – other

**Appendix Table S4a. E-RS Descriptive Statistics, Day 1**

<b>E-RS Scale</b>	<b># Items (Score Range)<sup>a</sup></b>	<b>Mean (SD)</b>	<b>Median</b>	<b>Observed Range</b>	<b>Floor Effect<sup>b</sup> N (%)</b>
Total	11 (0–40)	11.9 (6.7)	11	0.0–33.0	9 (4.8%)
RS-Breathlessness	5 (0–17)	5.9 (3.7)	6	0.0–16.0	18 (9.6%)
RS-Cough & Sputum	3 (0–11)	3.5 (2.3)	4	0.0–9.0	29 (15.4%)
RS-Chest Symptoms	3 (0–12)	2.5 (2.1)	2	0.0–9.0	46 (24.5%)

N=188

<sup>a</sup>Summation; item-level scoring varies across items (range: 3 to 6).<sup>b</sup>Ceiling effects were 0 across all scales.**Abbreviation:** E-RS, Exacerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms**Appendix Table S4b. Total and Inter-Subscale Correlations<sup>a</sup>**

<b>E-RS Scale</b>	<b>E-RS Scale</b>			
	<b>Total</b>	<b>RS-Breathlessness</b>	<b>RS-Cough &amp; Sputum</b>	<b>RS-Chest Symptoms</b>
Total	1.0	--	--	--
RS-Breathlessness	0.85	1.0	--	--
RS-Cough & Sputum	0.80	0.45	1.0	--
RS-Chest Symptoms	0.78	0.47	0.66	1.0

N=188

<sup>a</sup>Spearman's rank-order correlation; all coefficients significant,  $P < 0.0001$ .**Abbreviation:** E-RS, Exacerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms

**Appendix Table S5. Reproducibility of E-RS in Patients Reporting No Change for 2 Consecutive Days<sup>a</sup> (Stable Group)**

	N	Mean(SD) <sup>b</sup>	Mean(SD) <sup>a</sup>	Difference (SD)	P Value <sup>c</sup>	Effect Size	Pearson's Correlation	ICC <sup>d</sup>
<i>Days</i>		<i>1</i>	<i>2</i>					
RS-Total	76	9.62 (6.24)	9.66 (6.36)	-0.04 (2.88)	0.9053	-0.01	0.90	0.90
RS-Breathlessness	76	5.07 (3.65)	4.87 (3.63)	0.20 (1.95)	0.3794	0.05	0.86	0.86
RS-Cough & Sputum	76	2.82 (2.30)	2.88 (2.18)	-0.07 (1.15)	0.6185	-0.03	0.87	0.87
RS-Chest Symptoms	76	1.74 (1.86)	1.91 (2.07)	-0.17 (1.18)	0.2110	-0.09	0.82	0.82
<i>Days</i>		<i>2</i>	<i>3</i>					
RS-Total	65	9.69 (6.05)	10.1(6.48)	-0.43 (2.97)	0.2472	-0.07	0.89	0.89
RS-Breathlessness	65	4.86 (3.36)	5.26(3.58)	-0.40 (1.98)	0.1088	-0.12	0.84	0.83
RS-Cough & Sputum	65	3.02 (2.10)	3.08(2.06)	-0.06 (1.22)	0.6864	-0.03	0.83	0.83
RS-Chest Symptoms	65	1.82 (1.91)	1.78(1.99)	0.03 (1.26)	0.8448	0.02	0.79	0.79
<i>Days</i>		<i>3</i>	<i>4</i>					
RS-Total	69	10.5 (6.41)	10.1 (6.67)	0.39 (3.09)	0.2970	0.06	0.89	0.89
RS-Breathlessness	69	5.39 (3.80)	5.12 (3.86)	0.28 (2.19)	0.2997	0.07	0.84	0.84
RS-Cough & Sputum	69	3.22 (1.98)	3.01 (1.98)	0.20 (1.60)	0.2946	0.10	0.68	0.68
RS-Chest Symptoms	69	1.91 (1.95)	2.00 (2.09)	-0.09 (1.03)	0.4835	-0.04	0.87	0.87
<i>Days</i>		<i>4</i>	<i>5</i>					
RS-Total	62	10.4 (7.03)	10.8 (6.96)	-0.39 (2.66)	0.2558	-0.06	0.93	0.93
RS-Breathlessness	62	5.13 (3.83)	5.35 (3.54)	-0.23 (1.61)	0.2749	-0.06	0.91	0.90
RS-Cough & Sputum	62	3.06 (1.93)	3.10 (2.09)	-0.03 (1.24)	0.8385	-0.02	0.81	0.81
RS-Chest Symptoms	62	2.18 (2.28)	2.31 (2.34)	-0.13 (1.03)	0.3288	-0.06	0.90	0.90
<i>Days</i>		<i>5</i>	<i>6</i>					
RS-Total	68	10.3 (6.20)	10.4 (5.98)	-0.12 (2.43)	0.6915	-0.02	0.92	0.92
RS-Breathlessness	68	5.04 (3.23)	5.38 (3.33)	-0.34 (1.74)	0.1140	-0.10	0.86	0.86
RS-Cough & Sputum	68	3.22 (2.13)	3.16 (2.18)	0.06 (1.13)	0.6695	0.03	0.86	0.86
RS-Chest Symptoms	68	2.03 (2.05)	1.87 (1.95)	0.16 (1.03)	0.2002	0.08	0.87	0.87
<i>Days</i>		<i>6</i>	<i>7</i>					
RS-Total	69	10.3 (6.76)	10.6 (7.10)	-0.26 (2.27)	0.3424	-0.04	0.95	0.95
RS-Breathlessness	69	5.25 (3.81)	5.17 (3.82)	0.07 (1.77)	0.7346	0.02	0.89	0.89
RS-Cough & Sputum	69	2.91 (2.02)	3.03 (1.99)	-0.12 (0.99)	0.3356	-0.06	0.88	0.88
RS-Chest Symptoms	69	2.14 (2.15)	2.36 (2.27)	-0.22 (1.08)	0.1000	-0.10	0.88	0.88

<sup>a</sup>Patient reporting no change in their lung condition between the two days.<sup>b</sup>Score ranges: RS-Total, 0 to 40; RS-Breathlessness, 0 to 17; RS-Cough & Sputum, 0 to 11; RS-Chest Symptoms, 0 to 12.<sup>c</sup>From paired *t*-test.<sup>d</sup>Intraclass correlation coefficient.**Abbreviations:** E-RS, Exacerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms; ICC, intraclass correlation coefficient



**Appendix Table S6. Known-Groups Validity: E-RS Mean (SD) Scores for Stable Patients by Clinician Rating of Disease Severity, Day 1**

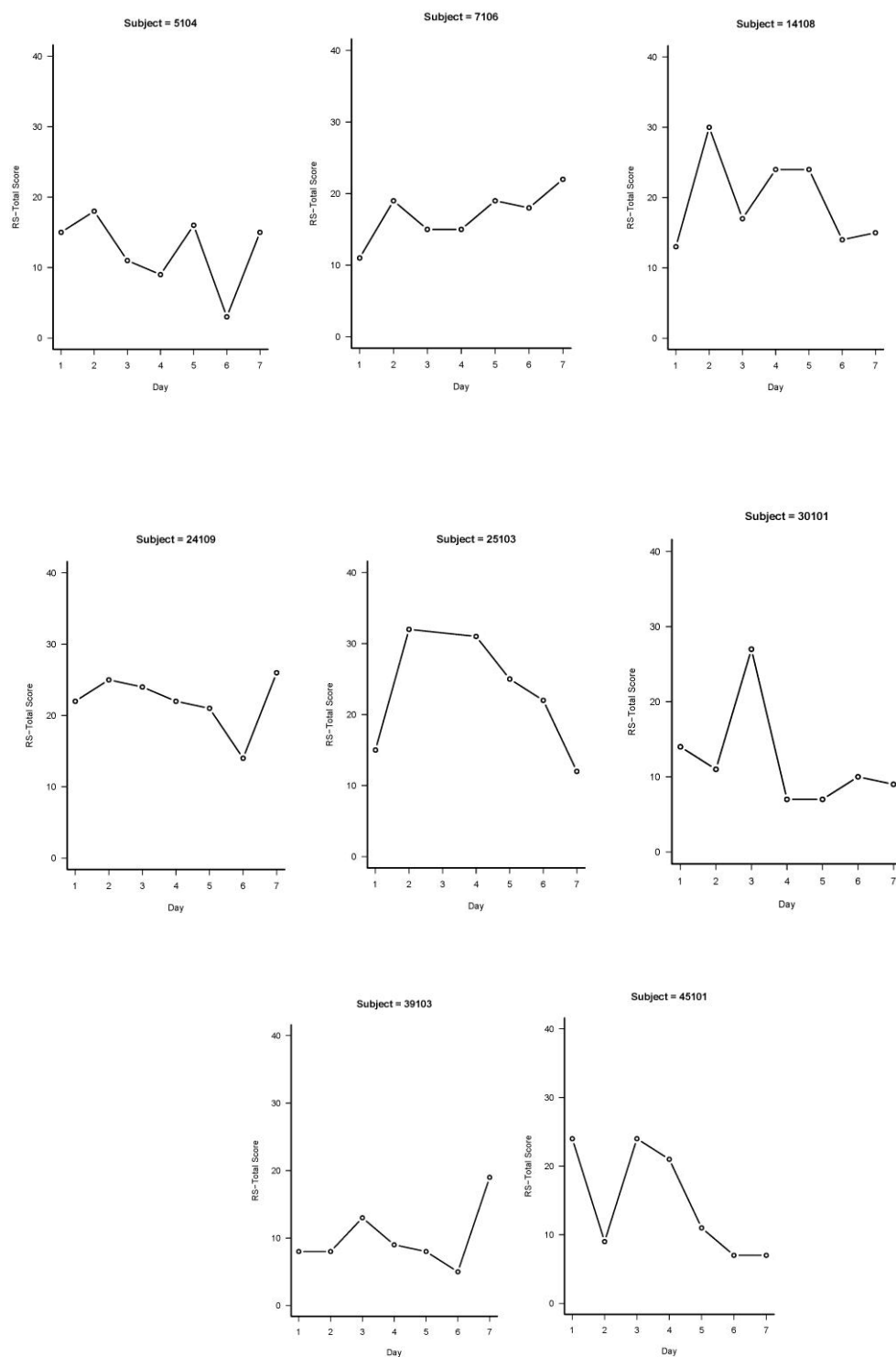
E-RS Scores (Range) <sup>a</sup>	Clinical Assessment of Disease Severity				Overall <i>F</i> Value <sup>a</sup>	Significant Pairwise Comparison <sup>b</sup>
	Mild N=25	Moderate N=82	Severe/Very Severe N=71	Very Severe N=10		
RS-Total (0–40)	9.0 (6.4)	12.5 (6.7)	12.2 (6.5)	12.4 (8.4)	3.6 <sup>†</sup>	A* B*
RS-Breathlessness (0–17)	4.3 (3.8)	6.0 (3.7)	6.3 (3.3)	7.3 (4.5)	2.8*	
RS-Cough & Sputum (0–11)	2.8 (2.4)	3.7 (2.1)	3.6 (2.3)	2.8 (2.4)	3.8 <sup>†</sup>	
RS-Chest Symptoms (0–12)	1.9 (1.9)	2.8 (2.2)	2.3 (2.1)	2.3 (2.5)	2.7*	

N=188, Stable Patients

<sup>a</sup>ANCOVA controlling for age, co-morbidity and baseline FEV<sub>1</sub><sup>b</sup>Using Scheffe's post-hoc tests, pairwise comparisons: A: Moderate vs. Mild; B: Severe vs. Mild\**P*<0.05<sup>†</sup>*P*<0.01**Abbreviations:** ANCOVA, analysis of covariance; E-RS, Exacerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms; FEV<sub>1</sub>, forced expiratory volume in 1 second

## Appendix

**Appendix Figure S1. RS-Total Score Sample Patient Variability Plots – Stable Patients Days 1-7<sup>a</sup>**



<sup>a</sup>RS-Total scores range from 0 to 40, with the higher values indicating greater severity of respiratory symptoms.