Supplementary Materials

Methods

Eligibility criteria

Individuals were required to have a smoking history of ≥10 pack-years, a COPD exacerbation which received documented treatment within 12 months prior to the study visit and able to provide informed consent and participate in the study. Patients were excluded if they had a current diagnosis of asthma or clinically relevant bronchiectasis, a concurrent significant, uncontrolled, active medical condition or disease state involving other organ diseases or systematic diseases; psychiatric conditions; cognitive impairment or any other reason that in the investigator's opinion, would place the patient at risk or interfere with study evaluation or affect participation in the study.

Part 1 design

Part 1 included nine FG discussions with a recruitment target of 45 patients, performed at three selected regional healthcare sites (three discussions taking place at each site) in the Japanese prefectures of Mie, Kyoto and Kanagawa (**Table S1**). Each FG consisted of 3–6 patients, facilitated by a topic guide consisting of open-ended questions to encourage spontaneous responses and lasted 2 hours, during which patients discussed their experiences related to changes in COPD symptoms and the impact of these changes on their well-being. The first hour consisted of open-ended questions regarding patient experiences of symptom worsening and the impact on their lung and breathing conditions, as well as probing to clarify concepts reported spontaneously by patients and to explore concepts not reported in response to open questioning. The second hour consisted of open-ended explanatory questions, including patients' criteria for seeking medical attention, and a rating exercise where they selected 5 words or phrases (items) to describe their symptom worsening to someone, and

ranked them by importance (1 to 5, with 1 being the most important). Subsequently, an expert panel met to review the items identified and make recommendations for candidate items for inclusion or exclusion in the draft item set for Part 2. The panel included three external respiratory specialists, an external patient-reported outcomes (PRO) specialist, and a sponsor company pulmonologist experienced in questionnaire development.

Part 2 design

Part 2 was composed of nine one-to-one CDIs with a recruitment target of 9 patients, performed at the same three healthcare sites as for Part 1 (three interviews taking place at each site; **Table S1**). CDIs were facilitated using a topic guide consisting of open-ended questions to encourage spontaneous responses. CDIs lasted approximately one hour where patients responded to the items identified in Part 1, and "think aloud" and "verbal probing" procedures were used. During their interviews, patients filled out a questionnaire about their experiences related to changes in chronic obstructive pulmonary disease symptoms and the impact of these changes on their general well-being. Patients were then asked about the relevancy of the questionnaire content, ease of completion and any further suggestions regarding item language, phrasing, and formatting. If patients mentioned that a question was difficult to understand, probes were used to ascertain which part was difficult and if the patient had any suggestions for improvement. The interviewer led the patient through each item and collected field notes including descriptions of issues and respondent behaviors such as hesitation and signs of frustration.

The answers from all questionnaires were compiled to quantitatively analyze patients' self-reported symptoms and their impacts. Additionally, audio recordings and notes from all CDIs were assessed to calculate the proportion of patients who correctly understood each question, while patients' interpretations of each question in their own words as well as the relevance of

each question were investigated. An expert panel was consulted to finalize the items to be taken forward to Part 3 of the study.

Part 3 design

Part 3 was performed at 11 sites with a recruitment target of 100 patients, which has been shown to be a sufficient population size [1] (**Table S1**). Patients visited a study hospital as part of their regular treatment or follow-up and were asked to complete the self-administered draft questionnaire developed in Part 2, consisting of 26 items assessing cough (2 items), breathlessness (12 items), activity limitation (6 items), and phlegm (6 items). Three sets of response options were used in the questionnaire. For Item 1, response options were "not at all", "a little", "some", "a great deal", "a very great deal"; Items 2–10 were "never", "rarely", "occasionally", "frequently", "almost always"; Items 11–20 were "not at all", "a little", "moderately", "quite a bit", "extremely". For item 21, responses included "never", "rarely", "occasionally", "frequently". Items 22 to 26 were optional questions about phlegm that were only completed by patients who selected "rarely", "occasionally", or "frequently" to Item 21.

Results

Item selection

The items and item combinations covered: increased cough or frequency, breathlessness, walking long distances or on stairs, limitation of social or daily activity, or volume of phlegm and color of phlegm. Four of these versions contained five items and one version contained six items. The overall response rates were very similar (62–66%). To define exacerbators for sensitivity and specificity analysis, two different definitions were developed based on the patients' responses to the seven items most frequently associated with an exacerbation using three different levels of endorsement thresholds for each definition. When three of these

items were endorsed, all five potential CERT-J versions showed moderate-high sensitivity and moderate-good specificity.

References

1. Yorke J, Moosavi SH, Shuldham C, et al. Quantification of dyspnoea using descriptors: development and initial testing of the Dyspnoea-12. Thorax. 2010;65(1):21–26. doi: 10.1136/thx.2009.118521.

Table S1. Participant Site list

Part 1 and 2	**Part 3**
Site (prefecture)	**Site (prefecture)**
Matsusaka Municipal Hospital (Mie)	Matsusaka Municipal Hospital (Mie)
Rakuwakai Otowa Hospital (Kyoto)	Rakuwakai Otowa Hospital (Kyoto)
Kawasaki Municipal Tama Hospital (Kanagawa)	Kawasaki Municipal Tama Hospital (Kanagawa)
	Iizuka Hospital (Fukuoka)
	Kanazawa University Hospital (Ishikawa)
	Karimata Clinic (Okinawa)
	Sakaide City Hospital (Kagawa)
	Shizuoka General Hospital (Shizuoka)
	Shimane University Hospital (Shimane)
	Tohoku Medical and Pharmaceutical University Wakabayashi Hospital (Miyagi)
	Niigata University Medical & Dental Hospital (Niigata)

Table S2. Response groupings for defining item endorsement levels

	Response options of each item categorized in each response group
First grouping	
Item 1	some, a great deal, a very great deal
Items 2–10	occasionally, frequently, almost always
Items 11–20	moderately, quite a bit, extremely
Item 21	occasionally, frequently
Second grouping	
Item 1	a great deal, a very great deal
Items 2–10	frequently, almost always
Items 11–20	quite a bit, extremely
Item 21	occasionally, frequently

Table S3. Ranking of items by high endorsement proportion of (A) items 1–21 and (B) items 22–26[a] in Part 3 (N=100)

A

	First groupings[b]	Second groupings[c]
Item number and description	**Patients with high endorsement (%)**	**Patients with high endorsement (%)**
19. Breathlessness – long distance walks	80.0	53.0
18. Difficulty breathing – long distance walks	78.8	52.5
17. Difficulty breathing – up hills	78.0	54.0
16. Difficulty breathing – up stairs	75.0	57.0
20. Tightness in the chest – long distance walks	69.0	43.0
15. Difficulty breathing – walking outside	61.0	38.0
1. Amount of cough	56.6	26.3
21. Frequency of phlegm	55.1	55.1
6. Wheezing	50.0	29.0
11. Daily activity limited due to difficulty breathing	44.0	27.0
12. Social activity limited due to difficulty breathing	39.0	23.0
8. Going out avoided due to difficulty breathing	37.0	26.0
13. Difficulty breathing – walking around room	36.4	23.2
14. Difficulty breathing – walking around home	34.0	23.0
3. Chest condition at night	32.3	17.2
2. Cough at night	32.0	16.0
4. Difficulty breathing at night	28.3	16.2
5. Breathlessness at night	28.0	15.0
7. Going out avoided due to cough	27.0	20.0
10. Conversation interrupted due to difficulty breathing	26.0	10.0
9. Conversation interrupted due to cough	23.0	7.0

B

Item number and description	**Patients with high endorsement (%)**
25. Color of phlegm (Brown, Green, Yellow)	60.2
23. Volume of phlegm (A great deal, Some)	53.8

24. Change in phlegm color (Yes)	49.5
22. Difficulty bringing up phlegm (Extremely, Quite a bit, Moderately)	47.3
26. Stickness of phlegm (Stickly, Very stickly)	47.3

[a]Items 22–26 were optional questions about phlegm that were only completed by patients who selected “rarely”, “occasionally”, or “frequently” to item 21; [b]First grouping: “some” through to “a very great deal”; [c]second grouping: “a great deal

Table S4. Association between demographic characteristics and item responses (N=100)

Item number	Age at the date of survey (years)	Gender[d]	Height (cm)	Living area[e]	Education[f]	Smoking status[g]	Pack-years	Disease duration[h]
1	rho=0.003[a] P=0.974	rho=-0.050[a] P=0.625	rho=0.025[a] P=0.808	rho=0.185[a] P=0.067	rho=0.012[a] P=0.903	rho=0.072[a] P=0.481	rho=-0.170[a] P=0.093	rho=0.000[a] P=0.996
6	rho=0.045 P=0.657	rho=-0.069 P=0.497	rho=-0.097 P=0.338	rho=0.097 P=0.337	rho=0.063 P=0.536	rho=-0.146 P=0.146	rho=-0.089 P=0.381	rho=0.156 P=0.122
8	rho=0.130 P=0.196	rho=-0.159 P=0.115	rho=-0.166 P=0.098	rho=-0.069 P=0.495	rho=0.015 P=0.885	rho=0.005 P=0.963	rho=-0.039 P=0.698	rho=0.175 P=0.082
11	rho=0.182 P=0.069	rho=-0.047 P=0.645	**rho=-0.233 P=0.020**	rho=-0.048 P=0.633	rho=-0.089 P=0.378	rho=-0.026 P=0.794	rho=0.174 P=0.083	rho=0.141 P=0.160
12	rho=0.166 P=0.098	rho=-0.018 P=0.858	**rho=-0.237 P=0.018**	rho=-0.010 P=0.917	rho=0.078 P=0.438	rho=0.028 P=0.779	rho=0.044 P=0.665	**rho=0.216 P=0.031**
15	rho=0.124 P=0.220	rho=-0.030 P=0.768	rho=-0.119 P=0.237	rho=-0.114 P=0.259	rho=0.115 P=0.256	rho=0.098 P=0.334	rho=0.147 P=0.145	**rho=0.288 P=0.004**
16	rho=0.073 P=0.472	rho=-0.082 P=0.417	**rho=-0.231 P=0.021**	rho=-0.088 P=0.387	rho=-0.022 P=0.829	rho=0.021 P=0.838	rho=0.127 P=0.209	**rho=0.322 P=0.001**
17	rho=0.045 P=0.658	rho=-0.030 P=0.771	**rho=-0.206 P=0.039**	rho=0.042 P=0.677	rho=0.024 P=0.814	rho=-0.063 P=0.533	rho=0.117 P=0.247	**rho=0.295 P=0.003**
18	rho=0.124[a] P=0.222	rho=0.012[a] P=0.910	rho=-0.156[a] P=0.123	rho=-0.019[a] P=0.848	rho=0.092[a] P=0.365	rho=-0.034[a] P=0.735	rho=0.113[a] P=0.265	**rho=0.331[a] P<0.001**
19	rho=0.132 P=0.189	rho=0.055 P=0.586	rho=-0.150 P=0.136	rho=0.102 P=0.311	rho=0.052 P=0.606	rho=-0.058 P=0.568	rho=0.126 P=0.211	**rho=0.284 P=0.004**
20	**rho=0.228 P=0.023**	rho=0.010 P=0.918	rho=-0.126 P=0.210	rho=0.074 P=0.463	rho=-0.051 P=0.615	rho=-0.092 P=0.364	rho=0.06 7P=0.506	**rho=0.212 P=0.034**
21	rho=-0.091[b] P=0.375	rho=-0.023[b] P=0.820	rho=0.116[b] P=0.257	rho=0.161[b] P=0.113	rho=0.028[b] P=0.786	rho=0.101[b] P=0.321	rho=-0.092[b] P=0.368	rho=0.143[b] P=0.161
22	**rho=0.231[c] P=0.026**	rho=-0.047[c] P=0.652	rho=-0.041[c] P=0.693	rho=0.070[c] P=0.508	rho=-0.138[c] P=0.186	rho=-0.056[c] P=0.591	**rho=0.278[c] P=0.007**	rho=0.200[c] P=0.054

23	rho=0.055[c] P=0.600	rho=-0.104[c] P=0.320	rho=0.106[c] P=0.312	rho=0.104[c] P=0.319	rho=-0.025[c] P=0.816	rho=0.073[c] P=0.485	rho=-0.037[c] P=0.722	rho=0.080[c] P=0.448
24	rho=0.067[c] P=0.521	rho=-0.035[c] P=0.737	rho=0.061[c] P=0.559	rho=0.187[c] P=0.073	rho=-0.074[c] P=0.481	rho=-0.152[c] P=0.146	**rho=0.241[c] P=0.020**	rho=0.005[c] P=0.962
26	rho=0.035[c] P=0.736	rho=-0.033[c] P=0.755	rho=-0.082[c] P=0.435	rho=0.099[c] P=0.343	rho=0.012[c] P=0.907	rho=-0.111[c] P=0.291	rho=0.097[c] P=0.353	rho=0.119[c] P=0.254

Note: Item 25 was omitted because it relates to phlegm color; items bolded p<0.05.

[a]N=99; [b]N=98; [c]N=93; [d]0=female,1=male; [e]0=city, 1=rural; [f]1=elementary or junior high, 2=high school, 3=junior college or technical junior college, 4=university or graduate school; [g]0=former, 1=current; [h]1=1–<5 years, 2=5–<10 years, 3=10–<15 years, 4=≥15 years.

Table S5. Correlation between items for 12 items related to activity and breathlessness

Item	**Item**	**Spearman's rho**
11. Daily activity limited due to difficulty breathing	12. Social activity limited due to difficulty breathing	0.85
17. Difficulty breathing – up hills	16. Difficulty breathing – up stairs	0.88
17. Difficulty breathing – up hills	19. Difficulty breathing – long distance walks	0.82
17. Difficulty breathing – up hills	19. Breathlessness – long distance walks	0.82
18. Difficulty breathing – long distance walks	19. Breathlessness – long distance walks	0.92
19. Breathlessness – long distance walks	20. Tightness in the chest – long distance walks	0.86

Table S6. Representative selected items identified from the selected 16 items to create an eight-item list for potential inclusion in the CERT-J

Item number and description of each item
1. Amount of cough
11. Daily activity limited due to difficulty breathing
12. Social activity limited due to difficulty breathing
16. Difficulty breathing – up stairs
19. Breathlessness – long distance walks
21. Frequency of phlegm
23. Volume of phlegm
24. Change in phlegm color

CERT-J, COPD Exacerbation Recognition Tool in Japan; COPD, chronic obstructive pulmonary disease.

Table S7. Sensitivity and specificity analysis results of each CERT candidate version

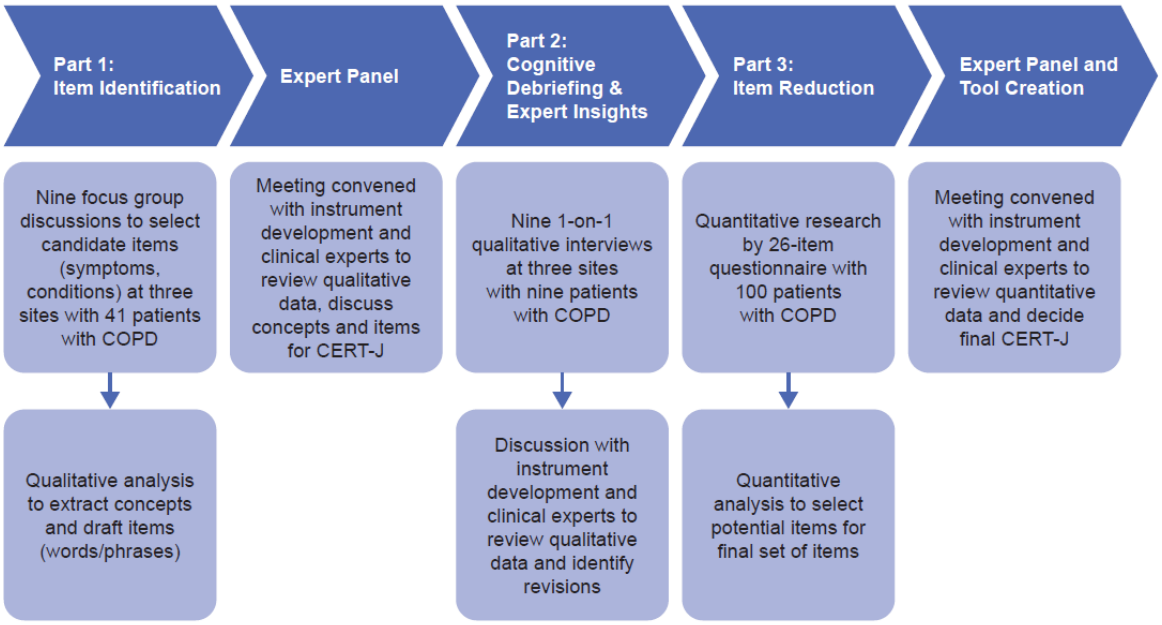
		Version 1	Version 2	Version 3	Version 4	Version 5
Endorsed ≥1 item in each CERT candidate	Sensitivity (%)	98.6	98.6	98.6	100.0	100.0
	Specificity (%)	12.5	12.5	12.5	6.3	6.3
	Kappa-value	0.16	0.16	0.16	0.10	0.10
Endorsed ≥2 items in each CERT candidate	Sensitivity (%)	91.8	91.8	95.9	93.2	97.3
	Specificity (%)	18.8	18.8	25.0	12.5	12.5
	Kappa-value	0.13	0.13	0.27	0.07	0.14
Endorsed ≥3 items in each CERT candidate	Sensitivity (%)	80.8	80.8	79.5	86.3	91.8
	Specificity (%)	56.3	56.3	75.0	56.3	56.3
	Kappa-value	0.32	0.32	0.43	0.40	0.49

Note: Version 1 = 19. Breathlessness – long distance walks, 16. Difficulty breathing – up stairs, 11. Daily activity limited due to difficulty breathing OR 12. Social activity limited due to difficulty breathing, 21. Frequency of phlegm OR 23. Volume of phlegm, 24. Change in phlegm color. Version 2 = 19. Breathlessness – long distance walks, 16. Difficulty breathing – up stairs, 11. Daily activity limited due to difficulty breathing, 21. Frequency of phlegm OR 23. Volume of phlegm, 24. Change in phlegm color. Version 3 = 19. Breathlessness – long distance walks, 16. Difficulty breathing – up stairs, 11. Daily activity limited due to difficulty breathing OR 12. Social activity limited due to difficulty breathing, 21. Frequency of phlegm, 24. Change in phlegm color. Version 4 = 19. Breathlessness – long distance walks, 16. Difficulty breathing – up stairs, 11. Daily activity limited due to difficulty breathing OR 12. Social activity limited due to difficulty breathing, 21. Frequency of phlegm OR 23. Volume of phlegm OR 1. Amount of cough, 24. Change in phlegm color. Version 5 = 19. Breathlessness – long distance walks,

16. Difficulty breathing – up stairs, 11. Daily activity limited due to difficulty breathing OR 12. Social activity limited due to difficulty breathing, 21. Frequency of phlegm OR 23. Volume of phlegm, 24. Change in phlegm color, 1. Amount of cough.

CERT, COPD Exacerbation Recognition Tool; COPD, chronic obstructive pulmonary disease.

Figure S1. Instrument development steps for the COPD exacerbation recognition tool



CERT-J, COPD Exacerbation Recognition Tool in Japan; COPD, chronic obstructive pulmonary disease.

Figure S2. Scatterplot of percentage of positive endorsement using the first and second grouping detailed in Table S2 (Part 3)