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

APPENDIX

NK Leidy, PhD[1]; CC Sexton, PhD[1]; PW Jones, PhD, FRCP[2]; SM Notte, MBA[1]; BU Monz, MD, MA, MPH[3]; L Nelsen, MHS[4]; M Goldman, MD[5]; LT Murray, MPH[1]; S Sethi, MD[6]

[1]Evidera, Bethesda, MD, US; [2]St. George's, University of London, London, UK; [3]Boehringer Ingelheim GmbH, Ingelheim, Germany; [4]Merck & Co Inc, Whitehouse Station, NJ, US; [5]AstraZeneca, Wilmington, DE, US; [6]University of Buffalo, Buffalo, NY, US

Corresponding Author:
Nancy Kline Leidy
Sr. Vice President, Scientific Affairs
Evidera
7101 Wisconsin Ave, Suite 600
Bethesda, MD 20814
Ph: +1-301-654-9729
Fax: +1-301-654-9864
E-mail: nancy.leidy@evidera.com

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.[1] 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

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[2] 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

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 [2] 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

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
Breathlessness	
Short of breath or breathless	*"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).* *"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).*
With personal care activities – washing/dressing	*"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).*
With indoor activities – cleaning, household work	*"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) .* *"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).* *"If I do any lifting or anything I have to bend over and catch my breath" (306).* *"Lifting anything kind of heavy- -I get shortness of breath" (103).* *"Carrying bundles, groceries and all that" (203).* *Emptying the dishwasher" (102), "scrubbing my floor" (202), "sweeping the floor" (303) "vacuuming" (203, 402),* and *"housework" (402).*
With outdoor activities – outside the home, yard work	*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).*
Cough & Sputum	
Cough	*"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).* *"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).* *"Really hard" (202), "really, really hard" (305)* and *"hacking" (304) (402) "I cough all day long on and off…" (306).* *"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).* *"…some days are really bad…and other days I don't have a problem" (402).*

Appendix

Symptom	**Quotation** Description, difficulty, severity, variability
Mucus (phlegm)	*"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'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).* *"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).* *"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 cough when I have phlegm building up in the chest and that's the way you expel it" (206).*
Difficulty bringing up mucus	*"Well, you know you need to cough up some mucus but it just don't seem to want to come up" (104).* *"Very difficult to get it to come up" (206) "you have to work at it" (202).* *"Can't seem to get anything up" (302, 305).* *"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).*
Chest Symptoms	
Congestion	*"Congestion is how you describe it." (101); Congested, congested….I guess there must be congestion in there" (401).* *"Sticky" (202), "stopped up" (306), "fluid on the lungs" (206). "Crap in your lungs" (102).* *"A lot of congestion…. All in my chest" (402).* *Yeah, it's not extreme, but it's not just a little bit, either" (306).* *"Well, I'm always congested. Always. I'm always-but it's really bad like in the morning" (402).* *Like if you hear a gurgling sound. It's congestion in there. It needs a way to get up" (402).* *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).* *"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).*
Discomfort	*[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).* *"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).*

Appendix

Symptom	**Quotation** Description, difficulty, severity, variability
Tight	*"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).* *"It's like something squeezing, it's a real tight heavy feeling sitting on your chest or something" (303).* *"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 lings 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).* *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).*
Respiratory Symptoms	
Inter-relationships; co-occurrence of respiratory symptoms	*"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).* *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).* *"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).* *"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).* *"If I have a bad day it's because I'm sticky and I can't get my breath…" (402).* *"…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).* *"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).*

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[a]

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

[a] 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.

1. 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.
2. 5-point scale, Not at all to Extremely
3. 5-point scale – other

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

E-RS Scale	# Items (Score Range)[a]	Mean (SD)	Median	Observed Range	Floor Effect[b] N (%)
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
[a]Summation; item-level scoring varies across items (range: 3 to 6).
[b]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[a]

E-RS Scale	E-RS Scale			
	Total	RS-Breathlessness	RS-Cough & Sputum	RS-Chest Symptoms
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
[a]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[a] (Stable Group)

	N	Mean(SD)[b]	Mean(SD)[a]	Difference (SD)	*P* Value[c]	Effect Size	Pearson's Correlation	ICC[d]
Days		*1*	*2*					
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
Days		*2*	*3*					
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
Days		*3*	*4*					
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
Days		*4*	*5*					
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
Days		*5*	*6*					
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
Days		*6*	*7*					
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

[a]Patient reporting no change in their lung condition between the two days.
[b]Score ranges: RS-Total, 0 to 40; RS-Breathlessness, 0 to 17; RS-Cough & Sputum, 0 to 11; RS-Chest Symptoms, 0 to 12.
[c]From paired *t*-test.
[d]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)[a]	Clinical Assessment of Disease Severity				Overall *F* Value[a]	Significant Pairwise Comparison[b]
	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†	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†	
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

[a]ANCOVA controlling for age, co-morbidity and baseline FEV_1

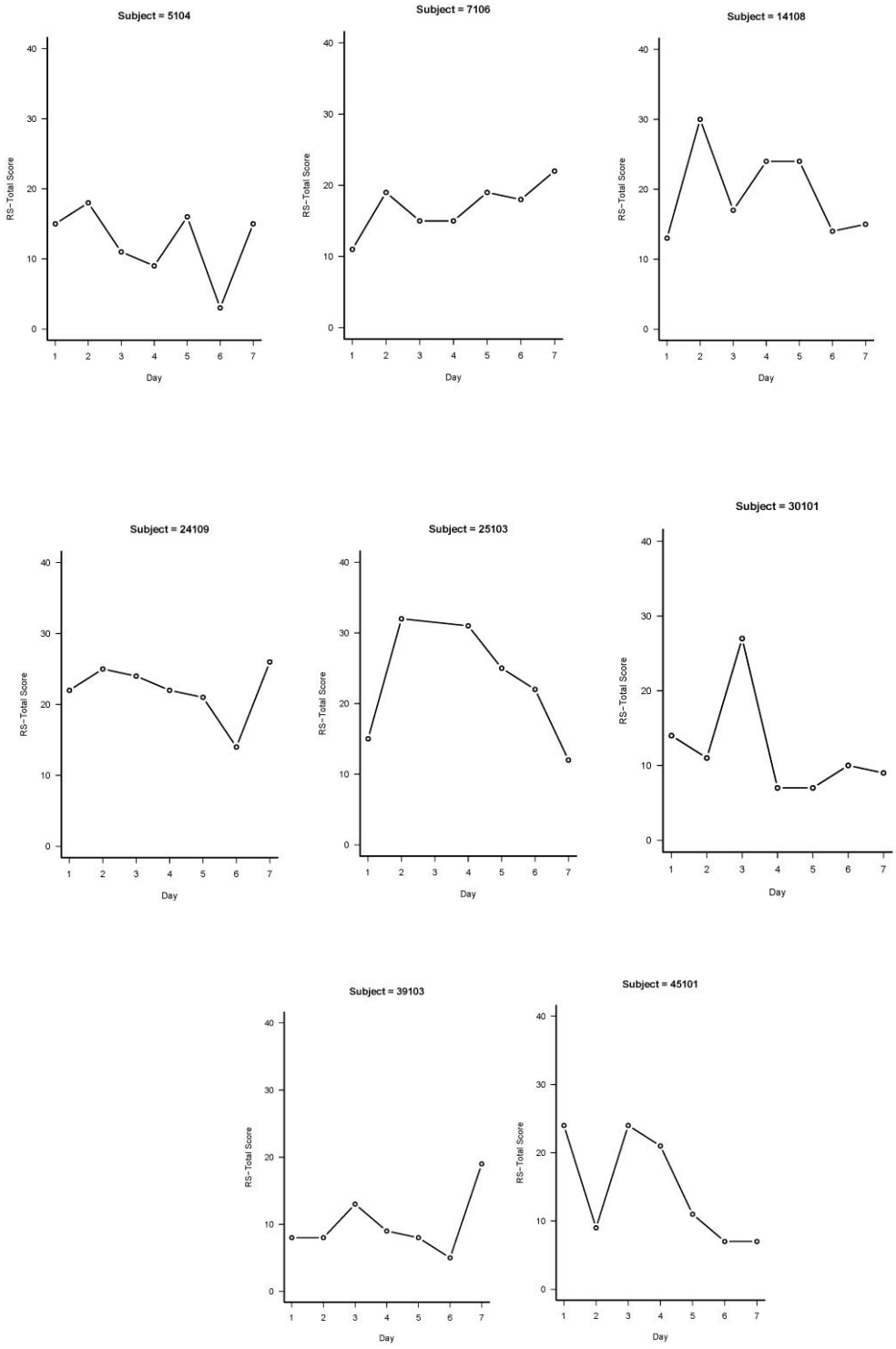
[b]Using Scheffe's post-hoc tests, pairwise comparisons: A: Moderate vs. Mild; B: Severe vs. Mild

*$P<0.05$

†$P<0.01$

Abbreviations: ANCOVA, analysis of covariance; E-RS, Exacerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms; FEV_1, forced expiratory volume in 1 second

Appendix Figure S1. RS-Total Score Sample Patient Variability Plots – Stable Patients Days 1-7[a]



[a]RS-Total scores range from 0 to 40, with the higher values indicating greater severity of respiratory symptoms.