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Development of the EXAcerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT): A Patient-Reported Outcome (PRO) Measure

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ABSTRACT

Background: This article describes the qualitative methods used to develop the EXAcerbation of Chronic Pulmonary Disease Tool (EXACT), a new patient-reported outcome (PRO) instrument for evaluating frequency, severity, and duration of exacerbations of chronic obstructive pulmonary disease (COPD).

Methods: Focus groups and interviews were conducted in the United States with COPD patients treated for exacerbations during the past 6 months. Participants were asked to describe exacerbation attributes, care-seeking cues, and indications of progression and recovery. An iterative process was used to identify themes in the data to inform instrument content and structure. Cognitive debriefing interviews were performed to evaluate and revise the draft item pool. Experts in COPD, instrument development, and clinical research participated in the process.

Results: Eighty-three subjects participated in elicitation focus groups or interviews ($n = 48$); elicitation interviews with cognitive debriefing ($n = 23$), or cognitive interviews alone ($n = 12$). Mean age of the sample was 65 years (SD = 10); 45% were male; mean FEV-1% predicted was 44% (SD = 16). Participants characterized exacerbations as a persistent increase in the severity of respiratory symptoms and other systemic manifestations accompanied by a dramatic reduction in activity. Specific attributes included shortness of breath, chest congestion, cough, sputum, chest discomfort, feeling weak or tired, sleep disturbances, and concern or worry. The diary card of 23 candidate items was debriefed in booklet and electronic format.

Conclusions: Qualitative data from patients and input from experts formed the basis of the EXACT's structure and item pool, ready for empirically based item reduction and reliability and validity testing.

Keywords: COPD, diary cards, exacerbations, instrument development, qualitative methods, respiratory symptoms, symptom assessment.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation with varying degrees of air sac enlargement, airway inflammation, and lung tissue destruction. The airflow obstruction characteristic of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and destruction of the gas-exchanging surfaces of the lung (emphysema), with the relative contribution of each varying from person to person [1]. Chronic bronchitis, often the target of anti-infective therapies for acute exacerbations (AECB), is a type of COPD that is defined by productive cough for 3 months or more in at least two consecutive years. Cough and sputum production may precede the development of airflow limitation; conversely, some patients develop significant airflow limitation without chronic cough and sputum production [1]. Cardinal symptoms of COPD are cough, sputum production, and breathlessness [2] with systemic consequences of disease that include deconditioning, exercise intolerance, skeletal muscle dysfunction or fatigue, anxiety, and depression among others [3].

The medical literature generally describes exacerbation as an acute, sustained worsening of the patient's underlying condition of COPD from the stable state and beyond normal day-to-day variability which may require a change in treatment [1,4,5]. These events are a major cause of morbidity and mortality in COPD [6–11]. Given the substantial humanistic and economic costs associated with exacerbations, reducing their frequency, severity, and duration is of great interest to patients, providers, and payers. This interest is reflected in the frequency with which investigators study interventions for the treatment or prevention of exacerbations, with occurrence and/or resolution serving as inclusion criteria or as primary or secondary endpoints in clinical trials [12–14].

Despite the importance of exacerbations in COPD, there has been no standardized, reliable, or valid method for quantifying these events in clinical studies [15]. To date, studies of exacerbation frequency have used two methods of assessment: 1) event-based, and 2) symptom-based [16–18]. The event-based method defines exacerbation frequency based on health-care utilization, i.e., clinic visits, emergency room visits, or hospitalizations, often with a superimposed requirement of a change in treatment, generally oral steroids or antibiotics. Utilization events have also been used as a proxy for severity, with unscheduled clinic or emergency room visits rated "moderate" and those requiring hospitalization labeled "severe" [5]. There are a number of problems associated with event-based definitions, including the bias introduced by regional differences in health policy (resulting in regions with liberal admission policies showing more frequent and more severe exacerbations) and misclassification bias

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because of failure to account for unreported events, estimated to be as high as 50% to 70% [8,9,18–20]. An event-based definition also fails to standardize change in the patient's underlying condition from their normal day-to-day variability, an essential feature of an exacerbation. The symptom-based method for defining exacerbations assesses this change through a patient-completed symptom diary card [4,8,21–23]. Unfortunately, there is substantial variability in both content and structure of these diaries across clinical studies, with little to no evidence of their content validity or performance properties. This not only raises questions about reliability and validity, but may also account for some of the inconsistencies in findings across otherwise similar study designs, and makes comparison of results across clinical studies or trials virtually impossible.

Clinical trials evaluating the efficacy of antimicrobial treatment for acute exacerbations of COPD have used a test-of-cure visit, generally at days 3 and/or 10, during which clinical investigators assess the subject's health status, determine clinical response, and recommend further treatment based on the individual clinician's subjective assessment and judgment. To date, there have been no standardized measures for assessing the severity of patient symptoms at baseline or follow-up or for quantifying the magnitude of change over time indicative of resolution. A standardized patient-reported outcome (PRO) instrument for assessing symptoms in AECB studies has been suggested in the FDA's Draft Guidance for Industry on Acute Bacterial Exacerbations of Chronic Bronchitis in Patients with Chronic Obstructive Pulmonary Disease [24].

Because the initial detection of an exacerbation originates with symptoms which are known directly by the patient and clinical assessments are based on patient report to the clinician, it is logical and desirable for clinical studies of exacerbations of COPD to gather reports directly from patients, through a PRO measure. To ensure quality, enhance efficiencies, and facilitate meta-analysis, it would be beneficial for the field to use a single, standardized PRO measure with evidence of content validity and known properties of reliability and validity. The Exacerbations of Chronic Obstructive Pulmonary Disease Tool—Patient Reported Outcomes (EXACT-PRO) Initiative is a program involving international experts in COPD, clinical research, instrument development, and US Food & Drug Administration (FDA) regulatory issues with unrestricted financial support from multiple pharmaceutical sponsors in the development of a single PRO instrument, known as the EXACT, to evaluate exacerbation outcomes in international trials of COPD.

This article presents the methods and results of the qualitative work that formed the basis of the EXACT. The purpose of this qualitative work was to understand how patients describe exacerbations, including their essential attributes and indications of onset, duration, and recovery; and to translate this understanding into a PRO instrument to capture frequency, severity, and duration of exacerbation in clinical studies of COPD. Figure 1a shows a schematic representation with definitions of frequency, severity, and duration of exacerbations as evaluated in prevention trials; Figure 1b depicts severity and duration of exacerbation as assessed in acute/anti-infective exacerbation treatment trials.

Background

Qualitative research methods are essential to the development of a PRO instrument, forming the basis for its content validity. Content validity refers to the adequacy of an instrument to measure what it purports to measure, reflected in the representativeness of the items and the methodological rigor with which the instrument is constructed or formulated [25,26]. Qualitative research is an inductive empirical method involving focus groups or 1:1 interviews in which the words and phrases of the study participants, recorded and transcribed, serve as the data [27–29]. Investigators apply systematic analytical methods to identify patterns or clusters of information in the data and present the findings in the form of themes and concepts. In the case of the development of a new PRO instrument, these themes and the words and phrases provided by study participants are used to inform the overall structure of an instrument, including content (questions or item stems, response options, and potential subscale or domain structure), recall period, frequency and mode or method of administration, and instructions for administration. Cognitive debriefing interviews are a specific type of qualitative method designed to uncover problems in the social-cognitive processes involved in completing an instrument, including difficulties with comprehension or understanding of concepts and terminology, problems knowing or remembering, and difficulty selecting a response consistent with experience. Based on these interviews, adjustments may be made in an instrument to enhance validity and/or improve ease of administration [26,28]. For an instrument to assess exacerbations of COPD, qualitative data from focus groups and interviews can provide a rich source of information about patient terminology and descriptions of these events, the manifestations or attributes that define them, and the actions patients may or may not take when these events occur to inform instrument development, while cognitive interviewing provides a method for evaluating and adjusting the new instrument as needed.

Prior to initiating qualitative work, a comprehensive review of the literature was performed, including an evaluation of the measures previously used to assess exacerbation frequency, severity and/or duration in clinical trials as well as the methods and results of these trials. No single, standardized measure was used and no publications describing development and validation of an instrument for quantifying these outcomes was uncovered. Published descriptions of diary cards used in clinical studies showed consistency in some content areas, including assessment of the respiratory symptoms of breathlessness, cough (frequency, severity), and sputum production (quantity), suggesting consensus that these are essential features of exacerbation. Rating methods for these attributes varied and included 4-point scales (none to severe), ratings of discomfort with cough (none to very uncomfortable or unbearable), and asking patients to indicate whether symptoms were more than usual (yes/no). Areas of content inconsistency included questions about: chest tightness; nighttime awakenings; sputum color, quantity and thickness; feeling weary, tired or faint; sore throat; nasal discharge or congestion; and, fever.

Qualitative studies describing exacerbations from the COPD patient's perspective offered insight into patient perceptions of these events [30–32]. Results of these studies showed that patients clearly understand the concept of exacerbation and are able to identify and describe these events. The concern they associate with exacerbations is reflected in the terminology they use, including "crisis," "attack" [31,32], and "frightening change" [30], with panic and dread associated with their onset [32]. Manifestations of an exacerbation described by patients participating in these qualitative studies included lower respiratory tract symptoms (breathing difficulty, changes in phlegm, increased cough, difficulty coughing up phlegm), upper respiratory symptoms (runny nose, sneezing), systemic signs and symptoms (anorexia, exhaustion, feeling weak, generally unwell, dizziness, sweating, cramping pain, and "other" ("grey" color, headaches, and unable to speak),

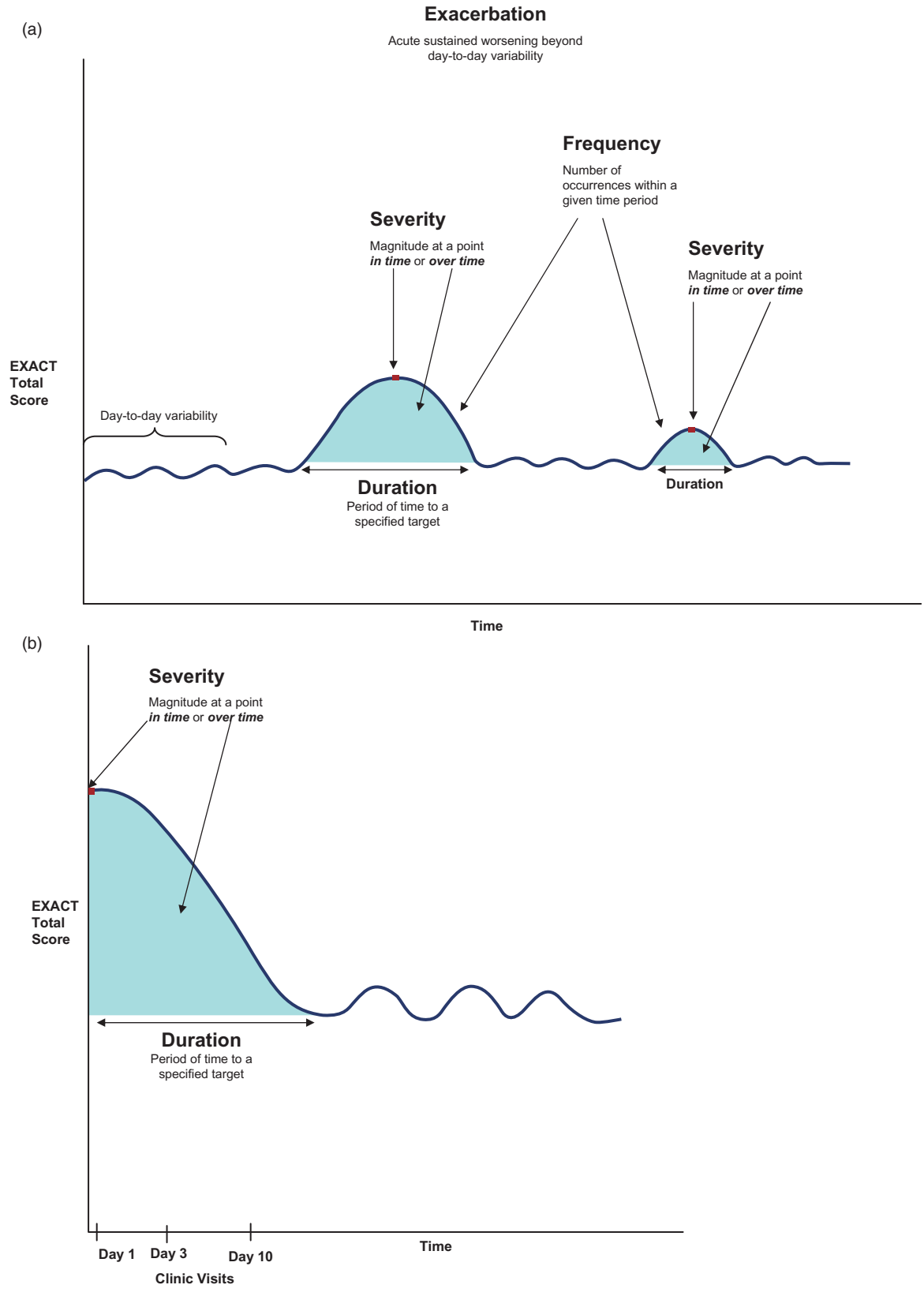

Figure 1 (a) Exacerbation Prevention Trial. (b) Acute/Anti-Infective Treatment Trial.

and changes in daily activity (slower, difficulty performing) [30,31].

The results of the literature review confirmed the need for a single, standardized measure with a core set of key attributes indicative of an exacerbation of COPD and provided background information for the development of the study protocols and data analyses that would form the basis for the new instrument.

Materials and Methods

Design

This instrument development study used a qualitative research design drawn from phenomenology and grounded theory [33]. The phenomenological approach emphasizes the "lived experience," with participants recruited for their experience with the phenomenon under study and interviewed to provide a detailed account of this experience. Data are coded to characterize the phenomenon, including its structure, core elements, and clusters of categories comprising the experience [34,35]. Although grounded theory is generally used to understand social processes, this approach can be applied to instrument development by drawing on its sampling and analytical methods. Participants with varied experiences with the target phenomenon are interviewed to explore its multiple dimensions, with analyses involving a constant comparison method with open, axial, and selective coding. Themes identified in the initial coding can be explored in follow-up interviews, with the entire process resulting in thematic descriptions of the phenomenon [36,37]. In this study, the goals of data collection and analyses were to understand participants' experiences of exacerbations with an emphasis on the words and phrases used to describe key attributes and the evolution and recovery process, and to translate these descriptions into a measurement approach for quantifying the frequency, severity, and duration of exacerbations in clinical studies.

The qualitative methods included focus groups and interviews to elicit patient descriptions of the exacerbation experience and cognitive debriefing interviews to evaluate the draft instrument. All groups and interviews involved participants with COPD and a recent history of exacerbation. A team of international pulmonary, clinical research, instrument development, and regulatory experts provided consultation throughout the development process. Two of the authors (PJ, SS) served as senior clinical consultants, providing input on methodology, interpretation, and content and structure of the instrument. In addition, two expert panel meetings were held to critique and discuss the qualitative study methods and results, including the proposed structure of the new PRO instrument and the content of its item pool. Panelists included the senior clinical consultants (PJ, SS), members of the EXACT-PRO Study Group (see acknowledgments), and one individual from each of the following FDA divisions: Study Endpoints and Labeling (SEALD), Pulmonary, Anti-Infective, and Special Pathogen. Representatives from each sponsor company and additional members of the FDA attended the meetings as observers and were invited to ask questions and comment during the proceedings.

Sample

To maximize representation, participants with COPD were recruited through pulmonary and primary care physician offices in four states in diverse regions of the United States: Arizona, Florida, Maryland, and Michigan. Inclusion and exclusion criteria were consistent with those used in pharmaceutical trials evaluating the efficacy and safety of preventive and anti-infective therapies for exacerbations of COPD. Inclusion criteria were as follows: age greater than or equal to 40 years; smoking for at least 10 pack/years; current medical diagnosis of COPD and/or chronic bronchitis, with the latter defined as cough and sputum production for at least 3 months in 2 consecutive years with or without airflow obstruction [1]; willing and able to provide written informed consent; able to participate in a group discussion; and able to speak and read English. All participants had a history of exacerbation in the past 6 months and a subset of patients had a history of a recent exacerbation, identified within 10 days of a clinic call, clinic visit, emergency room visit, or hospitalization for a medically confirmed worsening of the patient's condition, from the stable state and beyond normal day-to-day variation, that was acute in onset and necessitated a change in regular medication.

Exclusion criteria were as follows: current diagnosis of asthma with no obstructive disease (post bronchodilator >80%; FEV-1/FVC $\geq$70%), and no chronic bronchitis; current diagnosis of clinically relevant bronchiectasis; and, a concurrent medical or psychiatric condition or cognitive impairment that, in the investigator's opinion, would affect participation in the study.

During enrollment and following consent, participant's stable state pulmonary function test (PFT) values provided by the clinical site were reviewed to assure representation across varying levels of airway obstruction consistent with the target population. Specifically, the ratio of forced expiratory volume in one second to forced vital capacity (FEV-1/FVC) and FEV-1 as a percentage of predicted value were examined by Global Initiative for Chronic Obstructive Lung Disease (GOLD) [1] severity classification (see Table 1), with adjustments made during recruitment to make certain the final sample included a distribution of patients from Stages 2 and 3, with some representation from Stage 4.

Procedures

Qualitative data were collected in three rounds over a 7-month period (February through August, 2006). Round 1 ($n = 48$) involved focus groups and interviews designed to elicit concepts related to patient experiences, terminology, and attributes of exacerbation that would inform instrument development. This round included participants who had experienced an exacerbation in the previous 6 months ($n = 40$) or were within 10 days of an exacerbation ($n = 8$). Data from stable, nonexacerbating patients were collected through four focus groups ($n = 34$); supplemented by two 2:1 interviews (two participants, 1 interviewer, $n = 4$) and two 1:1 interviews ($n = 2$). The opportunity to interview participants in a 2:1 and 1:1 setting arose during focus group scheduling based on subject availability and provided an opportunity to assess respondent differences by method of data collection. Interviews with patients identified within 10 days of an exacerbation, all 1:1, were conducted to assess whether any concepts were missed because of participant recall.

Data were collected and analyzed for themes and subthemes until saturation was reached, defined as at least two focus group discussions and two interviews during which participants spontaneously introduced no new themes, beyond those identified previously, documented in the form of a saturation grid. Saturation was reached during Round 1, with the data used to inform the instrument's content, structure, and draft item pool. Methods and results were presented and discussed with experts during the first expert panel meeting.

To increase ethnic diversity of the sample, a second round of interviews were conducted. Round 2 involved 1:1 semi-structured

Table 1 Sample demographic and clinical characteristics

Characteristics	EXACT development		Further development with debriefing of draft items		Final debriefing	Total sample (N = 83)
	Focus groups (N = 40)	1:1 interviews (N = 8)*	1:1 interviews and cognitive debriefing (N = 23)	Cognitive debriefing (N = 3)	Cognitive debriefing with PDA (N = 9)	
Demographic						
Age, mean (SD)	68.4 (7.7)	65.8 (8.0)	58.3 (12.0)	65.3 (6.1)	69.1 (5.9)	65.3 (9.7)
Gender, male n (%)	15 (38%)	2 (25%)	13 (57%)	1 (33%)	6 (67%)	37 (45%)
Race/ethnicity n (%)						
White	40 (100%)	7 (88%)	0 (0%)	3 (100%)	9 (100%)	59 (71%)
Hispanic or Latino	0 (0%)	0 (0%)	11 (48%)	0 (0%)	0 (0%)	11 (13%)
Black or African American	0 (0%)	1 (13%)	12 (52%)	0 (0%)	0 (0%)	13 (16%)
Clinical						
COPD diagnosis—years since, mean (SD)	5.8 (4.1)	6.1 (2.5)	11.4 (7.5)	18.0 (13.7)	9.8 (4.7)‡	8.3 (6.4)
Spirometry†, mean (SD)						
FEV†-1(L)	1.2 (0.4)	0.9 (0.2)‡	1.0 (0.4)	1.0 (0.2)	1.3 (0.5)	1.1 (0.4)‡
FEV-1% predicted	48.6 (14.3)	34.7 (10.9)‡	41.0 (18.1)	39.3 (9.9)	43.4 (17.1)	44.4 (15.8)‡
GOLD§ 1 (FEV-1 ≥80% predicted)	2 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (11%)	3 (4%)
GOLD 2 (FEV-1 >50 and <80% predicted)	22 (55%)	1 (13%)	2 (9%)	0 (0%)	0 (0%)	25 (30%)
GOLD 3 (FEV-1 >30% and <50% predicted)	14 (35%)	5 (63%)	10 (44%)	3 (100%)	5 (56%)	37 (45%)
GOLD 4 (FEV-1 >30% and <50% predicted + chronic respiratory failure)	2 (5%)	2 (25%)	11 (48%)	0 (0%)	3 (33%)	18 (22%)
MMRC Dyspnea score, n (%)¶						
0–1	2 (5%)	1 (13%)	7 (31%)	1 (33%)	6 (67%)	17 (21%)
2	12 (30%)	3 (38%)	6 (26%)	1 (33%)	2 (22%)	24 (29%)
3–4	25 (63%)	4 (50%)	8 (35%)	1 (33%)	1 (11%)	33 (47%)
SGRQ Total Score, Mean (SD)	52.5 (18.0)	51.7 (20.9)	63.9 (18.0)	67.8 (29.8)	43.7 (13.9)	54.7 (19.1)

*Patients had diagnosis of an exacerbation within the last 10 days at recruitment; all other groups had a diagnosis in the last 6 months.
†Stable state; FEV-1: forced expiratory volume in one second.
‡Data missing for 1 patient.
§Global Initiative for Chronic Obstructive Lung Disease (GOLD).
¶As reported by the patient.

concept elicitation interviews with participants of African American and Hispanic descent ($n = 23$) to assess consistency in themes and terminology, identify any new themes, and re-assess saturation. Following the elicitation component of the interview, each participant took part in an evaluative cognitive debriefing interview of the draft item pool in paper–pen booklet format. In addition to the 23 participants, 3 Caucasian subjects participated in evaluative cognitive interviews alone. Methods and results of the Round 2 interviews were presented and discussed with experts during the second panel meeting.

Round 3 of the study involved cognitive debriefing interviews with COPD patients ($n = 9$) using the final item pool programmed into a personal digital assistant (PDA). These interviews also provided an opportunity to conduct a usability assessment with the device to gain insight into specific participant or site training that might be required during the implementation of the ensuing item reduction and validation study.

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. Trained, experienced interviewers conducted all focus groups and interviews using semi-structured interview guides designed to facilitate discussion and optimize consistency across groups and individuals. A trained assistant was present during focus groups to take notes and facilitate discussion as needed, and an experienced researcher observed the proceedings and provided recommendations to the facilitator and assistant as needed during planned breaks. Group discussions lasted approximately 2 hours. Interviews with participants within 6 months of an exacerbation were performed in clinic offices and lasted one to two hours. Participants who were identified within 10 days of a clinic visit for exacerbation were interviewed by telephone or in-person, as they preferred, using a focused interview guide to minimize patient burden. These interviews lasted approximately 20 minutes and addressed the patients' immediate experiences with their current exacerbation, including indications of onset, severity, and recovery. All groups and interviews were audio-recorded and transcribed for analyses.

Measures

To characterize the sample, participants completed a set of self-administered questionnaires at the conclusion of their focus group or interview, including a sociodemographic questionnaire, the Modified Medical Research Council (MMRC) dyspnea rating scale, and the St. George's Respiratory Disease Questionnaire (SGRQ). The MMRC ranges from 1 ("no breathlessness except with strenuous exercise") to 5 ("too breathless to leave the house") [38,39]. The 76-item SGRQ assesses the impact of respiratory disease on health status using a total score and three subscale scores (Symptoms, Activity, and Impacts) [40]. Scores range from 0 to 100, where higher scores indicate poorer health status. For those participating by telephone ($n = 7$), questionnaires were completed at home and returned by mail. Clinical data, including medical diagnosis and PFT values, were provided by the clinical site.

Analyses

Sample sociodemographic and clinical characteristics were summarized descriptively using SAS Version 9.1.3. The qualitative analysis software program Atlas.*ti* version 5.0 was used to

organize the transcript data for coding and analyses. Focus group moderators and interviewers (KH, JP) reviewed and cleaned the data prior to analyses.

For data gathered during Round 1, four team members, including the two focus group moderators and interviewers (KH, JP) and two experienced researchers (NKL, TW), examined the transcript data and developed a coding dictionary of themes and subthemes. Two team members (KH, JP) used this dictionary to code independently the data. When new themes not included in the initial coding dictionary were identified they were discussed with the other team members, the coding dictionary was updated, and the data were reanalyzed to ensure that the new theme was fully captured. Coded data were compared across coders and the few discrepancies were resolved through consensus among the research team. The final, coded data set was then stratified and examined across gender and disease severity (GOLD stage) to evaluate representativeness of themes and subthemes and assure applicability of instrument content and structure across these groups.

The item pool, response options, and recall period for the instrument were developed based on themes and subthemes identified in the qualitative data, with the participants' words and phrases used to inform wording. Items were developed using an iterative process of development, review, revision, discussion, and revision, with reference back to the qualitative data to inform decision-making. After the initial set of draft items was developed, an item tracking matrix was created to document the nature and rationale for revisions. Senior clinical research experts (PJ, SS) participated in the review/revision process and an expert in PRO translation from the EXACT-PRO Study Group (SE) provided comments on cultural and linguistic issues associated with various words and phrases used in the draft item pool. Qualitative data gathered during the elicitation interviews conducted during Round 2 were examined for new terminology, descriptions, and/or themes that should be used to revise the initial draft item pool.

Results of the cognitive debriefing interviews conducted during Rounds 2 and 3 were examined for insight into participant interpretation of the items, making certain that understanding was consistent with the intent. Revisions were based on participant comments with consideration given to data gathered during elicitation focus groups and interviews and input from experts.

Results

Sample

Demographic and clinical characteristics of the study sample overall and by data collection round are shown in Table 1. Of the 83 participants, 45% were male, 71% self-identified as white, 13% Hispanic or Latino and 16% Black or African American. Mean FEV-1% predicted for the sample was 44% with participants distributed across GOLD stages 2, 3, and 4.

Patient Description of Exacerbation

Three major themes and five subthemes were identified in the data: 1) definition; 2) attributes (subthemes: respiratory and systemic); and 3) progression (subthemes: awareness, cues to care-seeking, recovery indicators). Themes and subthemes were consistent across focus groups and interviews and across ethnicity, gender, and GOLD stage. Descriptions of the themes and subthemes each are as follows:

Definition. Participants described an exacerbation as an "event" or "episode," characterized by an increase in the severity of respiratory symptoms and other systemic manifestations that occur over a two-to-three day period and is accompanied by a marked reduction in activity. They contrasted the persistence of the event with one or two "bad days" and with acute situations of breathlessness or cough for which relief occurs within a very short period of time.

Attributes. Table 2 presents the specific attributes participants ascribed to exacerbations with sample quotations. Two attribute themes were identified in the data: respiratory symptoms and systemic manifestations. Respiratory symptoms included cough, sputum production, chest discomfort, and difficulty breathing. Participants described cough in terms of chest congestion and frequency. Many described chest congestion that could progress to the point of "feeling full." Frequency of the cough ranged from every now and then to every two or three minutes to coughing all the time without a break. Participants used the terms mucus, phlegm, or "stuff" when referring to sputum, describing it in terms of volume, persistence, and color. Change in sputum color was used as a cue to care seeking, with participants using descriptive terms indicating a progression from "clear" to "yellowish, orange" to "smoky green," and finally to "brownish, dark green, lime green." Chest discomfort was characterized as feeling hurt or sore in the chest or ribcage, often attributed to severe or continuous coughing. Participants used the terms "difficulty breathing," "unable to breath," "shortness of the breath" and "couldn't breathe" to characterize breathlessness. Difficulty breathing was described in terms of general severity, "not getting enough air in" or "extreme shortness of breath," as well as being related to activity, "I was short of breath doing activities where I wasn't normally short of breath" or "I had to gasp for air every few steps." Participants often described situations during an exacerbation in which they were short of breath during an activity they normally did not associate with breathlessness.

Systemic manifestations of exacerbation included limitations of activity, feeling weak or tired, sleep disturbance and feeling concerned or worried. Participants described a full range of activity limitation with exacerbations, often associated with breathlessness and feeling weak or tired. Activity limitations included problems performing usual activities around the home or difficulty performing basic activities of daily living, such as morning care or simple meal preparation. Severe episodes made walking across the room or getting out of bed almost impossible. Weak and tired was described in terms of: "Low energy, didn't want to do anything, lethargy, malaise, or whatever the term is"; "It cuts you at the knees." Sleep disturbances varied, from sleeping all the time, to severe disruption at night often attributed to cough and/or breathing difficulty. Worry or concern about their health state included feeling tense, edgy, scared, and worried.

Progression. The data revealed three subthemes related to progression: an awareness of change in their condition, cues to seeking care, and indicators of recovery. Table 3 shows sample quotations for these subthemes. At the onset of an event, participants noticed a worsening of one or more respiratory symptom, such as an increase in cough frequency and/or more labored breathing and/or a change in sputum production that lasted beyond one or two "bad days." This change together with one or more systemic attributes led to an awareness that "something was not right" and the conclusion that they were having an "episode." The decision to seek care was prompted by any of several factors, including a change in sputum color, extreme breathlessness, anxiety, or the continued persistence of their worsened state: "My breathing was starting to get a tiny bit labored . . . it progressively got worse and worse and worse," and the decision they would not

Table 2 Patient-reported attributes of exacerbation with sample quotes

Respiratory symptoms—patient quotes

Cough

Frequency
- Every now and then, I might cough.
- I was coughing like every 2–3 minutes.
- Coughing all the time. . .

Sputum

Volume
- Some little pieces like balls. . .
- I was bringing stuff up, not a lot.
- It was really gross, and lots of it.
- A lot of phlegm. . .

Color
- Clear
- Yellowish, orange
- Smoky green
- Brownish, dark green, lime green

Congestion
- Dry cough. . .
- I felt like I had stuff in my chest.
- A lot of congestion. . .
- My chest feels so full.

Difficulty
- It was there, you could hear it. I just couldn't bring it up.
- It gets thick and it gets stuck.
- It just wouldn't come up and you can't force it up.
- There was phlegm or something that wanted to come up, it just wouldn't come up.

Chest Discomfort
- At night and in the mornings, it feels like somebody standing on my chest when I get up.
- My chest will be like tight, and it will be a little sore right in here, in the middle part.
- It was like someone was sitting on your chest, but it wasn't as though I couldn't breathe. Maybe that's hard to imagine; you've got this heavy feeling.

Difficulty Breathing

Severity
- My breathing was not as good as it normally is.
- Sometimes I'll have trouble breathing and can't get my breath.
- I was struggling to breathe, you know, getting short of breath.
- Just the breathing; I fought for every breath.
- Extreme shortness of breath. Extreme to the point where trying to go like this to get up, I couldn't.

Activity-related
- The way I describe it to the doctor is that I was short of breath doing activities where I wasn't normally short of breath.
- It was hard for me to walk without getting out of shortness of breath real bad. I would stay upstairs in my apartment. I had to go upstairs. I tried to limit it to that because of my breathing. If I am going up a slow—like a low incline in the sidewalk or so forth, I get of breath. If I am carrying groceries, I get out of breath.
- When I managed to get out of bed, I might get out of breath just trying to do some normal things like empty the dishwasher.

Systemic manifestations—patient quotes

Activity limitation
- I stopped doing most of the things—I tried to rest as much as I can.
- It takes you thinking about it before you get anything done, five or six times before you decide to do anything.
- But to physically do anything, I didn't even think of doing anything.

Tired or weak
- Well, I get fatigued just in my normal stuff, but this was more, like more naps or just needing to lay down and not having the energy to do anything Yes, very tired, very weak.
- Feeling weak and no energy. . .
- Yeah, because you lose your energy. You have no energy and all I wanted to do was sleep.
- I get so tired that I'm actually weak and shaky.

Psychological state
- It kind of makes you edgy, like a little bit of anxiety because your breathing is not normal.
- Because I was worried about it. I was worried that I didn't know what was going to happen.
- Once I see that shortness of breath, I get kind of scared.

Sleep disturbance
- I was very tired, but the coughing and the feeling I was so bad, that I couldn't sleep very well.
- I waken several times a night gasping for breath.
- Sleeping too much. . .
- More than normal. You just can't stay awake enough to satisfy yourself. Every time you turn around you want to go to sleep.

Table 3 Patient descriptions of exacerbation progression

Awareness/onset			
Increase cough • I noticed a tickling, coughing pretty much.	Change in sputum • All of a sudden I built up congestion. • Thick and I knew I was in trouble. • It [sputum] seemed to be more severe, more often, and I'd cough up a white phlegm but it was real thick. You have a hard time even getting it out of your mouth.	More labored breathing • For about a couple of weeks, it kept getting . . . I noticed my breathing wasn't coming up to par. • It gets to the point where you cannot breathe.	Combination • I just started having a lot more coughing and more difficulty breathing doing everyday things that I wouldn't normally have a problem with. • Probably . . . first . . . is the no energy and the shortness of breath then followed by the phlegm.
Cues to seek care			
Sputum color • I began coughing yellow. When that happens the doctor says to you that's the infection. • I went to the doctor because I was coughing up yellow. That's a red flag for me. • I know when it's green. I've got to go somewhere. • When I'm sick it's brownish.	Extreme breathlessness • When you're really having trouble breathing, you go to the doctor. • After a few days of having trouble breathing. • The more I saw that I had shortness of breath, that triggered me calling the doctor. • I couldn't breathe anymore.	Anxiety • It was just getting harder and harder to breathe, and I was really scared. • I woke up coughing, choking, very short of breath. It scared the hell out of me. • It just scared me. It scared me not being able to cough and breathe and feel very vulnerable at that time. • It makes you worry more. • If it's more than a week, then I really begin to be concerned.	Energy • I go [to the doctor] for the lack of energy even if I didn't have that panicky feeling. • I say wow, I didn't do nothing but I'm tired. • I was weak and tired. I couldn't breathe. I'd been laying down.
Recovery			
Cough • Coughing less and it's getting clearer. • Not coughing as much . . . • Easing up of the coughing . . . • The coughing stopped, not stopped completely, but it went back to normal. • The cough was gone. Sputum • I will measure my days by "was it a five handkerchief day? Or am I down to only a two handkerchief day"? • It was coming up easier, and not as difficult. It would pop up better. The color kept getting lighter.	Difficulty breathing • The breathing got better first. • The first thing I noticed probably was the easing of the breathing. • I could just feel it every day that what would take me five minutes one day would take me three minutes the next day, and pretty soon my breathing was back to normal. • As the week progressed, I could breathe more normally. • My breathing was easier, and I felt better. • I started breathing a little better.	Sleep • I started sleeping better. • I sleep all the way through the night now. Tired or weak • I didn't feel quite as tired. • Basically, I'm able to stay out of bed. Psychological state • I felt like now I can sit and enjoy an evening with my husband instead of thinking I'm going to fall apart. • I wake up feeling better and my mental attitude is very positive.	Activities • I felt secure enough to take a shower without someone being there. • I was able to brush my teeth without getting out of breath or coughing in between. • I was able to do things . . . make tea for myself, able to walk to the bathroom by myself and not having to stop and feel like I'm going to die. • I went [out] for a few hours, and gradually I went up to my ten hours a day.

be able to self-treat or bear it out: "I couldn't take it anymore. I couldn't breathe. I couldn't walk through the house." Participants felt they were recovering from an episode when they noticed consistent improvement in their respiratory symptoms, more normal sleep patterns, feeling less weak or tired, and an easing of their concern or worry, followed or accompanied by a gradual resumption of their usual daily activity. Recovery was often subtle; and with thought, participants indicated they knew they were "out of it" when their confidence and ability to walk outside or go to the store had returned.

All of the participants described events or episodes during which they did not contact a health care professional. The choice to report events depended on duration and severity of the attributes of an exacerbation and other activities going on in their lives.

Instrument Structure and Item Pool

Existing literature, expert knowledge of the condition, and the qualitative data from experienced patients all supported the use of a daily diary to capture frequency, severity, and duration of exacerbations of COPD. Given the typical age of patients with COPD, the nature and severity of this condition during stable and acute states, and the participant's description of the impact of exacerbations on their functioning, it was clear that the instrument should be simple and easy to complete with short, crisp questions and clear response options. One diary approach considered was ecologic momentary assessment, in which respondents would be signaled to complete the instrument electronically at random intervals throughout the day [41]. This approach was deemed inappropriate because of the presence of multiple items that together would require several minutes to complete, the 6-to 12-month duration of prevention trials, and the altered sleep/wake patterns characteristic of exacerbations. A second option was a morning and evening diary with participants assessing their symptoms at both time periods. This was considered inconsistent with the qualitative data and item content which was heavily dominated by descriptions of daytime attributes, indicating a twice daily diary would be unnecessarily burdensome for participants in long-term or acute intervention trials.

A once daily assessment method was selected, with participants completing the diary at the close of each day, just

prior to bedtime, reflecting back on their day and providing an overall rating for each of the attributes assessed. There is empirical evidence suggesting a close correspondence between end-of-day assessment and aggregated momentary measures for symptoms of pain and fatigue [42], and this approach would be simpler to complete over long periods of time and during acute illness, thereby enhancing data quality, including compliance.

The instrument was drafted as a daily diary with a pool of 23 candidate items and formatted into an easy-to-read paper–pen questionnaire booklet for use during the first set of cognitive debriefing interviews (Round 2). During these interviews, participants were asked about their interpretation of the items and how they selected their responses, with specific interest in the approach they used to rate their symptoms for the day. Subjects easily reflected back over the day as they rated each symptom, selecting the response that best represented their experiences that day. They were also asked to describe situations in which they would assign a higher or lower severity rating based on the day's experience, responding easily to this query. Participants confirmed results of the existing data related to the day-to-day variability of symptoms, adding that the items were able to capture this variability. Based on input from these participants and discussion during the second expert panel meeting, adjustments were made in the draft item pool and recorded in the item-tracking matrix.

Given the design of the daily diary card and increasing evidence of the superiority of electronic diaries (e-diaries), consideration was given to administration of the measure using a personal digital assistant (PDA) in the subsequent item reduction and validation study. Electronic diaries (e-diaries) have a number of advantages of over paper diaries, including greater data quality, data management efficiency and improved patient compliance with rates reported to be as high as 83 to 94% [43–48]. There was also evidence to suggest that older adults with chronic health conditions have successfully used e-diaries in clinical studies, including international trials [43,44]. The Tungsten E2 was selected for its ease of use, clear display, screen size enabling the item stem and response option to appear on one screen without need for scroll bars, and simple navigation through tapping, all features consistent with recommendations for older adults [49]. The 23 revised items were programmed into the device for the final debriefing interviews (Round 3) and as a way to pilot test the device.

Following Round 3, one of two conceptually redundant items was dropped and another was split into two items for added clarity. Observing the participants with the PDA, none had any difficulty using the device with minimal instruction. All reported that it was easy to use, expected it would take less time to complete than the diary booklet, and stated they would not have a problem using the device in a 6-to 12-month study. Eight of the nine participants expressed a clear preference for the PDA over the booklet with the ninth reporting neutrality.

A preliminary conceptual framework showing the key domains of exacerbation, sample content of the items, and number of items in the final item pool is provided in Figure 2. At this point, the 23-item e-diary was considered ready for empirically based item reduction with performance testing of the final instrument, including an evaluation of its dimensionality, factor structure, reliability, validity, and responsiveness.

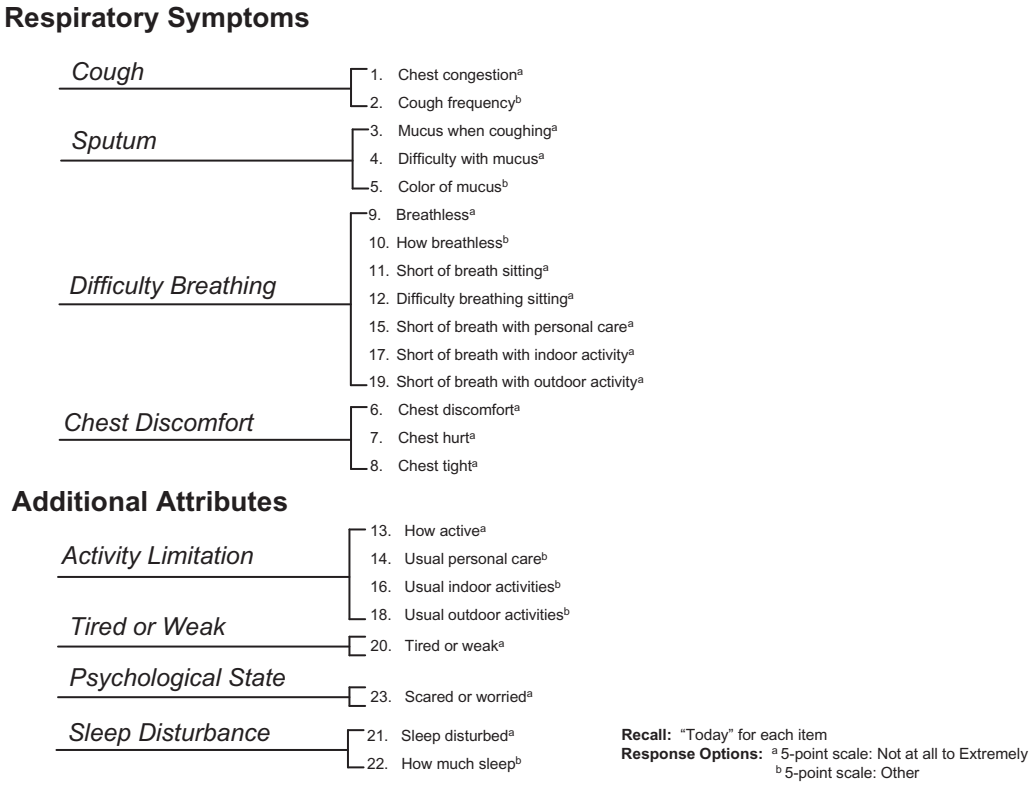

Figure 2 Preliminary Conceptual Framework for the 23-Item Pool.

Discussion

This study was conducted as the first phase of the multiphase EXACT-PRO Initiative to develop a new instrument for standardizing PRO assessment of exacerbations of COPD. Focus groups and interviews were conducted with patients who had experienced exacerbations of COPD using enrollment criteria similar to those used in preventive and acute/anti-infective therapy trials to make certain the content and structure of the instrument was consistent with patient-reported descriptions of these events. International experts in pulmonology and clinical research participated in the process to assure content validity from a medical perspective, while an instrument development and a translation expert contributed to structure, wording, and format. Cognitive debriefing interviews ascertained that participants interpreted the items as intended, while results of usability assessment of the PDA suggested the device was easy to use with relatively little instruction.

Participant descriptions of exacerbations of COPD and the characteristic features of these events were consistent with clinical definitions of a sustained worsening in the patient's condition beyond normal day-to-day variability that is acute in onset and may necessitate a change in regular medication [1,4,5]. Participants added clarity to this definition by characterizing the worsening as either acute or gradual, with the onset lasting several days, thereby differentiating exacerbations from one or two "bad days" that are characteristic of their day-to-day variability. Participants also described changes in self-care that included greater use of rescue medications and a reduction in activity, consistent with results of the Kessler et al. [31] study in which participants described taking additional medication or resting as part of their exacerbation self-management.

Patient symptom descriptions were generally consistent with those described in previous qualitative work and offered additional clarity related to day-to-day variability, and specific attributes of exacerbation, severity, and progression. Participants in the present study not only described increased breathlessness, cough, and sputum production with exacerbation, but provided detailed descriptions of chest discomfort and systemic manifestations of these events, including feeling weak or tired, sleep disturbance, and feeling worried or concerned, all associated with a dramatic reduction in activity, minimal basic activities of daily living and prohibiting instrumental activities of daily living. This set of symptoms extends the traditional symptom triad of breathlessness, cough, and sputum production characteristic of COPD that serve as the common core of previous exacerbation diaries. The additional attributes assessed in the new measure reflect the patient's experience with exacerbations and may contribute to greater measurement precision.

The fact that the participants described experiences characteristic of an exacerbation that they did not report to a health-care provider is consistent with quantitative studies of unreported events [9,10,18–20]. These results support previous suggestions that exacerbation frequency in COPD has been underestimated and that the efficacy of treatment may be understated when this outcome is defined by health care utilization.

Conclusion

This article described the methods and results of the first phase of the EXACT-PRO Initiative designed to develop a standardized PRO measure for assessing the frequency, severity, and duration of exacerbation in clinical studies of COPD. To address content validity, the EXACT's structure and pool of 23 candidate items were based on data gathered through focus groups and interviews and cognitive debriefing interviews involving patients with COPD with a recent history of exacerbation. Clinical research, instrument development, and translation experts provided input throughout the development process. Based on this work, the EXACT-PRO Initiative moved into Phase II, a prospective study of exacerbating and stable patients designed to reduce the number of items and test the final instrument, known as the EXACT, for validity, reliability, and responsiveness.

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