The Exacerbations of Chronic Pulmonary Disease Tool (EXACT)

Patient-Reported Outcome (PRO)

USER MANUAL

(Version 7.0)

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TABLE OF CONTENTS

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1.0 INTRODUCTION

1.1. Background

Exacerbations are an important feature of chronic obstructive pulmonary disease (COPD), leading to significant morbidity and mortality.[1-4] Reducing the frequency, severity, and duration of acute exacerbations is of great interest to patients, providers, and payers. These same parameters are often used as primary or key secondary endpoints in clinical trials, including pre- and post-marketing pharmaceutical trials evaluating the efficacy and safety of maintenance and acute-treatment trials for COPD.

Despite widespread commitment to understanding exacerbations of COPD and the effects of treatment, there has been no consensus on their empirical definition and no standardized approach to measurement.[5] Historically, exacerbations have been defined in terms of health care utilization, e.g., number of clinic visits, emergency room, or urgent care visits with oral steroid or antibiotic treatment, or hospitalizations for an exacerbation. Health care events have also been used as a proxy for exacerbation severity, with exacerbations requiring an unscheduled clinic or emergency room visit characterized as "moderate," and those requiring hospitalization as "severe."[6, 7] Various approaches have been used to quantify exacerbations that are unreported and self-treated at home, often characterized as "mild."

There are a number of limitations associated with the health care resource utilization (HCRU)-based definition of exacerbation. First, clinic contacts and visits are initiated by patients based on their assessment of the episode, relationship with the provider, cost coverage, and personal or family preferences for care. With as many as 50% to 70% of exacerbations unreported,[3, 8] this definition seriously underestimates exacerbation frequency. Second, HCRU definitions do not take into consideration, standardize, or control for the change or severity of patient symptoms or the physician's assessment of exacerbation. Third, HCRU events, particularly hospital admissions, are related to health policy or coverage within a given country or region. Patients undergoing treatment in regions with relatively liberal hospital admission policies will have more frequent and more "serious" exacerbations, while those in regions with conservative admission policies will have less frequent and/or fewer "serious" episodes. These limitations have implications for prevalence estimates in epidemiologic studies, affect estimates in studies examining the link between exacerbations and disease trajectory, and influence site selection and treatment outcomes in clinical trials.[9]

A standardized symptom-based method of assessing exacerbations can address many of these limitations. This approach is often traced back to definitions proposed by Anthonison et al.[10], who used an empirical definition to identify and classify exacerbations in a clinical trial designed to test the benefits of antibiotic therapy. Seemungal et al.[3] extended this definition for the East London (UK) prospective cohort study, to understand causes and mechanisms of exacerbations of COPD. Since that time, diary cards have been used in a significant number of prospective clinical studies and trials to document symptom severity and identify unreported exacerbations. Although most cards include dyspnea, cough, and sputum, the actual items used to capture these symptoms vary greatly, making comparison across studies virtually impossible and may account for some of the inconsistency in findings across otherwise similar investigations. Further, none of the cards were developed using well-known psychometric procedures with documentation consistent with United States (US) Food and Drug Administration (FDA)

and European Medicines Agency (EMA) guidelines for patient-reported outcomes (PROs).[11, 12] Standardizing the symptom assessment of COPD exacerbations through a common tool and metric will further our understanding of these important events, including the prodromal, acute, and recovery phases, and the effects of treatment.

1.2. The EXACT-PRO Initiative

The EXACT-PRO Initiative (**EXA**cerbations of **C**hronic Pulmonary Disease **T**ool – Patient-Reported Outcome) brought together clinical, research, methodology, and regulatory experts to develop a new PRO instrument to standardize the symptomatic assessment of exacerbations of COPD for evaluating frequency, severity, and duration of exacerbations in clinical trials of COPD. The Initiative was conducted under the leadership of Evidera scientific staff and supported through unrestricted funds provided by multiple pharmaceutical companies (www.exactproinitiative.com). To protect the integrity of the EXACT, Evidera holds all copyrights related to the tool. The instrument is available for use with permission obtained through Evidera (see Section 7.0).

1.3. Purpose of the EXACT

The EXACT is a 14-item daily diary designed to provide a direct measure of patient-reported symptoms of COPD exacerbation. EXACT data complement and extend information provided by traditional HCRU data by capturing unreported, symptom-defined events, and standardizing the evaluation of symptoms around medically treated events (MTEs), including magnitude of change around events seen in the emergency room or clinic and before and after hospitalization. Advantages of a standardized, validated daily diary-based symptom assessment in exacerbation studies include uniform metrics, reduced recall bias, and the ability to fully characterize exacerbations of COPD, including the estimated 50% to 70% of events that are unreported.[2, 3, 9]

The EXACT Total score is an interval-level scale ranging from 0 to 100, where higher scores indicate a more severe condition. The EXACT Total score is used to assess exacerbations of COPD.

2.0 CONTEXT OF USE

Although this section of the user manual is designed to assist pharmaceutical sponsors in the selection and/or use of the EXACT for their specific needs, the information is also relevant to broader uses, including non-pharmaceutical trials, natural history studies, and instrument validation studies.

2.1. Disease and Target Population

2.1.1. COPD, Including Chronic Bronchitis

The EXACT was developed and validated for use in patients with COPD, including chronic bronchitis. COPD is characterized by persistent airflow limitation with varying degrees of air sac enlargement, airway inflammation, and lung tissue destruction. "The chronic airflow limitation characteristic of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person. Emphysema, or destruction of the gas-exchanging surfaces of the lung (alveoli), is a pathological term that is often (but incorrectly) used clinically and describes only one of several structural abnormalities present in patients with COPD."[13, pp.1] Chronic bronchitis, often the target of antimicrobial therapies for acute bacterial

exacerbations of COPD (ABECB-COPD), involves persistent or repeated inflammation of the bronchi with excessive bronchial mucus and productive cough with sputum production on most days for 3 consecutive months in at least 2 consecutive years.[14] Cough and sputum production may precede the development of airflow limitation; conversely, some patients develop significant airflow limitation without chronic cough and sputum production.[13] Per the FDA Guidance on ABECB-COPD trials, "because of the overlap of symptoms in patients with chronic bronchitis and/or emphysema and the limitations of the definition of chronic bronchitis, it is more appropriate to use the term COPD to describe the underlying disease in this patient population."[14, pp.6]

2.1.2. Exacerbations of COPD

Exacerbations are events characterized by an acute, sustained worsening in the patient's COPD beyond normal day-to-day variability, including an increase in respiratory symptoms such as dyspnea, cough, and sputum production.[13] The EXACT was designed to standardize the assessment of the patient's condition in order to capture this dynamic process.

2.1.3. Other Respiratory Conditions - Excluded

Patients with clinically relevant bronchiectasis are often excluded from exacerbation trials and are therefore excluded from the target population for trials using the EXACT. Although asthma is considered a disease of chronic airflow obstruction, the EXACT was not designed for use in this patient population. In addition, although the instrument may prove useful in patients with cystic fibrosis, alpha-1 antitrypsin deficiency, or obliterative bronchiolitis, these COPD phenotypes were not included in the instrument development process and are therefore not part of the target population for the instrument at this time.

2.1.4. Clinical Trial Designs: Maintenance/Prevention and Acute-Treatment

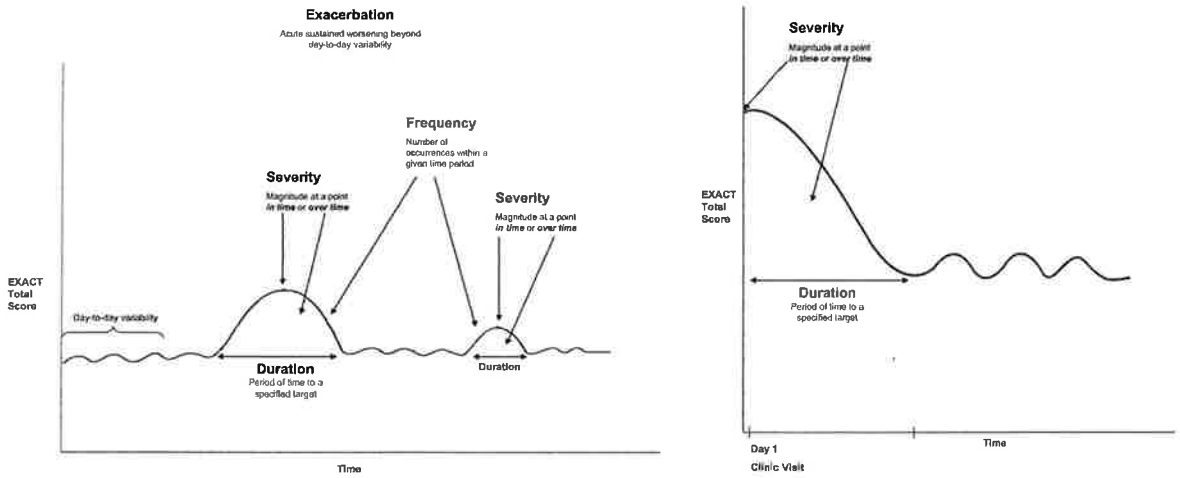
The EXACT was designed for use in 2 types of clinical trials:

1) Maintenance/prevention trials, testing the efficacy of therapies to modify or prevent COPD exacerbations (reduce their frequency, severity and/or duration). Historically, these trials have been 6 to 12 months in duration, enrolling patients during a stable state.
2) Acute-treatment trials evaluating therapies to treat exacerbations of COPD (reduce their severity, duration, or recurrence). These trials enroll patients during an acute exacerbation of COPD, e.g., anti-microbial drugs for ABECB-COPD.

Figures 1a and 1b show a schematic representation of exacerbations for these types of trials.[15]

Figures 1a and b. Dimensions of Exacerbation Assessment by Trial Type[a]

1a. Maintenance/Prevention Trials **1b. Acute-Treatment Trials**



[a]Reprinted with permission from Leidy et al. 2010.[15]

2.2. Maintenance/Prevention Trials

2.2.1. Target Population

Although there is evidence that exacerbations occur across all levels of airway obstruction, exacerbation prevention trials often enrich their sample by including more severe patients who are considered at highest risk of clinic visits or hospitalizations for exacerbations. Inclusion criteria for these trials are generally as follows:

- Clinical diagnosis of COPD or chronic bronchitis
- Forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio <0.70 post-bronchodilator
- FEV_1 % predicted <80%
- >40 years of age
- Current or former smoker
- Smoking history >10 pack years
- >1 exacerbation in the previous 6 to 12 months, seen in a clinic or emergency room and treated with steroids or antibiotics or requiring a hospital admission.
- No exacerbation requiring treatment within 4 to 6 weeks of enrollment

2.2.2. Study Endpoints

The FDA Draft COPD Guidance (2007) instructs sponsors to "define exacerbations in a way that is clinically meaningful, and specify criteria to determine when worsening of symptoms become an exacerbation. Criteria to consider in defining exacerbation include worsening of shortness of breath, increased sputum volume, increased purulence of sputum, worsening in symptoms requiring changes in treatment, or worsening of symptoms requiring urgent treatment or hospitalization."[16, pp.8] The EMA COPD Guideline (2012) states, "Definitions of exacerbation and severity of the exacerbation need to be standardized to allow comparisons between different interventions in different settings."[17, pp.8]

Table 1.0 shows the intended use of the EXACT in relationship to existing methods for evaluating outcomes in international trials evaluating the efficacy of maintenance therapies for reducing frequency, severity, or duration of exacerbations in patients with COPD. Note that the EXACT is not intended to replace currently recommended methods for defining exacerbation outcomes in maintenance/prevention trials of COPD.[16, 17] Rather, the EXACT is used to complement these endpoints by quantifying and standardizing the severity of patient-reported symptoms associated with exacerbations that are medically treated in clinic and urgent care settings. In addition, the EXACT quantifies the frequency, severity, and duration of reported and unreported symptom-defined events, i.e., acute sustained symptom worsening that exceeds a defined threshold. Unreported, symptom-defined events are often characterized as "mild" and described as "an increase in respiratory symptoms that can be controlled by the patient with an increase in usual medication."[17, pp.8]

Exacerbations requiring hospitalization are categorized as "severe" events, and are included in the computation of the exacerbation rate for medically treated events. The EXACT can be used to assess symptom severity and change associated with medical decisions to hospitalize the patient. In addition, scores may be used to track symptom severity and change during the post-discharge recovery period. Although EXACT data may be collected during hospitalization, scores should be considered exploratory. Rating the "severity" of a patient's condition in a hospital setting to test the effects of treatment is complex. In this setting, patient acuity levels include patient signs, symptoms, laboratory values, and level of treatment, such as intubation, oxygenation, and medications for symptom relief or agitation. The APACHE II (Acute Physiology and Chronic Health Evaluation II) is an example of an acuity rating used in intensive care.

Table 1.0. Standardizing Exacerbation Outcomes in Clinical Studies of COPD

Endpoint[a]	Definition	Measurement Approach	
		Medically-Treated Events (MTEs)	**Symptom-Defined Events:**
Frequency Event rate	– Event rate: per person per year – Event definition: acute sustained symptomatic worsening of COPD; treated with antibiotics, steroids, in hospital, or self-treated at home	Number of health care resource utilization (HCRU) events: – Clinic or urgent care visit for an acute sustained symptomatic worsening of COPD, treated with antibiotics and/or steroids – Hospitalization for an acute sustained symptomatic worsening of COPD EXACT score changes may be used to document change in symptoms associated with HCRU events.	Number of symptom-defined events: – Acute, sustained symptomatic worsening of COPD, defined as an increase in EXACT score ≥9 points for 3 days or ≥12 points for 2 days, above Baseline Reported: accompanied by clinic or urgent care visit with antibiotic and/or steroid treatment or hospitalization Unreported[b]: no associated visit or hospitalization; self-treated at home
Time to first event **Time to subsequent (next) event**	– Days from initiation of treatment/placebo to first event – Days from recovery to subsequent (next) event	First HCRU Event: – Days to Day 1, clinic or urgent care visit – Days to Day 1, hospitalization Subsequent HCRU event: – Days from end of treatment for first HCRU event to Day 1 of next HCRU event	First symptom-defined event: – Days to Day 1 of sustained increase in EXACT score exceeding event threshold Subsequent symptom-defined event: – Days from Recovery from first symptom-defined event to Day 1 of next symptom-defined event
Proportion of patients with ≥ 1 event	– % patients with ≥1 event	% with ≥1 HCRU event: – % with ≥1 clinic or urgent care visit – % with ≥1 hospitalization	– % with ≥1 symptom-defined event: – % with ≥1 unreported symptom-defined event
Severity	– Degree or magnitude of the event(s)	Type of treatment: – Moderate: antibiotics or steroids – Severe: hospitalization Symptom severity: – Maximum EXACT score during the HCRU event – Change in EXACT score, baseline to HCRU Day 1 – Mean EXACT score during treatment; area under the curve (AUC)	Unreported, symptom-defined events: – Mild: self-treated at home[b] Symptom severity: – Maximum EXACT score during the event – Change in EXACT score, baseline to event Day 1 – Mean EXACT score during the event; AUC
Duration	– Length of the event(s)	Duration of treatment: – Days of treatment with antibiotics or steroids – Days of hospitalization	Duration of symptoms: – Days from symptom onset to symptom recovery – Recovery: improvement in EXACT score ≥9 points from the maximum value, sustained for ≥7 days

[a]Consistent with the FDA Draft COPD Guidance, if 1 of these endpoints is chosen as the primary efficacy endpoint, the others also should be assessed to ensure that another exacerbation outcome has not worsened. [16, pp 8]

[b]Characterized as "mild" in EMA COPD Guideline.[17]

2.2.3. Endpoint Positioning

Exacerbation frequency, severity, and/or duration, as outlined in Table 1.0, may serve as primary, co-primary, secondary, or exploratory endpoints, as appropriate to the study design.

For pharmaceutical trials, specific endpoint selection, positioning, and measurement approach are determined by the study sponsor in concert with the appropriate regulatory review agencies. An example of an endpoint model for a maintenance/prevention trial using the EXACT is provided in Appendix A. Sponsors are responsible for providing product-specific endpoint models to the Agency as part of their submission process.

2.2.4. Target Claims (Medical Product Development)

Target claims were discussed at the initiation of the EXACT-PRO Initiative to inform the instrument development process. The following claims were agreed upon and used as a reference point throughout the development and qualification review process, including Expert Panel Meetings (2006–2008), discussions with the FDA and EMA and in the EXACT-PRO qualification dossier:

- Reduces the frequency of acute exacerbations of COPD
- Reduces the duration of acute exacerbations of COPD
- Mitigates/attenuates/reduces the severity of acute exacerbations of COPD

Intended product claims should be consistent with these generic target claims and specified in a manner consistent with the endpoints and outcomes outlined in Table 1.0.

It is important to note that statistical analyses of the validation data showed the presence of 3 respiratory symptom domains or clusters embedded within the EXACT: Breathlessness, Cough & Sputum, and Chest Symptoms. Scores on these domains may be used in an exploratory manner to further understand the respiratory-symptom specific manifestations of exacerbations of COPD. Only the EXACT Total score is used for symptom-defined exacerbation outcomes, as outlined in Table 1.0. (Note that respiratory symptom claims are addressed in the EXACT-Respiratory Symptoms [E-RS] User Manual).

Product-specific claims and labeling language are the responsibility of the sponsor and should be based on product attributes, study design and hypotheses, and discussions with the appropriate regulatory agencies.

2.3. Acute-Treatment Trials

Reliability, validity, and responsiveness of EXACT scores were tested in a prospective study in which patients with COPD were enrolled at the time of a clinic visit for a medically confirmed and treated exacerbation of COPD.[18] Further tests of reliability, validity, and sensitivity to change during medically treated events were performed in data from 3 randomized controlled trials of preventive therapies, where patients with COPD were enrolled during a stable state and followed over time.[19] To date, the EXACT-PRO Initiative has not had data to evaluate the performance of the EXACT in a randomized controlled clinical trial evaluating the effects of treatment on patients with COPD enrolled in a state of clinical exacerbation at Baseline.

Pharmaceutical sponsors wishing to use the EXACT for evaluating the efficacy of therapies for the treatment of acute exacerbations, including ABECB-COPD, should discuss this directly with the appropriate regulatory agencies.

2.3.1. Target Population

Sponsors are responsible for assuring that trial patients have a diagnosis of COPD and acute exacerbation.[14]

Inclusion criteria for the first EXACT validation study, when patients were enrolled during a clinic visit for exacerbation, included the following:

- Clinical diagnosis of COPD or chronic bronchitis
- FEV_1/FVC ratio <0.70 post-bronchodilator
- FEV_1 % predicted <80%
- >40 years of age
- Current or former smoker
- Smoking history >10 pack years
- >1 exacerbation in the previous 6 to 12 months, seen in a clinic or emergency room and treated with steroids and/or antibiotics or requiring a hospital admission.

Patients enrolled in ABECB-COPD trials may be younger (≥35 years), with a history of mild COPD determined by spirometry.[14]

2.3.2. Study Endpoints

Acute exacerbation trials generally use parallel group designs with trial duration driven by the study objectives. For ABECB-COPD drug development, superiority trials are recommended, including placebo-controlled, dose-response, and/or superiority over another antimicrobial.[14] The FDA Guidance on ABECB-COPD Antimicrobial Treatment specifies that patients characterized as severe (e.g., requiring hospitalization) should be excluded from trials.[14] This guidance also states that "a well-defined and reliable method of assessing patient symptoms should be used for ABECB-COPD trials. Accordingly, we recommend use of a valid and reliable PRO instrument as the primary outcome measure."[14, pp.10]

In this context of use, the EXACT quantifies patient symptoms of acute exacerbations of COPD treated in an outpatient setting (clinic and urgent care), from the day of diagnosis and enrollment into the trial through the designated follow-up period. The direction and magnitude of symptomatic change, improvement or worsening, can be determined and compared across treatment groups.

Note that for those interested in exacerbations treated in the hospital setting, EXACT severity scores may be collected and assessed during hospitalization; however, these data should be considered exploratory. Rating the "severity" of a patient's condition in a hospital setting to test the effects of treatment in that setting is complex. In this setting, patient acuity levels include patient signs, symptoms, laboratory values, and level of treatment, such as intubation, oxygenation, and medications for symptom relief or agitation.

The APACHE II is an example of an acuity rating used in intensive care. The EXACT may be used to assess symptom severity and change post-hospital discharge.

2.3.3. Endpoint Positioning

In clinical research, outside the context of regulated pharmaceutical trials, the EXACT may be used as a primary, co-primary, or secondary endpoint in acute-treatment trials.

For pharmaceutical trials, specific endpoint selection, positioning, and measurement approach are determined by the study sponsor in concert with the appropriate regulatory review agencies. An example of an endpoint model for an acute-treatment trial using the EXACT is provided in Appendix A. Sponsors are responsible for providing product-specific endpoint models to the Agency as part of their submission process.

2.3.4. Target Claims (Medical Product Development)

The following generic target claims for acute-treatment trials were adopted at the initiation of the EXACT-PRO Initiative to inform the instrument development process.

- Mitigates/attenuates/reduces the severity of exacerbations treated in clinic or emergency room (outpatient) settings
- Reduces/speeds time to symptomatic improvement of exacerbations treated in clinic or emergency room (outpatient) settings

It is important to note that there are 3 respiratory symptom domains or clusters embedded in the EXACT: Breathlessness, Cough & Sputum, and Chest Symptoms.[18, 20] Scores on these domains may be used in an exploratory manner to further understand respiratory-symptom specific manifestations of COPD exacerbations and the effects of treatment.

Product-specific claims and labeling language are the responsibility of the sponsor and should be based on product attributes, study design and hypotheses, and discussions with the appropriate regulatory agencies.

2.4. International Use

To assure suitability of the EXACT for international studies, international content experts served on an expert panel and international experts within sponsoring organizations were consulted throughout the instrument development, validation, and analysis process. A translation expert served as an expert panelist and provided consultation on words and phrases in the original US English version known to be difficult to translate equivalently in other cultures and languages. In addition, discussions were held prior to and during the expert panel meetings regarding the comparability of qualitative data gathered in the US and proprietary data from previous international studies conducted by individual EXACT-PRO Initiative sponsors.

The EXACT has been translated into multiple languages, with cognitive interviews performed in patients with COPD in the target countries. See the EXACT-PRO Initiative website (www.exactproinitiative.com) for the current list of translations. Results of this work support the conceptual equivalence of the items

and use of the instrument in international trials. Methods used to translate the EXACT are described in Section 6.0.

Performance properties of EXACT scores in international studies were examined in the context of 2 randomized controlled trials, as outlined in Section 4.0. One trial included patients from Australia, Canada, Germany, Japan, Korea, Philippines, Poland, Russia, Slovakia, Taiwan, Ukraine, and the US. The second included patients from Bulgaria, Czech Republic, Hungary, Poland, Romania, and Slovakia. Reliability, validity, and responsiveness estimates for these international studies were consistent with previous estimates.

2.5. Method of Administration

The EXACT is a self-administered daily diary, completed by respondents each evening before bedtime. The instrument was developed with eDiary administration in mind, with cognitive interviews performed using both paper-pen booklet and personal digital assistants (PDAs) to ensure respondent understanding in both modes and user acceptance of the PDA. The Palm® Tungsten E2 was the electronic device used in this qualitative study and in the initial quantitative validation study. Since that time, the ePRO field has evolved further and a variety of handheld devices have been used. Specifications for administering the EXACT via electronic devices, information related to device selection, and a description of the EXACT ePRO Vendor Certification Program to maximize consistent use across vendors and devices are provided in the EXACT-PRO Initiative website (www.exactproinitiative.com).

Certain circumstances may require administration of the instrument using paper-pen format. As noted above, a paper-pen diary booklet was developed and has been qualitatively evaluated for ease of use and understanding during the cognitive interviewing procedures. Should a sponsor wish to administer the instrument using a paper-pen diary in a pharmaceutical trial, they should discuss this with the appropriate regulatory agency. Sponsors are responsible for providing any data needed to support performance comparability.

Additional information on other methods of administration is provided in Section 7.0 of this User Manual. Information on site and patient training is found in Section 8.0.

3.0 EXACT FDA QUALIFICATION

In 2014, the FDA released a draft guidance document titled the "Qualification of Exacerbations of Chronic Pulmonary Disease Tool for Measurement of Symptoms of Acute Bacterial Exacerbation of Chronic Bronchitis in Patients with Chronic Pulmonary Disease."[21, pp.1]

This draft guidance document states: "the EXACT is qualified as a well-defined and reliable measure of symptoms of ABECB-COPD, for use in Phase 2 studies,"[21, pp.1] of "outpatients with acute bacterial exacerbations of chronic bronchitis in patients with COPD who meet the clinical trial entry criteria as described in the guidance for industry *Acute Bacterial Exacerbations of Chronic Bronchitis in Patients with Chronic Obstructive Pulmonary Disease: Developing Antimicrobial Drugs for Treatment.*"[14,21, pp.2] The EXACT is "intended for ultimate use as a primary or secondary endpoint in confirmatory clinical trials" and "to support labeling claims related to change in ABECB-COPD symptoms."[21, pp.2]

4.0 DEVELOPMENT AND VALIDATION PROCESS - OVERVIEW

4.1. Development and Initial Validation

Development and validation procedures for the EXACT were consistent with guidelines for PRO instrument development proposed by the FDA and EMA[11, 12] and well-known psychometric procedures. The process involved over 500 people, including 493 patients with COPD and 18 professionals from the US and Europe with expertise in pulmonary medicine, clinical research, instrument development, and pharmaceutical regulation. A comprehensive review of the published literature was performed as a first step in instrument development to identify and evaluate existing PRO instruments used in clinical trials of exacerbations of COPD. This informed the development of protocols and interview guides used in the qualitative research that formed the foundation of the tool.

To ensure and document content validity, 83 men and women with a diagnosis of COPD and history of exacerbations participated in focus groups or interviews to elicit concepts for instrument development purposes.[15] An iterative analytical process was used to identify themes and concepts in the qualitative data to inform instrument content and structure. A draft instrument comprising 23 items was subjected to cognitive interviewing methodology in patients with COPD. During 2 advisory panel meetings, experts critiqued the research methods and results and assisted in the design of a prospective study to reduce the number of items and evaluate the performance characteristics of the instrument in patients with acute and stable COPD.

The next phase of instrument development and validation process involved a prospective 2-group observational validation study of 410 patients with COPD.[18, 20] Acute patients with a clinician-confirmed exacerbation (N=222) completed the draft item pool and additional items via an electronic diary each evening before bedtime on Days 1–28 of their exacerbation and again on Days 60–67, with clinical assessments performed on Days 1, 10 (±2), 29 (±2), 60 (±7), and 68 (±7). The second group, 188 patients considered clinically stable, completed the diary over a period of 7 days.

Item analyses and Rasch item-response theory (IRT) were used to derive the final 14-item EXACT.[20] The EXACT Total score is computed by using logit values and a simple look-up table to yield interval-level scores ranging from 0 to 100 where higher scores indicate a more severe condition. The Total score is used for characterizing symptom-defined events, including the determination of the patient's stable baseline, onset of an event (threshold of sustained worsening) and recovery (threshold of sustained improvement), and assessing symptom severity around MTEs.

Tests of the reliability, validity, and responsiveness of EXACT scores were performed using an *a priori* statistical analysis plan (SAP) with follow-up secondary analyses. Scores exhibited high levels of internal consistency and reproducibility. Evidence of construct validity included the ability to discriminate acute and stable groups and sensitivity to change over time in the acute group.[18] Results of the validation study were presented and critiqued during a third expert panel meeting; the outcome of additional secondary analyses and proposed interpretation guidelines were discussed during a fourth meeting.

4.2. Validation in Clinical Trials

The first validation study provided strong evidence of the reliability, validity, and responsiveness of EXACT scores and informed the scoring rules for determining onset and recovery of symptom-defined

events.[18] However, new instruments need to be subjected to multiple tests of reliability and validity. In the case of the EXACT, prospective data were needed to replicate the initial estimates of reliability, validity, and responsiveness; assess the performance of EXACT scores from stable through acute states; and test the sensitivity of the onset and recovery rules, ideally in a randomized controlled pharmaceutical trial.

To address these needs, the performance properties of EXACT scores were tested using data from 3 Phase II, multicenter, randomized, double-blind, placebo-controlled clinical trials provided by 2 pharmaceutical companies. One was a 6-month trial conducted in the US (N=235) and 2 were 12-week multi-national trials (N=749; N=597); patients were enrolled when clinically stable. Inclusion criteria included a medical diagnosis of COPD with a FEV_1 % predicted <80% and at least 1 MTE during the prior year. SAPs for the validation analyses were completed *a priori* with methods and results presented in reports that were submitted to regulatory agencies (FDA, EMA) as part of the qualification process.[22] Methods and results of these validation analyses are published in Annals of the American Thoracic Society.[19]

4.3. Sensitivity to Treatment Effects

To serve as an outcome measure in clinical trials, an instrument must also show sensitivity to treatment effects. In a non-pharmaceutical setting, Halpin and colleagues' 4-month randomized trial of the effect of health risk winter alert calls on exacerbation rate found that patients receiving calls had fewer symptom-defined (EXACT) events (34% vs. 53%) and that these events were shorter (8.2 ± 2.0 vs. 10.1 ± 1.9 days) and less severe (area under the curve [AUC] 65 ± 21 vs. 115 ± 22) than events in patients receiving no calls.[23] Although not statistically significant due to sample size limitations, the large effect sizes were consistent with the EXACT's sensitivity to treatment effects, with results providing insight into the effect of weather and early intervention on exacerbations of COPD with implications for further research.

In the drug development setting, significant treatment effects were found in the ATTAIN study, a 6-month international Phase III randomized, controlled clinical trial testing the efficacy of aclidinium for the maintenance treatment of COPD (N=828).[24, 25] This trial showed significant differences in exacerbation rates between each active treatment group and placebo, with consistent findings for HCRU and symptom-defined exacerbations, as follows:

Medically-treated (HCRU) events:

- 200 µg: 28% (rate ratio 0.72, 95% CI [0.52, 0.99], p<0.05)
- 400 µg: 33% (rate ratio 0.67, 95% CI [0.48, 0.94], p<0.05)

Symptom-defined (EXACT) events:

- 200 µg: 28% (rate ratio 0.72, 95% CI [0.55, 0.94], p<0.05)
- 400 µg: 29% (rate ratio 0.71, 95% CI [0.54, 0.93], p<0.05)

To date, the EXACT has not been tested in a randomized controlled clinical trial where subjects are enrolled during a clinic visit for acute exacerbation, such as ABECB-COPD antimicrobial trials.

5.0 INSTRUMENT DESCRIPTION

5.1. Structure

The EXACT is a 14-item daily diary, designed for electronic administration. Patients/respondents are instructed to complete the diary each evening just prior to bedtime, reflecting back on their experiences "today." Daily administration is essential in order to capture change in the patient's condition over time, including worsening, improvement, and stabilization. There is no weekly or monthly version of the EXACT.

The conceptual framework for the EXACT is provided in Appendix A.

5.2. Time to Complete

Based on data from the initial validation study, patients with a range of exacerbation and COPD severities are able to complete the EXACT electronically in less than 3 minutes. The time to complete the diary decreases as patients become more familiar with instrument content and structure over the first 7 days of administration.

5.3. Readability Assessment

Readability score indices for the EXACT are as follows: Flesch Reading Ease score = 72.0; Flesch-Kincaid Grade Level = 5.7. Both readability scores analyze the length of a text's sentences and the number of syllables per word to derive their score. The Flesch Reading Ease score is rated from 0–100, with higher numbers indicating greater reading ease. The Flesch-Kincaid Grade Level score indicates a US grade-level reading equivalency level, with the average US writing and reading comprehension level between 7th and 8th grade.[26]

These scores, together with the qualitative data confirming patient familiarity with the attributes captured in the EXACT and the language used in the instrument, suggest the readability of the instrument is appropriate for the target patient population.

5.4. Scoring

5.4.1. Daily Scores

The EXACT Total score is computed across the 14 items and has a theoretical range of 0 to 100, with higher values indicating a more severe condition. The total score is used in the determination of exacerbation frequency, severity, and duration of exacerbation. Specifically, changes in the total score are used to define onset and recovery from an exacerbation event and the magnitude of that event.

Additional information regarding the patient's condition can be obtained through 3 domain scores embedded in the measure: Breathlessness, Cough & Sputum, and Chest Symptoms. These scores also range from 0 to 100, with higher scores indicating more severe symptoms.

Algorithms and SAS programming language for computing daily scores on the EXACT are provided in Appendix B.

5.4.2. Frequency, Severity, Duration

The EXACT provides information frequency (counts), severity (score), and duration (days) of symptom-defined events and the severity of symptoms around MTEs. Several threshold values are required to use the EXACT to assess symptom-defined exacerbations, including values indicating onset and recovery of an exacerbation event in individual patients.

Deteriorations (increase in EXACT Total score) greater than or equal to 9 points sustained for 3 days or 12 points for 2 days indicate an EXACT event has occurred. Improvement (decline in EXACT Total score) of greater than or equal to 9 points from the maximum observed value during the first 14 days of an event that is sustained for 7 days indicates recovery, with the first of the 7 days serving as the recovery day. Severity is indicated by the worst (i.e., highest) EXACT score during the course of the event.

Additional information related to scoring frequency, severity, and duration of events is provided in Appendix B.

6.0 TRANSLATIONS

6.1. Translation Methodology

To optimize quality and availability and to ensure consistent use of translated versions of the EXACT across studies, Evidera oversees all translations of the instrument and maintains the EXACT translation files for distribution. Translation methods follow the Principles of Good Practice for Translation and Cultural Adaptation, an ISPOR Task Force Report,[27] including item definition; dual forward translation; reconciliation; dual back translation; back translation review; harmonization; in-person cognitive testing with COPD patients in each target country using a standardized interview script; analysis of cognitive testing results; clinician review as-needed to verify terminology; finalization; and dual proofreading.

A critical step in ensuring consistency across translations was the development of an item definition document (IDD) which was distributed to all linguistic teams. The IDD provided linguists with the item stems and item response options, as well as the intended meaning/interpretation of terms in the item/response options. Foreseeable translation issues and points of clarification were also outlined and linguists were provided with a list of acceptable and unacceptable alternative terms or phrases to consider when necessary. Linguists were instructed to use this information in the translation of the EXACT. Furthermore, linguists were instructed that for words and phrases that are repeated throughout the EXACT, it was imperative that a consistent translation be created (e.g., "moderately" was to be translated consistently for each response option), or, if this was not possible, that the reason be carefully detailed in the report.

The purpose of following a formal translation methodology that includes linguistic validation is to obtain translated versions of the EXACT that are both conceptually equivalent to the English source version and easily understood by the target population.

6.2. Available Translations

A list of available translations is provided on the EXACT-PRO Initiative website (www.exactproinitiative.com), and is updated as new translations become available. Translation

certificates ensuring good practices in translation and cultural adaptation for each translation are available upon request. Please note that licensing fees may apply.

As languages are tested in additional countries or other issues arise, modifications can be made to translations based on the results of this new information. Therefore, licensees are strongly encouraged to download translations directly from the website with each use.

Translations are available for the EXACT only; translation of device-specific instructions for ePRO administration is the responsibility of the sponsor and ePRO vendor.

7.0 METHODS OF ADMINISTRATION

7.1. Paper-Pen Administration

The EXACT was designed and tested as an eDiary on a handheld device. With the exception of qualitative data from cognitive interviews, which supported content validity using paper-pen format, no data are available on the performance characteristics of the EXACT in this format. Limitations of paper-pen diaries include the inability to determine respondent compliance with daily data entry, the inability to track respondent entries and/or compliance in real time, inability to prevent skipped items or responses, as well as the inability to prevent marking more than 1 response for the same question.

Electronic administration is *strongly* recommended. If paper-pen mode *must* be used, the English version of the booklet format used in the cognitive interviewing phase of instrument development is recommended and is available under a licensing agreement with Evidera. Translated versions of the booklet format are not available. Transferring and formatting certified translations of the EXACT into a booklet format suitable for use in an international study is the responsibility of the sponsor.

7.2. Electronic Data Capture

7.2.1. Electronic Handheld Devices

During the item reduction and validation study, patients completed the EXACT on a PDA device, the Palm® Tungsten E2. Since that time, a variety of handheld devices have been used.

Specifications for administering the EXACT via handheld devices and information related to device selection and a description of the EXACT ePRO Vendor Certification program is provided on the EXACT-PRO Initiative website (www.exactproinitiative.com).

7.2.2. Tablet, Laptop, Web-based Systems

Performance characteristics of the EXACT administered via tablet, laptop, or desktop computer are not yet available. Those interested in using a web-based system should consider screen size and presentation style (what respondents see) across web-based platforms and devices and attempt to optimize consistency and ease of use across study patients.

7.2.3. Interactive Voice Response (IVR)

Data on the performance characteristics of the EXACT administered via IVR are not yet available. However, Evidera can provide a script for IVR administration and guidance on design and features for the system upon request. General guidelines include:

- A response must be selected to proceed to the next question.
- The instructions should remind the patient that there are 14 items. Sample script includes:

  You will be asked 14 questions. After each question and each of the response choices are read to you, please press the corresponding number on your telephone to indicate your answer. You can press the appropriate response at any time.

- In order to allow the patient enough time to think back over the entire day, include a delay response after 5 seconds if the patient has not responded to a question (e.g., "to repeat the question, press #").
- Include a cue that would encourage patients to answer all of the questions (e.g., "You have completed half of the questions. You have only 7 more to finish.").

7.3. ePRO Implementation

The sponsor is responsible for selecting and contracting with the ePRO vendor and ensuring that the proper licenses are in place. *ePRO vendors are not licensed nor permitted to distribute the EXACT in any form or language without the appropriate license in place, nor are they permitted to translate the instrument independent of Evidera*. To ensure consistency across studies, Evidera holds and distributes all translations of the EXACT.

Certain ePRO devices have character/space limitations that can make it difficult to load or view certain languages. Sponsors should keep this in mind when selecting an ePRO device to ensure suitability across the languages to be used in the study/trial.

Each ePRO vendor has their own method of uploading translations. Sponsors are advised to confirm the format required by the selected ePRO vendor to upload translations into their specific software/system (e.g., Excel file, Word document, string document, etc.) at the beginning of a project. Evidera will provide all licensed translations in a Word document. Each translation is written out in a 2-column table, with the English on the left and the translated text on the right. The sponsor or ePRO vendor is responsible for converting the translation into a format compatible with the selected ePRO vendor's requirements.

Evidera strongly recommends screenshot proofreading for each language prior to final programming and deployment, even if an ePRO vendor has worked with an EXACT translation previously.

Please see the EXACT-PRO Initiative website (www.exactproinitiative.com) for additional information on the EXACT ePRO certification program and list of certified vendors.

7.4. Additional Diary Questions

Investigators may be interested in asking study patients to complete additional questions, such as rescue medication use, sputum color, or health care utilization, as part of their electronic diary. Any additional

questions should be asked *either before or after* the EXACT items. Because context is important to the reliability and validity of a measure, additional questions should *not be intermingled* with the EXACT.

7.5. Maintenance, Storage and Compliance of eData

In recognition of the FDA guidelines on electronic data capture,[12] Evidera recommends that plans for the maintenance, storage, and transmission of electronic data be developed and documented in compliance with current guidelines and best practices prior to initiating use of the EXACT. Transmission logs/tracking systems with audit trails should be used to ensure quality data capture.

8.0 STUDY SITE AND PATIENT TRAINING

8.1. Study Site Training and Administration

Study personnel should be trained on the following procedures to introduce a patient to the EXACT.

- Sit down with the patient at the beginning of the study and show them an example of the EXACT diary in the mode or device on which it is to be administered.
- Inform the patient that the EXACT is to be completed every evening, just before going to bed.
- Instruct patients to reflect on their day and answer the questions based on how they felt over the day.
    - Instruct the patient to respond in a way that is representative of the entire day.
- Remind patients that there are no right or wrong answers.
- Highlight for patients that the EXACT has 14 items.
    - All 14 items are to be answered daily for the study period as specified in the study protocol.
    - Point out that answers cannot be skipped. (This is particularly important for the paper-pen format. The ePRO device should be programmed not to move forward until an answer is selected.)
    - If a patient is unsure how to answer an item, instruct the patient to select the answer that best describes how they feel.

8.2. Training Specific to ePRO Administration

Study personnel should be trained on the following procedures if the EXACT is administered using an ePRO platform.

- Have the patient log-in to the ePRO device using a specific password and then read and answer all of the 14 questions to ensure comprehension of the EXACT and ePRO device.
- If the patient is responsible for sending in their data, have the patient practice this step.
- Remind patients that the data entry periods have defined lengths and that the ePRO device has alarms to remind the patient to enter data at the correct time.

- Patients should be instructed to upload the EXACT diary data per study protocol.
- The site may be responsible for initiating the Patient ID in the tracking database as (if) provided by the ePRO vendor.
- The site may be responsible for reviewing/ensuring the EXACT diary data is being uploaded by patients at the protocol-specified times.
- Per study protocol, the site (or clinical trial monitor) should monitor the data upload to ensure no missing data and take appropriate actions based on protocol directives.
- ePRO battery levels can also be monitored through many tracking databases and should be watched closely when possible.
- Patients should be provided take-home instructions on how to use the device and send data (if applicable).

Additional information on device-specific training should be provided by the ePRO vendor.

8.3. Training Specific to Paper-Pen Administration

Administration of the EXACT in paper-pen format is not recommended. If this method is absolutely necessary, the diary booklet format used in cognitive interviews should be used. The following guidelines for personnel training should be followed:

- Have the patient read the instructions on the cover sheet of the EXACT and ensure the instructions are understood.
- Remind the patient that the EXACT is to be completed every evening, just before going to bed.
- Have the patient answer all of the 14 questions to ensure comprehension of the EXACT items.
- At each study-specific clinic visit, ask the patient to bring in their old EXACT diary booklet(s), in order to exchange it for a new one.
- At each study visit, the site is responsible for reviewing the completed EXACT diary at that time to ensure completeness.
    - If answers/days have been left blank, query the patient about the reason.

        ** Do **not** ask patients to complete the missing fields.

    - If more than 50% of the data are missing:
        - Follow-up with the study principal investigator to ensure that the patient is still eligible.
        - Initiate follow-up phone calls as needed to the patient to remind them to complete the EXACT diary as outlined in the study-specific protocol.

9.0 WEBSITE

The EXACT-PRO Initiative website (www.exactproinitiative.com) is an excellent source of information about the EXACT and E-RS. The website has 2 parts, with users given public access and/or licensed user-only access. The public website presents information about the EXACT and E-RS, including an overview of both instrument's development, an up-to-date list of available translations, ePRO information, publications, licensing information, regulatory resources, and frequently asked questions. The user-only website is available to academic and pharmaceutical licensees and includes downloadable copies of the EXACT, E-RS and related User Manuals, scoring programs and test data to facilitate EXACT scoring, PRO overview and EXACT/E-RS development slide decks, and password-protected EXACT translations. Licensees should always download translations directly from the website in order to ensure the most up-to-date version is used. Please email exactpro@evidera.com to obtain your user-only account information and translation passwords.

10.0 COPYRIGHT AND LICENSING

To protect the integrity of the instrument, the EXACT instrument, the User Guide and Scoring Instructions, EXACT Scoring program, EXACT test data, and any portions, subsets or versions of the above, any modifications to the above, translations of the above, or derivative works based on the above (regardless of whether made by Evidera, Licensee, or others), together with all intellectual property rights contained in or related to any of the foregoing, are owned by Evidera, previously United BioSource Corporation (EXACT© 2013, Evidera, Inc. All rights reserved.). The instrument may not be used or altered in any way without prior, written permission from Evidera.

The EXACT is available for use under a formal licensing agreement. Please contact a member of the Evidera EXACT team (exactpro@evidera.com) for additional information.

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APPENDIX A:

EXAMPLE ENDPOINT MODELS AND CONCEPTUAL FRAMEWORK

Example Endpoint Models

Note: Provided for illustrative purposes; not intended as comprehensive or exclusionary.

Table A.1. Example Endpoint Model – Maintenance/Prevention Trial[a]

Efficacy Endpoints	Measure
Primary	
Reduction in exacerbation frequency	Rate (per person per year) – All MTEs Rate – Moderate (clinic visits or urgent care) Rate – Severe (hospitalizations)
Key Secondary Endpoints	
Reduction in unreported events[b]	Rate (per person per year) Unreported (symptom-defined) events (EXACT)
Time to first exacerbation	Days from treatment initiation to first event Days to first clinic visit or hospitalization Days to first unreported, symptom-defined event[b] (EXACT)
Reduction in exacerbation severity	Frequency of Severe, Moderate, Mild Events Frequency of Hospitalizations (Severe) Frequency of Clinic Visits (Moderate) Frequency of Unreported Events (Mild[b]) Symptom severity for exacerbations treated in the clinic or at home (unreported) (EXACT severity score)
Improvement in airflow obstruction	Post-dose FEV_1
Safety Objectives and Endpoints	
Presence of drug-related adverse events	Adverse event reporting form
Exploratory Endpoints	
Duration of symptom-defined events	Day 1 to Recovery Day (EXACT)
MTE treatment duration	Length of oral corticosteroids, antibiotics, or hospital stay
Change in health status	St. George's Respiratory Questionnaire

[a]See Table 1.0 "Standardizing Exacerbation Outcomes in Clinical Studies of COPD" for measurement descriptions.
[b]Characterized as "mild" in EMA COPD Guideline.[i]

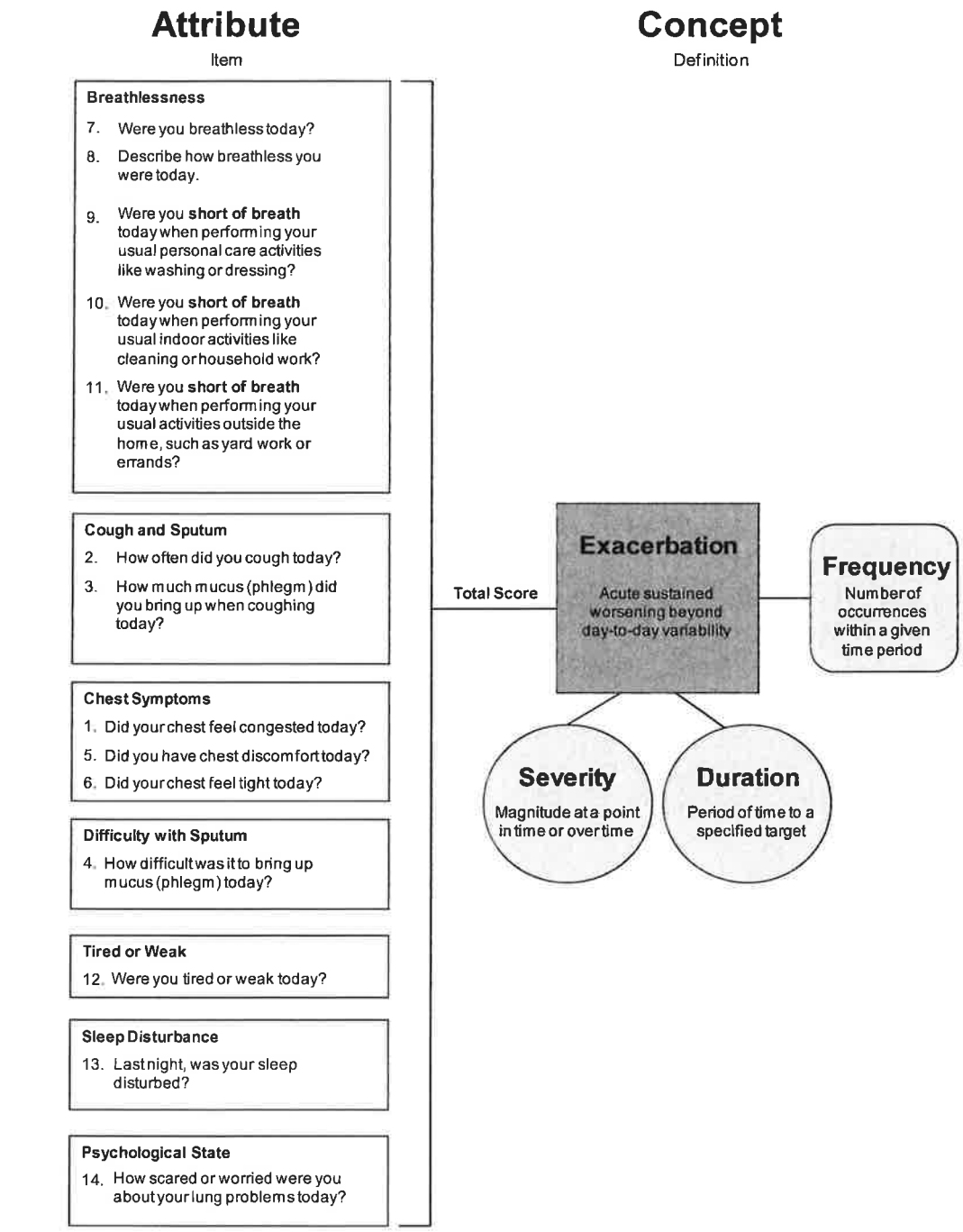
[i] European Medicines Agency, Respiratory Drafting Group. Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD). EMA/CHMP/483572/2012. 2012; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/08/WC500130880.pdf. Accessed October, 2014.

Table A.2. Example Endpoint Model – Acute-Treatment Trial

Efficacy Endpoints	Measure
Primary	
Time to symptom improvement	Days to symptom-defined recovery (EXACT)
Key Secondary Endpoints	
Number of patients with a clinically meaningful response at Day X (Responders)[a]	N (%) patients with symptom-defined recovery by Day X. (EXACT)
Clinical relapse or recurrence	Symptomatic worsening after recovery (EXACT) and need for change in medication with microbiological testing to distinguish persistent versus new pathogen)
Number of treatment failures by Day Z	Persistent symptoms (EXACT) with need for change in medication *or* death by Day Z
Exacerbation symptom severity	Symptom severity score during the event (EXACT)
Safety Objectives and Endpoints	
Presence of drug-related adverse events	Adverse event reporting form
Exploratory Endpoints	
Medical treatment duration	Length of oral corticosteroids, antibiotics, or hospital stay
Change in rescue medication use	Daily diary of albuterol use
FEV_1	Post-dose FEV_1 at Day Z or time of EXACT pre-specified value
Change in health status	St. George's Respiratory Questionnaire

[a]May include or require independent clinician assessment of recovery with no need for change in treatment, Day X.

Figure A.1. Conceptual Framework



APPENDIX B:

EXACT SCORING INSTRUCTIONS

EXACT SCORING ALGORITHMS AND ANALYTICAL DEFINITIONS

Introduction

The **EXA**cerbations of **C**hronic Pulmonary Disease **T**ool (EXACT™) is a patient-reported outcome (PRO) measure designed to standardize the method for evaluating the frequency, severity, and duration of both reported and unreported acute exacerbations of COPD and chronic bronchitis in international studies and clinical trials.

The EXACT Total score is computed across the 14 items and has a theoretical range of 0 to 100, with higher values indicating a more severe condition. The total score is used in the determination of exacerbation frequency, severity and duration of exacerbation. Specifically, changes in the total score are used to define onset and recovery from an exacerbation event and the magnitude of that event.

Additional information regarding the patient's condition can be obtained through 3 domain scores embedded in the measure: Breathlessness, Cough & Sputum, and Chest Symptoms. These scores also range from 0 to 100 with higher scores indicating more severe symptoms.

EXACT Programming Macros

Evidera has created 2 SAS programs to aid licensed users in scoring the EXACT. Program ExactDaily.sas is used to compute EXACT total scores or subscale scores from item responses. Program ExactEpisodes.sas is used to identify exacerbations in clinical studies enrolling patients considered clinically stable. It does not compute EXACT total scores or subscale scores. The program ExactEpisodes.sas identifies the day of onset and first day of recovery, computes the duration of each episode, and creates an output file with supportive information. This program should not be used for data from subjects enrolled during an acute exacerbation of COPD.

For licensed users who are implementing the EXACT exacerbation-identification algorithm in a language other than SAS, test data is available to ensure programming is correctly identifying symptom-defined events using the EXACT events.

Both programs, along with supporting documentation and the test data set are available to download under the licensed user-only access section of the EXACT-PRO Initiative website (www.exactproinitiative.com).

The following sections describe how the EXACT daily scores are computed and symptom-defined events identified.

Computing EXACT Daily Scores

Raw Scores

Raw scores are assigned to each item response option, as shown in Table 1 of this Appendix. Note that items 3, 8, 9, 10, 11, and 14 have unique scoring instructions. Item responses should be converted to item-level scores as the first step in scoring.

The recommended programming for the electronic EXACT diary does not allow a study patient to skip individual items. If a patient tries to skip a question, a message should appear to prompt the patient to

complete the question. Thus, no missing data are expected for individual items in the electronic data capture setting.

EXACT Total Score

An EXACT Total score should be computed for each day of diary collection. The EXACT Total score is based on a logit scoring system with conversion to a 0 to 100 scale for ease of interpretation and use. The scores are computed using a simple conversion table, by hand or electronically (e.g., software data interface for ePRO devices or statistical software, such as SAS®). To compute the EXACT Total score:

Convert each original item response code to an item-level raw score, by matching the responses to Table 1 below. For example, for question 1, if the data-collection form or system encodes the response of "Not at all" as code 1, recode it to a zero (0) to match Table 1, question 1. Note that some questions group certain original item response codes into a single item-level raw score; for example, question 3 groups original responses of "A little" and "Some" into the item-level raw score of 1.

Sum the item-level raw scores of the 14 EXACT items to form the raw summed score. Note: do not sum the original item responses; sum the recoded values obtained in the step described above.

For each raw summed score, look up the corresponding EXACT Total score from Table 2 of this appendix. The EXACT Total score ranges from 0 to 100. Sample SAS program code for converting raw summed scores to the EXACT Total score is provided in Table 3 of this appendix.

If the EXACT Total score is 0, change it to missing. This scoring rule is based on previous validation work demonstrating that moderate-to-severe COPD patients will experience symptom(s) each day, and a score of zero on all 14 EXACT items is likely to represent a situation where in order to complete the diary quickly, the respondent did not accurately report their daily symptom(s).

Where no diary entry exists for a given day, create a record in the data file for that day and enter a missing value for the EXACT Total score. Each day a patient is followed in the study must have a record for the day, even if there is no data and the EXACT Total score is missing.

Domain Scores

Three respiratory symptom domains are also embedded within the EXACT measure: Breathlessness, Cough & Sputum, and Chest Symptoms.

To compute domain scores:

Item assignments to domains are as follows. Please note that items 4, 12, 13, and 14 do not correspond to a domain score and are not used in domain-specific analyses.

Breathlessness – Items 7, 8, 9, 10, and 11

Cough & Sputum – Items 2 and 3

Chest Symptoms – Items 1, 5, and 6

For each day, sum the item-level raw scores of the items comprising the domain to form the domain raw summed score. If no diary entry exists for a given day, leave the domain raw summed score missing.

Each domain raw summed score has its corresponding "EXACT Domain" score. For each domain raw summed score, look up the corresponding EXACT domain score from Table 3 below. If no diary entry exists for a given day, leave the EXACT domain score missing.

If the daily EXACT domain score is 0, change it to missing. This scoring rule is based on previous validation work demonstrating that moderate to severe COPD patients will experience symptom(s) each day, and a score of zero on all 14 EXACT items is likely to represent a situation where in order to complete the diary quickly, the respondent did not accurately report their daily symptom(s).

Computing Event Frequency, Duration, and Severity

All exacerbation parameters are based on the EXACT Total score.

Baseline EXACT Total Score

For studies enrolling patients during a stable baseline period, baseline EXACT values are computed and used to identify the onset of EXACT events.

Baseline is defined as a period during which the patient is considered within his/her condition as stable or their usual state (i.e., study run-in period prior to randomization). The baseline EXACT score is the mean within-patient score over 7 days, with data present for a minimum of 4 of the 7 days. If fewer than 4 days of data are available, the EXACT Baseline score cannot be calculated.

Resetting Baseline EXACT Total Score

Over the course of a trial/study, Baseline should be reset every 4 weeks (28 days) in the absence of an EXACT-based event to allow for improvements or deterioration in disease state over time, as follows:

Event-free Periods (Stable Reset Baseline - $Baseline_{SR\#}$)

For patients who do not experience an EXACT-based event during Weeks 1 to 4 of the study, Baseline is reset beginning Day 1, Week 5. Data from the last 7 days of the 4 week period (Week 4; Days 22–28) are used for this purpose, with a minimum of 4 days of data required to compute the reset value ($Baseline_{SR1}$). If 4 of the last 7 days of data are not present, the Baseline will not be reset; the previous Baseline value will be used until the next reset period.

Using this reset Baseline ($Baseline_{SR1}$), the data are examined moving forward from Week 5, Day 1 for evidence of an EXACT-based event during the subsequent 4 weeks (Week 5, Day 1 to Week 8, Day 7). In the absence of such an event, the Baseline is reset again ($Baseline_{SR2}$) beginning Day 1, Week 9. Data from the last 7 days of the 4 week period (Week 8; Days 1–7) are used for this purpose, with a minimum of 4 days of data required to compute the reset value ($Baseline_{SR2}$). If 4 of the last 7 days of data are not present, the Baseline will not be reset; the previous Baseline value will be used until the next reset period.

The resetting process continues every 28 days throughout the duration of the study or until an EXACT event occurs (see instructions below). Resetting is not required for studies less than 28 days duration.

Re-Setting Following an EXACT Event (Event Reset Baseline - $Baseline_{ER\#}$)

If or when an EXACT event occurs, the patient's Baseline value is re-established following recovery. To reset Baseline values following an exacerbation, the patient's mean EXACT score during the fourth week following Recovery (Days 22–28 post-Recovery) is used. If the patient experiences a new EXACT event during this 4 week period (Days 1 to 28 post-Recovery), the Baseline is not reset until the fourth week following Recovery from that subsequent event. A minimum of 4 days of data are required to reset Baseline. If 4 of the last 7 days of data are not present, the Baseline will not be reset; the previous Baseline value will be used until the next reset period.

The reset Baseline following Recovery from the first exacerbation ($Baseline_{ER1}$) is used to identify subsequent events during the next 4 week period. In the absence of an event during this 4 week period, the Baseline value is reset again ($Baseline_{ER2}$), beginning Recovery Week 5, Day 1, using data from the final 7 days of the 4-week event-free period (Recovery Week 4; Days 1–7 post-Recovery). If 4 of the last 7 days of data are not present, the Baseline will not be reset; the previous Baseline value will be used until the next reset period.

This process of resetting Baseline in the absence of an EXACT event continues through the duration of the study.

Event Frequency

Two parameters are required to identify event frequency: (1) Baseline and (2) Onset. Baseline has been previously described. Onset is defined as the first day in which the patient experiences an acute, sustained worsening of their baseline condition.

Onset

Onset is identified in 1 of 2 ways: *Either* (1) an increase in EXACT score ≥12 points above the patient's mean Baseline for 2 consecutive days, with Day 1 of the 2 days serving as Day_1 (Onset) of the event **OR** (2) an increase ≥9 points above the patient's mean Baseline for 3 consecutive days, with Day 1 of the 3 days serving as Day_1 (Onset) of the event. The presence of either constitutes Onset of an event. Note that the requirement of consecutive days is the reason the data file must have a record for every day for a patient, even if the EXACT score is missing.

Event Duration

Event Duration requires identification of the following parameters: (1) Onset; (2) 3-day Rolling Average; (3) Maximum Observed Value; (4) Threshold for Improvement; and (5) Recovery. It is possible that Improvement may occur at multiple time points during an event and that this Improvement may or may not reflect full Recovery.

3-day Rolling Average

A 3-day Rolling Average is used to account for day-to-day variability in EXACT scores. This is operationalized as a 3-day rolling of the mean EXACT score [Day_{x-1}, Day_x, Day_{x+1}], with the Day 1 computation based on Days 1 (Onset) and 2 of the event; Day 2 as the mean of days 1, 2, 3; and continuing forward sequentially (Days 2, 3, 4; Days 3, 4, 5, etc.). Only 1 of the 3 data points needs to be present for this computation. The 3-day Rolling Average is initiated on Day 1 of Onset and ends on Day 1 of Recovery.

Maximum Observed Value (MOV)

The Maximum Observed Value (MOV) is the highest rolling average EXACT score observed in the context of an EXACT exacerbation within the first 14 days of the exacerbation. The MOV is allowed to increase over the first 14 days of an exacerbation. Starting on day 15 of an exacerbation, the MOV stays at the level on the 14th day for the remainder of the exacerbation.

Threshold for Improvement

Improvement is a decrease in the rolling average EXACT score ≥9 points from the previous day's MOV during an event.

Recovery

Recovery is defined as the first day in which a patient experiences a persistent, sustained improvement in their condition. See above for the definition of Improvement. Improvement must be present for 7 consecutive days. The first day of the 7-day period is designated the day of Recovery (Day_R).

Based on the scoring algorithm for Recovery, EXACT exacerbations can be categorized as Recovered, Censored, or Persistent Worsening. Recovered is defined as an EXACT exacerbation meeting the Recovery definition outline above. Censored is defined as an EXACT exacerbation that began within 28 days of study termination and did not meet the Recovery definition during that time period. Persistent Worsening is defined as an EXACT exacerbation that never meets the Recovery criteria, i.e., the patient's EXACT scores never meet the Recovery definition. All analyses including Recovery should be based on resolved events only, unless otherwise specified.

New Event

Score increases consistent with Onset and occurring any time after the 7th day of the Recovery period are counted as a new event. To identify a new exacerbation, use the last available Baseline value. The reset Baseline value ($Baseline_{RX}$) is used if a patient's Baseline was re-established prior to the EXACT exacerbation; otherwise the original Baseline value from study initiation is used. If no new event is experienced during the 4 week period post-Recovery, Baseline is reset in the manner described previously. There may be a new event beginning on the day after the day of recovery, but not on the day of recovery.

Duration

Duration is the length of time in days from Onset to Recovery. Duration is calculated as the difference, in days, between the day of Onset (Day_1) and the day of Recovery (Day_R). The day of Recovery (Day_R) is not included in calculating Duration days.

Event Severity

Severity is the highest EXACT Total score during the period from Onset (Day1) to Recovery (Day_R), not using the 3-day rolling average.

Table 1. Annotated EXACT for Raw Score Assignment

The following annotates the raw item-level score values associated with each text response for the EXACT items. Please take note of items with collapsed response scale scoring, highlighted in **bold.**

1. Did your chest feel congested today?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	4. Extremely
2. How often did you cough today?	0. Not at all
	1. Rarely
	2. Occasionally
	3. Frequently
	4. Almost constantly
3. How much mucus (phlegm) did you bring up when coughing today?	0. None at all
	1. A little
	1. Some
	2. A great deal
	3. A very great deal
	NOTE: Score "A little" and "Some" the same.
4. How difficult was it to bring up mucus (phlegm) today?	0. Not at all
	1. Slightly
	2. Moderately
	3. Quite a bit
	4. Extremely
5. Did you have chest discomfort today?	0. Not at all
	1. Slight
	2. Moderate
	3. Severe
	4. Extreme
6. Did your chest feel tight today?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	4. Extremely

7. Were you breathless today?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	4. Extremely
8. Describe how breathless you were today:	0. Unaware of breathlessness
	1. Breathless during strenuous activity
	2. Breathless during light activity
	3. Breathless when washing or dressing
	3. Present when resting
	NOTE: Score "Breathless when washing or dressing" and "Present when resting" the same.
9. Were you short of breath today when performing your usual personal care activities like washing or dressing?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	3. Extremely
	4. Too breathless to do these
	NOTE: Score "Severely" and "Extremely" the same.
10. Were you short of breath today when performing your usual indoor activities like cleaning or household work?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	3. Extremely
	3. Too breathless to do these
	NOTE: Score "Severely," "Extremely," and "Too breathless to do these" the same.
11. Were you short of breath today when performing your usual activities outside the home such as yard work or errands?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	3. Extremely
	3. Too breathless to do these
	NOTE: Score "Severely," "Extremely", and "Too breathless to do these" the same.

12. Were you tired or weak today?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	4. Extremely
13. Last night, was your sleep disturbed?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	4. Extremely
14. How scared or worried were you about your lung problems today?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	3. Extremely
	NOTE: Score "Severely" and "Extremely" the same.

Table 2. Raw Summed Score to Scale Score Conversion Table for EXACT Total Score

Raw Summed Score	EXACT Total Score	Raw Summed Score (continued)	EXACT Total Score
0	0	26	50
1	8	27	51
2	13	28	52
3	17	29	53
4	20	30	54
5	23	31	55
6	25	32	57
7	27	33	58
8	28	34	59
9	30	35	60
10	31	36	61
11	33	37	63
12	34	38	64
13	36	39	65
14	37	40	67
15	38	41	68
16	39	42	70
17	40	43	72
18	41	44	73
19	42	45	75
20	43	46	77
21	44	47	80
22	46	48	83
23	47	49	87
24	48	50	92
25	49	51	100

This conversion table converts raw summed scores to a 0 to 100 scale, for ease of interpretation.

Table 3. Raw Summed Score to Scale Score Conversion Table for EXACT Domains

Domain Raw Summed Score[a]	Breathlessness Domain Score	Cough & Sputum Domain Score	Chest Symptoms Domain Score
0	0	0	0
1	11	13	12
2	19	25	23
3	25	39	31
4	30	56	38
5	34	72	45
6	38	86	52
7	42	100	58
8	45		65
9	48		72
10	52		79
11	56		88
12	60		100
13	65		
14	71		
15	78		
16	87		
17	100		

[a]The maximum score for the chest symptoms domain is 12. The maximum score for the Cough & Sputum domain is 7.

Table 4. SAS® Coding Instructions for Computing Daily Scores

The following example assumes all original item responses are coded as 0, 1, 2, 3, 4, etc. on the data collection forms or electronic data capture system, ordered from least severe to most severe. In this case, only items 3, 8, 9, 10, 11, and 14 need to be recoded to form item-level scores. If the original codes begin with 1 for least severe (e.g., 1, 2, 3, 4, 5 for question 1), then the codes must be shifted to a 0 starting point for all items before these SAS statements can be used.

1. Assign raw score values associated with each response category for the EXACT items:	if q3 in (**1**,**2**) then q3=**1**;
	else if q3 in (**3**) then q3=**2**;
	else if q3 in (**4**) then q3=**3**;
	if q8 in (**3**,**4**) then q8=**3**;
	if q9 in (**3**,**4**) then q9=**3**;
	else if q9 in (**5**) then q9=**4**;
	if q10 in (**3**,**4**,**5**) then q10=**3**;
	if q11 in (**3**,**4**,**5**) then q11=**3**;
	if q14 in (**3**,**4**) then q14=**3**;
	rawsum=sum (of q1-q14);
	breathlesssum=sum (of q7-q11);
	coughsum=sum (of q2 q3);
	chestsum=sum (of q1 q5 q6);

2. Assign the EXACT Total score for each raw summed score:	select (rawsum); when(**0**) Exact_total=**0**; when(**1**) Exact_total=**8**; when(**2**) Exact_total=**13**; when(**3**) Exact_total=**17**; when(**4**) Exact_total=**20**; when(**5**) Exact_total=**23**; when(**6**) Exact_total=**25**; when(**7**) Exact_total=**27**; when(**8**) Exact_total=**28**; when(**9**) Exact_total=**30**; when(**10**) Exact_total=**31**; when(**11**) Exact_total=**33**; when(**12**) Exact_total=**34**; when(**13**) Exact_total=**36**; when(**14**) Exact_total=**37**; when(**15**) Exact_total=**38**; when(**16**) Exact_total=**39**; when(**17**) Exact_total=**40**; when(**18**) Exact_total=**41**; when(**19**) Exact_total=**42**; when(**20**) Exact_total=**43**; when(**21**) Exact_total=**44**; when(**22**) Exact_total=**46**; when(**23**) Exact_total=**47**; when(**24**) Exact_total=**48**; when(**25**) Exact_total=**49**; when(**26**) Exact_total=**50**; when(**27**) Exact_total=**51**; when(**28**) Exact_total=**52**;

	when(**29**) Exact_total=**53**; when(**30**) Exact_total=**54**; when(**31**) Exact_total=**55**; when(**32**) Exact_total=**57**; when(**33**) Exact_total=**58**; when(**34**) Exact_total=**59**; when(**35**) Exact_total=**60**; when(**36**) Exact_total=**61**; when(**37**) Exact_total=**63**; when(**38**) Exact_total=**64**; when(**39**) Exact_total=**65**; when(**40**) Exact_total=**67**; when(**41**) Exact_total=**68**; when(**42**) Exact_total=**70**; when(**43**) Exact_total=**72**; when(**44**) Exact_total=**73**; when(**45**) Exact_total=**75**; when(**46**) Exact_total=**77**; when(**47**) Exact_total=**80**; when(**48**) Exact_total=**83**; when(**49**) Exact_total=**87**; when(**50**) Exact_total=**92**; when(**51**) Exact_total=**100**; otherwise;
3. Assign the Breathlessness domain score for each domain raw summed score:	select (breathlesssum); when(**0**) Breathlessness=**0**; when(**1**) Breathlessness=**11**; when(**2**) Breathlessness=**19**; when(**3**) Breathlessness=**25**; when(**4**) Breathlessness=**30**; when(**5**) Breathlessness=**34**; when(**6**) Breathlessness=**38**; when(**7**) Breathlessness=**42**; when(**8**) Breathlessness=**45**; when(**9**) Breathlessness=**48**; when(**10**) Breathlessness=**52**; when(**11**) Breathlessness=**56**; when(**12**) Breathlessness=**60**; when(**13**) Breathlessness=**65**; when(**14**) Breathlessness=**71**; when(**15**) Breathlessness=**78**; when(**16**) Breathlessness=**87**; when(**17**) Breathlessness=**100**;
4. Assign the Cough & Sputum domain score for each domain raw summed score:	select (coughsum); when(**0**) Coughsputum=**0**; when(**1**) Coughsputum=**13**; when(**2**) Coughsputum=**25**; when(**3**) Coughsputum=**39**; when(**4**) Coughsputum=**56**; when(**5**) Coughsputum=**72**; when(**6**) Coughsputum=**86**; when(**7**) Coughsputum=**100**;

5. Assign the Chest Symptom domain score for each domain raw summed score:	select (chestsum); when(**0**) Chestsymptom=**0**; when(**1**) Chestsymptom=**12**; when(**2**) Chestsymptom=**23**; when(**3**) Chestsymptom=**31**; when(**4**) Chestsymptom=**38**; when(**5**) Chestsymptom=**45**; when(**6**) Chestsymptom=**52**; when(**7**) Chestsymptom=**58**; when(**8**) Chestsymptom=**65**; when(**9**) Chestsymptom=**72**; when(**10**) Chestsymptom=**79**; when(**11**) Chestsymptom=**88**; when(**12**) Chestsymptom=**100**;