E-RS (EXACT-Respiratory Symptoms)

USER MANUAL

(Version 3.0)

October 2014

Contact Information:

EXACT-RS Initiative
Evidera
7101 Wisconsin Avenue, Suite 1400
Bethesda, MD 20814
Phone: 1-301-654-9729
Fax: 1-301-654-9864
exactpro@evidera.com

Web Site: www.exactproinitiative.com

Evidera

TABLE OF CONTENTS

Development of the E-RS was supported by unrestricted funds and/or data provided by the following companies:

AstraZeneca; Boehringer Ingelheim;
Merck & Co, Inc; and Mpex Pharmaceuticals (now Aptalis)

1.0 INTRODUCTION

1.1. Background

Chronic obstructive pulmonary disease (COPD) is a treatable but progressive disease, characterized by persistent airflow limitation with varying degrees of air sac enlargement, airway inflammation that is not fully reversible, and lung tissue destruction. The disease manifests itself in the cardinal respiratory symptoms of breathlessness, cough, and sputum production.[1-7] Spirometry is essential for the diagnosis of COPD and useful for evaluating the efficacy of treatments intended to affect changes in airflow limitation. Despite its usefulness in assessing changes in airflow obstruction over time, spirometry cannot measure or evaluate respiratory symptoms. In fact, studies have found that correlations between patient report of respiratory symptoms and forced expiratory volume in 1 second (FEV_1) are weak[4, 8] and that patient perception of the impact of disease and their health-related quality of life are more closely related to respiratory symptoms than is FEV_1.[9, 10] Clearly, respiratory symptoms are an important component of how patients with COPD feel and function. In order to evaluate the effect of treatment on respiratory symptoms of COPD, a reliable and valid patient-reported outcome (PRO) measure of respiratory symptom severity is needed.

Despite consensus on the defining respiratory symptoms characteristic of COPD, there is no validated diary for evaluating their severity in clinical trials. Several multi-dimensional health status questionnaires, administered periodically during the course of a trial, include information on respiratory symptoms and their impact, but do not capture this information on a daily or weekly basis. Further, they do not include subscales that specifically measure the severity of breathlessness, cough and sputum, and chest symptoms. The Breathlessness, Cough, and Sputum Scale (BCSS),[11, 12] is a daily symptom diary that has been tested for reliability and validity and used in clinical trials of COPD, but was not developed according to the United States (US) Food and Drug Administration (FDA) PRO Guidance.[3] To date, no instrument that assesses the respiratory symptoms of COPD has included patient involvement in the concept elicitation and item generation process—a necessary step in providing evidence of content validity consistent with the FDA PRO Guidance.[3]

1.2. Purpose of the E-RS

The EXACT-Respiratory Symptoms (E-RS) scale was designed to address the need for a standardized PRO measure for evaluating the effect of treatment on the severity of *respiratory symptoms in stable COPD*.

The 11 respiratory symptom items comprising the E-RS are part of an existing measure, the 14-item EXAcerbations of COPD Tool (EXACT). To maintain consistent context of completion, the E-RS is NOT administered separately from the EXACT. The intent is to have 2 uses for 1 set of questions. The EXACT provides information related to acute exacerbations of COPD (frequency, severity, duration of symptom-defined events, and severity and recovery of medically-treated events) while the E-RS provides information specific to respiratory symptoms—severity of respiratory symptoms overall and severity of breathlessness, cough and sputum, and chest symptoms specifically.

All 14 items are completed by patients each evening, prior to bedtime. If a user is not interested in the assessment of exacerbations, the 14 items must still be administered so the context of completion is not altered and score reliability, validity, and responsiveness characteristics are applicable.

The RS-Total score is designed to serve as a primary or secondary efficacy endpoint in clinical trials evaluating the effect of treatment on the severity of respiratory symptoms of COPD. The RS-Total score is computed by taking the sum of the items comprising the instrument. The 3 subscales embedded in the measure, RS-Breathlessness, RS-Cough & Sputum, and RS-Chest Symptoms, can be used as secondary or supportive endpoints to show the effect of treatment on these specific respiratory symptoms.

To protect the integrity of the E-RS, Evidera holds the copyright of the tool with use permitted under a licensing agreement.

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 E-RS for their specific needs, the information is also relevant to broader uses, including non-pharmaceutical trials and natural history studies.

2.1. Disease and Target Population

2.1.1. COPD, Including Chronic Bronchitis

The E-RS 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 1 of several structural abnormalities present in patients with COPD."[4, pp.1] Chronic bronchitis involves persistent or repeated inflammation of the bronchi with excessive bronchial mucus and productive cough for 3 months or more in at least 2 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.[4]

2.1.2. Sample Inclusion Criteria for Clinical Trials

The E-RS is intended for use in the following target population:

- Clinical diagnosis of COPD or chronic bronchitis
- Age: ≥40 years of age
- Current or former smoker with a history of at least 10 pack years
- Stable COPD, defined as being exacerbation-free within 60 days of enrollment

The E-RS was validated in samples from studies with the following inclusion criteria:

- Clinical diagnosis of COPD or chronic bronchitis
- 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
- Symptomatic: breathlessness, cough, sputum, and/or chest congestion

The context of use for the E-RS is currently limited to this target population. Sponsors interested in evaluating the effects of treatment on respiratory symptoms in milder samples and/or those without a history of treatment for COPD exacerbation are responsible for providing evidence of reliability, validity, and responsiveness of the E-RS scores in that target population.

Sponsors are responsible for providing the Agency with requested information related to E-RS score reliability and validity estimates for their study populations.

2.1.3. Other Respiratory Conditions - Excluded

Although asthma is considered a disease of chronic airflow obstruction, the E-RS was not designed for use in this patient population nor those with clinically relevant bronchiectasis. 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 E-RS at this time.

2.2. Clinical Trial Design and Objectives

The E-RS is intended for use in clinical studies, including Phase II and III randomized, controlled trials testing the efficacy and safety of new treatments for patients with COPD. These trials are generally 12 weeks in duration; however, the study length, number and nature of treatment arms, and specific outcome assessments and assessment intervals are determined by the sponsor, based on the target product profile, target claims, and related data requirements. Trials simultaneously examining exacerbation outcomes may last 6 to 12 months.

2.3. Endpoint Positioning

E-RS scores may serve as primary, co-primary, secondary, or exploratory endpoints in clinical trials designed to evaluate the effect of treatment on the severity of respiratory symptoms of COPD, as appropriate to the product and trial design. For pharmaceutical trials, specific endpoint selection and positioning is determined by the study sponsor in concert with the appropriate regulatory review agencies. Examples of endpoint models with respiratory symptom outcomes and the E-RS are provided in

Appendix A. Sponsors are responsible for providing product-specific endpoint models to the Agency as part of their submission process.

2.4. Target Claims (Medical Product Development)

For those interested in using the instrument to collect data in trials designed to support pharmaceutical labeling and/or promotional claims, the following target claims were discussed at the initiation of E-RS development and were included in the E-RS evidence dossiers submitted to the FDA and European Medicines Agency (EMA) for instrument qualification.

- Treatment YY reduces the severity of respiratory symptoms of COPD
- Patients treated with YY reported significantly lower respiratory symptom severity scores than patients treated with XX following ZZ weeks of treatment
    - If the RS-Total score is statistically significant, results for each domain will be presented, consistent with a step-down analytical approach and in the interest of full disclosure:
        - Patients with COPD treated with YY reported significantly greater reduction in breathlessness severity following ZZ weeks of treatment.
        - Patients with COPD treated with YY reported significantly greater reduction in cough and sputum severity following ZZ weeks of treatment.
        - Patients with COPD treated with YY reported significantly greater reduction in chest symptom severity following ZZ weeks 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.

2.5. International Use

To assure suitability of the EXACT—the E-RS parent instrument—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 5.0.

Performance properties of E-RS scores in international studies were examined in the context of 2 randomized controlled trials, as outlined in Section 3.0. 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.

2.6. Method of Administration

The E-RS is always administered as part of the 14-item EXACT, which is a 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 on 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 6.0 of this User Manual. Information on site and patient training is found in Section 7.0.

3.0 DEVELOPMENT AND VALIDATION PROCESS - OVERVIEW

3.1. Development and Initial Validation

The 11 respiratory symptom items comprising the E-RS are part of the 14-item EXACT diary. Content validity is supported through the literature, secondary analyses of qualitative data gathered during the development of the EXACT, and results of an additional prospective qualitative study of patients with stable COPD and no history of exacerbation for at least 12 months.[13] The naming convention was adopted to recognize the origin of the items. The E-RS is not intended to be completed in isolation, but rather is completed by study participants as part of the EXACT.

A 2-step process was used to assess and document the extent to which the E-RS adequately and accurately reflects respiratory symptoms of COPD in a stable state. In Stage 1, qualitative analyses were performed on data gathered during the development of the EXACT (n=63 stable participants; concept elicitation), with analyses focused on the nature and severity of symptoms during a stable state. In Stage 2, focus groups were conducted in a new sample of clinically stable patients (n=21), eliciting data on the

type and severity of their respiratory symptoms. Results of this qualitative research showed 3 categories of respiratory symptoms patients experience when stable: breathlessness, cough and sputum, and chest symptoms, with specific content within each category mapping to the E-RS.[13]

In Phase II, tests of the reliability, validity, and responsiveness of E-RS scores were performed with validation data from the parent instrument (EXACT) using an *a priori* statistical analysis plan (SAP) specific to the E-RS and follow-up post hoc analyses.[13] Exploratory factor analysis (EFA) of the 11 E-RS respiratory items in patients with stable COPD showed the presence of 3 factors that can serve as symptom subscales: RS-Breathlessness (5 items), RS-Cough & Sputum (3 items), and RS-Chest Symptoms (3 items). Evidence of E-RS score internal consistency, reproducibility, responsiveness, and construct validity was also confirmed.[13]

3.2. Validation in Clinical Trials

The first validation study provided evidence of the reliability, validity, and responsiveness of E-RS scores. However, new instruments need to be subjected to multiple tests of reliability and validity. In the case of the E-RS, data were needed to evaluate score performance over longer periods of time. For regulatory review purposes, the instrument also needed testing within the context of a randomized, controlled clinical trial in the target population.

To address these needs, the performance properties of the E-RS 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 had a medical diagnosis of COPD with a FEV_1 % predicted ≤80% and at least 1 medically treated exacerbation the prior year. SAPs for the validation analyses were completed *a priori* with methods and results presented in reports suitable for submission to regulatory agencies as part of the qualification process and published.[14, 15]

3.3. Sensitivity to Treatment Effects

In each of the 3 clinical trials used for validation analyses, the experimental drugs showed no therapeutic effect. Although this facilitated reliability and validity analyses, responsiveness to treatment relative to placebo could not be evaluated. Tests of sensitivity to change were based on changes observed in criterion variables generally associated with symptomatic change. Results showed E-RS scores were sensitive to change in patients showing improvement in health status (3 of 3 trials), symptoms (2 of 2 trials), or exercise tolerance (3 of 3 trials) from Baseline to month 3. Exploratory analyses suggest E-RS scores are also sensitive to symptomatic worsening over 12 weeks.[15]

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).[16] This study showed a significant effect of treatment on respiratory symptoms: (RS-Total score, $p<0.001$, both doses), with subscale analyses showing effects for RS-Breathlessness, ($p<0.001$, both doses), RS-Cough & Sputum (400 µg: $p<0.001$; 200 µg: $p<0.05$), and RS-Chest Symptoms (400 µg: $p<0.001$; 200 µg: $p<0.01$).[16]

Similar findings were seen in a 6-week Phase IIIb randomized, controlled, multicenter clinical trial conducted in the Czech Republic, Germany, Hungary, and Poland, testing the efficacy of aclidinium

versus placebo and tiotropium on COPD symptoms (N=400). This study showed a significant effect of aclidinium and tiotropium on respiratory symptoms versus placebo. Specifically, respiratory scores for aclidinium versus placebo were significant for the RS-Total (mean score improvement = -2.0; p<0.0001) and all domain scores, including RS-Breathlessness (mean score improvement = -1.1; p<0.0001), RS-Chest Symptoms (mean score improvement = -0.5; p<0.01), and RS-Cough & Sputum (mean score improvement = -0.4; p<0.01).[5]

3.3.1. Interpretation Guidelines

Based on results across criterion- and distribution-based methods used in the analyses of the 3 clinical trial datasets, the following responder definitions for symptomatic improvement are proposed:[15]

RS-Total ≥ -2.0 (scale range: 0–40)

RS-Breathlessness ≥ -1.0 (scale range: 0–17)

RS-Cough & Sputum ≥ -0.70 (scale range 0–11)

RS-Chest Symptoms ≥ -0.70 (scale range: 0–12)

Results of exploratory analyses in these datasets suggest symmetrical thresholds for symptomatic decline (i.e., applying ≥ + 2.0; ≥ + 1.0; ≥ + 0.70; ≥ + 0.70 for Total and subscale scores, respectively for symptom worsening). Given the magnitude of symptomatic improvement in responders and symptomatic decline in those whose symptoms worsened, these definitions may also be conservative estimates.[15]

4.0 INSTRUMENT DESCRIPTION

4.1. Structure

The 11 respiratory symptom items comprising the E-RS are part of the 14-item EXACT. The 11 items on the E-RS capture the severity of the cardinal respiratory symptoms of COPD, including breathlessness, cough, sputum, chest congestion, and chest tightness. The RS-Total score quantifies respiratory symptom severity. The 3 subscales embedded in the measure include RS-Breathlessness, RS-Cough & Sputum, and RS-Chest Symptoms (3 items excluded from E-RS score computation assess worry/concern, sleep disturbance, and feeling weak or tired, which are not respiratory symptoms of COPD).

Patients/respondents are instructed to complete the 14-item 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.

The conceptual framework for the E-RS is provided in Appendix A.

4.2. Time to Complete

The E-RS is completed as part of the EXACT daily diary. The initial validation study for the EXACT found that the instrument could be completed in less than 3 minutes by patients with a range of exacerbation

severities. Results indicated not only that patients were able to complete the 14 items quickly, but also that the time it took to complete the EXACT decreased over the first 7 days of administration.

4.3. 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.[17]

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

4.4. Scoring

A daily Total score (RS-Total score) and 3 subscale scores (RS-Breathlessness, RS-Cough & Sputum, and RS-Chest Symptoms) can be computed from the E-RS. The daily RS-Total score is computed by summing the raw score assigned to each of the 11 items and has a theoretical range of 0 to 40, with higher values indicating more severe respiratory symptoms. The same simple summation procedure is used for obtaining the 3 daily domain scores of the E-RS: RS-Breathlessness is the sum of items 7, 8, 9, 10, and 11 (score range 0–17); RS-Cough & Sputum is the sum of items 2, 3, 4 (score range 0–11); and RS-Chest Symptoms is the sum of items 1, 5, 6 (score range 0–12).

Computational instructions are provided in Appendix B.

5.0 TRANSLATIONS

As a derivative measure of the 14-item EXACT, the 11-item E-RS is completed as part of the EXACT daily diary. The information on translations outlined below references the parent instrument.

5.1. 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,[18] 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.

5.2. 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.

6.0 METHODS OF ADMINISTRATION

As a derivative measure of the 14-item EXACT, the 11-item E-RS is completed as part of the EXACT daily diary. The information on methods of administration outlined below references the parent instrument.

6.1. 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.

6.2. Electronic Data Capture

6.2.1. 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.

6.2.2. 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.

6.2.3. 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.").

6.3. 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.

6.4. 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.

6.5. Maintenance, Storage and Compliance of eData

In recognition of the FDA guidelines on electronic data capture,[3] 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.

7.0 STUDY SITE AND PATIENT TRAINING

As a derivative measure of the 14-item EXACT, the 11-item E-RS is completed as part of the EXACT daily diary. The information on study site and patient training outlined below references the parent instrument.

7.1. 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.

7.2. 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.

7.3. 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.

8.0 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.

9.0 COPYRIGHT AND LICENSING

To protect the integrity of the instrument, the EXACT instrument, including the E-RS, the User Guide and Scoring Instructions, Scoring programs, 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.

10.0 REFERENCES

1. Calverley PMA, Georgopoulos D. Chapter 2. Chronic obstructive pulmonary disease: symptoms and signs. *Eur Respir Mon.* 2006;38:7-23.

2. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Pinto Plata V, Cabral HJ. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med.* 2004;350(10):1005-1012.

3. Food and Drug Administration. Guidance for industry on patient-reported outcome measures: use in medical product development to support labeling claims. Silver Spring, MD: Center for Drug Evaluation and Research (CDER). 2009; http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf. Accessed October, 2014.

4. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Diagnosis, Management, and Prevention of COPD. 2013; http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013Feb13.pdf. Accessed October, 2014.

5. Beier J, Kirsten AM, Mruz R, Segarra R, Chuecos F, Caracta C, Gil EG. Efficacy and safety of aclidinium bromide compared with placebo and tiotropium in patients with moderate-to-severe chronic obstructive pulmonary disease: results from a 6-week, randomized, controlled Phase IIIb study. *COPD.* 2013;10(4):511-522.

6. Siafakas NM, Celli BR. Chapter 14. Overall management of stable chronic obstructive pulmonary disease. *Eur Respir Mon.* 2006;38:258-265.

7. Viegi G, Pistelli F, Sherrill DL, Maio S, Baldacci S, Carrozzi L. Definition, epidemiology and natural history of COPD. *Eur Respir J.* 2007;30(5):993-1013.

8. Ries AL. Impact of chronic obstructive pulmonary disease on quality of life: the role of dyspnea. *Am J Med.* 2006;119(10 Suppl 1):12-20.

9. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Oga T, Izumi T. A comparison of the level of dyspnea vs disease severity in indicating the health-related quality of life of patients with COPD. *Chest.* 1999;116(6):1632-1637.

10. Schlecht NF, Schwartzman K, Bourbeau J. Dyspnea as clinical indicator in patients with chronic obstructive pulmonary disease. *Chron Respir Dis.* 2005;2(4):183-191.

11. Leidy NK, Rennard SI, Schmier J, Jones MK, Goldman M. The breathlessness, cough, and sputum scale: the development of empirically based guidelines for interpretation. *Chest.* 2003;124(6):2182-2191.

12. Leidy NK, Schmier JK, Jones MK, Lloyd J, Rocchiccioli K. Evaluating symptoms in chronic obstructive pulmonary disease: validation of the Breathlessness, Cough and Sputum Scale. *Respir Med.* 2003;97 Suppl A:S59-70.

13. Leidy NK, Sexton CC, Jones PW, Notte SM, Monz BU, Nelsen L, Goldman M, Murray LT, Sethi S. Measuring respiratory symptoms in clinical trials of COPD: reliability and validity of a daily diary. *Thorax.* 2014;69(5):443-449.

14. Leidy NK, Murray LT. Patient-reported outcome (PRO) measures for clinical trials of COPD: the EXACT and E-RS. *COPD.* 2013;10(3):393-398.

15. Leidy NK, Murray LT, Monz BU, Nelsen L, Goldman M, Jones PW, Dansie EJ, Sethi S. Measuring respiratory symptoms of COPD: performance of the EXACT- Respiratory Symptoms Tool (E-RS) in three clinical trials. *Respir Res.* 2014;15(1):124.

16. Jones P, Agusti A, Bateman E, Singh D, Lamarca R, de Miquel G, Caracta C, Garcia Gil E. Aclidinium bromide in patients with chronic obstructive pulmonary disease: improvement in symptoms and health status in the ATTAIN study. *Chest.* 2011;140(4_MeetingAbstracts):547A-547A.

17. Xu W, Collet JP, Shapiro S, Lin Y, Yang T, Wang C, Bourbeau J. Negative impacts of unreported COPD exacerbations on health-related quality of life at 1 year. *Eur Respir J.* 2010;35(5):1022-1030.

18. Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value Health.* 2005;8(2):94-104.

APPENDIX A:

EXAMPLE ENDPOINT MODELS AND CONCEPTUAL FRAMEWORK

Sample Endpoint Models

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

Table A.1. Reduction in Respiratory Symptom Severity – Co-Primary Endpoint

Trial Duration: 2-week run-in period followed by randomization to 12 weeks of treatment.

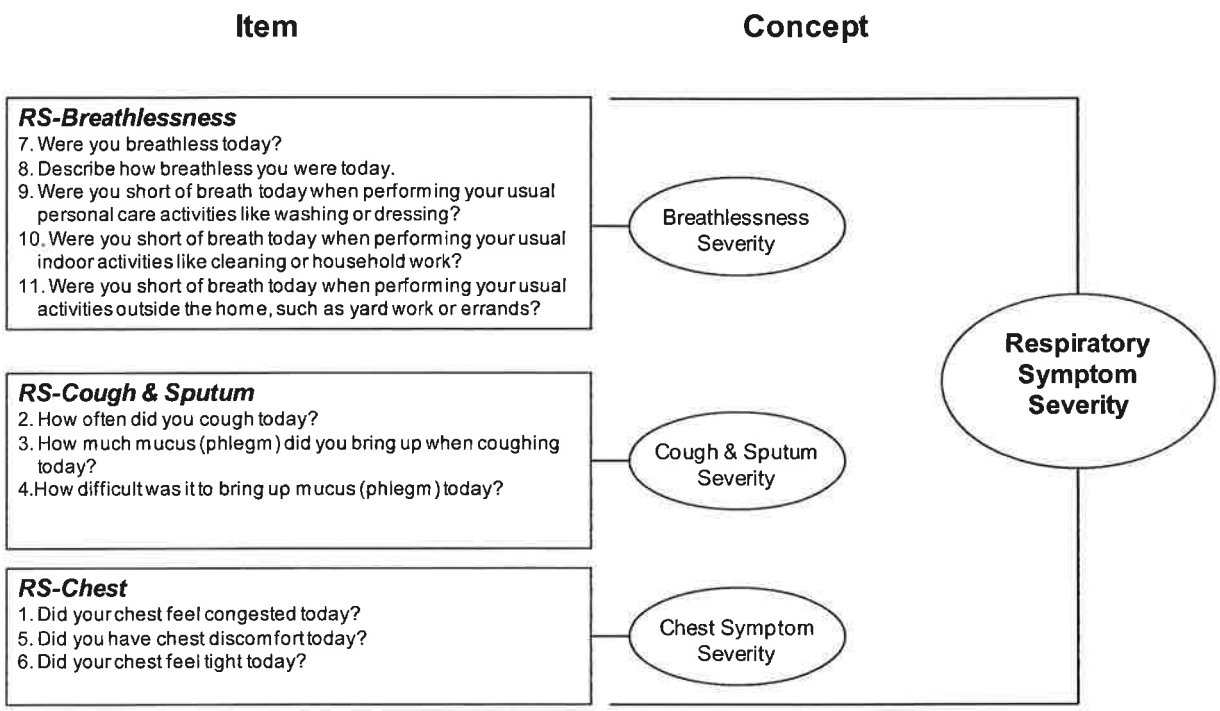
Efficacy Endpoints	Measure
Co-Primary	
Improvement in FEV_1	FEV_1
Reduction in respiratory symptom severity	E-RS: mean RS-Total score
Key Secondary Endpoints	
Reduction in breathlessness severity	E-RS: RS-Breathlessness score
Reduction in cough and sputum severity	E-RS: RS-Cough & Sputum score
Reduction in chest symptom severity	E-RS: RS-Chest score
Rescue medication use	Daily diary of albuterol use
Safety Objectives and Endpoints	
Presence of drug-related adverse events	Adverse event reporting form
Exploratory Endpoints	
Time to reduction in respiratory symptom severity	RS-Total: time to prespecified score
Nighttime awakenings	Daily diary of nighttime awakenings
Health status	St. George's Respiratory Questionnaire

Table A.2. Reduction in Respiratory Symptom Severity – Co-Primary Endpoint

Trial Duration: 2-week run-in period followed by randomization to 6 months of treatment.

Efficacy Endpoints	Measure
Primary	
Improvement in FEV_1	FEV_1
Reduction in respiratory symptom severity	E-RS: RS-Total score
Key Secondary Endpoints	
Reduction in time to first exacerbation	Medically-treated event (MTE)
Reduction in breathlessness severity	E-RS: RS-Breathlessness score
Reduction in cough and sputum severity	E-RS: RS-Cough & Sputum score
Reduction in chest symptom severity	E-RS: RS-Chest score
Health status	St. George's Respiratory Questionnaire
Safety Objectives and Endpoints	
Presence of drug-related adverse events	Adverse event reporting form
Exploratory Endpoints	
Time to reduction in respiratory symptom severity	E-RS: time to prespecified RS-Total Score
Nighttime awakenings	Daily diary of nighttime awakenings
Reduction in rescue medication use	Daily diary of albuterol use
Frequency of exacerbations	EXACT and MTEs
Time to first exacerbation	Time to first MTE Time to first symptom-defined event (EXACT)

Figure A.1. Conceptual Framework



APPENDIX B:

E-RS SCORING INSTRUCTIONS

E-RS SCORING INSTRUCTIONS

Item-Level Scores

Item-level scoring is identical for items common to the EXACT and E-RS.

Convert each original item response code to an item-level raw score, by matching the responses to Table 1 of this Appendix. 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.

The recommended programming for the electronic diary does not allow a study patient to skip individual items. Thus, no missing data are expected for individual items in the electronic data capture setting.

RS-Total Score

A daily RS-Total score is derived by summing across the 11 item-level scores. Note: do not sum the original item responses; sum the recoded values obtained in the step described above. Scores range from 0 to 40.

E-RS Subscale Scores

For each subscale, sum the item-level scores across the items comprising the scale. Note: do not sum the original item responses; sum the recoded values obtained in the step described above.

RS-Breathlessness: Sum scores of items 7, 8, 9, 10, 11 (score range 0–17);

RS-Cough & Sputum is the sum of items 2, 3, 4 (score range 0–11);

RS-Chest Symptoms is the sum of items 1, 5, 6 (score range 0–12).

Daily Scores - File Structure

RS-Total and Subscale scores should be computed for each day of diary collection. If no diary entry exists for a given day, enter missing values. Each day a patient is followed in the study must have a record for the day; days with no E-RS data have the assigned missing value.

Table 1. Annotated E-RS for Raw Score Assignment

The following annotates the raw score values associated with each response category for the E-RS 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.