PRO Instruments

EXACT® PROgram FAQs

Frequently asked questions

What is the regulatory (qualification) status of the EXACT?

On 13 April 2015, the EMA released a Draft Qualification Opinion of Qualification of Exacerbations of Chronic Pulmonary Disease Tool (EXACT), and EXACT-Respiratory Symptoms Measure (E-RS) for Evaluating Treatment Outcomes in Clinical Trials in COPD. This document specifies that the EXACT is qualified as an exploratory endpoint in drug development trials for the prevention of exacerbations in COPD and the E-RS is qualified as an exploratory endpoint in drug development trials evaluating the effect of treatment on respiratory symptoms of COPD.

On 9 January 2014, the FDA released a **Draft Guidance on the Qualification of the EXACT for the Measurement of Symptoms of Acute Bacterial Exacerbations of Chronic Bronchitis in Patients with Chronic Obstructive Pulmonary Disease**. This document specifies that the EXACT is qualified as a measure of symptoms of acute bacterial exacerbation of chronic bronchitis in patients with COPD.

On 8 March 2016, the FDA released a **Draft Guidance on Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease, a Patient-Reported Outcome, for the Measurement of Severity of Respiratory Symptoms in Stable Chronic Obstructive Pulmonary Disease: Qualification for Exploratory Use**. This document specifies that the E-RS: COPD total score is qualified for exploratory use as a PRO instrument to measure respiratory symptoms of stable COPD in clinical studies.

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Can the EXACT and E-RS be used as a primary, co-primary or key-secondary endpoints in clinical trials?

Yes. Users are free to decide how best to select and position EXACT-defined endpoints in their studies and trials. Pharmaceutical sponsors using the instrument in a drug development program should consult with the appropriate regulatory agency (FDA, EMA) regarding their product, trial design, and endpoint model before proceeding to pivotal trials.

In pharmaceutical exacerbation prevention trials, regulatory agencies (FDA, EMA) define COPD exacerbations as HCRU or "medically treated events" (MTEs), i.e., clinic or emergency room visits, hospitalizations, accompanied by a change in treatment. The EXACT was not designed to replace this definition. Rather, the EXACT was created to supplement this endpoint, providing standardized, quantitative data on the severity of symptoms associated with MTEs, as well as data on the frequency, severity, and duration of unreported symptom-defined events.

Note that the EXACT PROject is not pursuing further qualification of these instruments with the FDA or EMA. Both organizations are familiar with the measures and have development and validation documents on file. Pharmaceutical sponsors should work directly with the agency (agencies) as they consider the use and positioning of these measures and endpoints in their drug development programs.

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Has the EXACT or E-RS appeared in product labels?

As of December 2018, the E-RS has appeared in the following European labels (EMA): Duaklir, Elebrato Ellipta, and Trelegy Ellipta.

Both instruments have been used in pharmaceutical trials.

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Can the EXACT or E-RS be used or adapted for use in studies of patients with other diseases?

Although the EXACT was developed and validated for use in COPD, there has been interest in evaluating the suitability of the instrument for evaluating exacerbations and respiratory symptoms in other conditions, including asthma, interstitial pulmonary fibrosis (IPF), cystic fibrosis, and alpha-1 antitrypsin deficiency.

The E-RS:IPF is an adaptation of the E-RS:COPD developed and tested for use in studies of patients with interstitial pulmonary fibrosis. Note that the EXACT PROject is not pursuing qualification of the E-RS:IPF with the FDA or EMA. If you are interested in doing this, please contact **CRGexactpro@thermofisher.com**.

A licensing agreement and qualitative and quantitative work are required to test and support the use of the EXACT and/or E-RS in new populations.

Please contact **CRGexactpro@thermofisher.com** if you are interested in different contexts of use for the EXACT or E-RS.

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How does the E-RS:COPD complement and extend existing PRO measures?

Respiratory symptoms are an important component of how patients with COPD feel and function. Despite consensus on the defining respiratory symptoms characteristic of COPD and the importance of symptom relief to patients and clinicians, there is no standardized, validated diary for evaluating symptom outcomes in clinical trials.

- The Breathlessness, Cough, and Sputum Scale (BCSS) (**Leidy et al. 2003**) 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 (**FDA 2009**).

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.

There are also a number of symptom-specific questionnaires that capture dyspnea or cough. These instruments do not assess each of the defining respiratory symptoms of COPD on a daily basis.

The E-RS was designed to quantify the severity of respiratory symptoms of COPD (breathlessness, cough and sputum, chest symptoms) on a daily basis; thereby capturing day-to-day variability of the patient experience. Developed and validated according to FDA PRO Guidelines, daily and mean weekly scores can be used to characterize respiratory symptom experience and response to treatment.

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Why should the 11-item E-RS:COPD be administered as part of the 14-item EXACT?

Instructions to administer the 11-item E-RS as part of the 14-item EXACT ensure consistent context for item completion across studies. It also permits users to run post-hoc exploratory or secondary analyses using the EXACT scoring algorithms to inform future research.

Subject completion time for the 14-item diary is less than three minutes. We concluded that the advantages of consistent context and dual analytical opportunities (E-RS and EXACT) more than outweigh any marginal effects of reducing the diary by three items.

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When do I use the EXACT versus the E-RS:COPD?

The 14-item EXACT was developed to standardize the symptomatic evaluation of acute exacerbations of COPD and chronic bronchitis. The total score is used to characterize the severity of COPD exacerbations, including unreported and medically treated events (those seen in clinic, urgent care, and hospital settings) and track symptom recovery over time. Threshold rules are used to identify unreported, symptom-defined events which can be described in terms of their frequency, severity, and duration. The EXACT is used to evaluate outcomes in trials testing the effect of treatment on acute exacerbations or to prevent exacerbations of COPD.

The 11-item E-RS quantifies the severity of respiratory symptoms of COPD, including breathlessness, cough, sputum, chest congestion, chest discomfort, and chest tightness. The E-RS was developed to evaluate the effect of treatment on respiratory symptom severity of COPD, i.e., to test the extent to which treatments improve respiratory symptoms, particularly when patients are stable/non-exacerbating.

Because the E-RS is embedded in the EXACT, either or both may be used in a trial, with the underlying hypotheses pre-specified during trial design. Context of use and example endpoint models are included in the User Manual for each measure.

Several example scenarios are as follows.

A 28-day acute intervention trial testing the effect of an anti-infective therapy

- Patients are enrolled during an acute state. The EXACT is used to track symptomatic recovery from the exacerbation.

A 12-month exacerbation prevention trial

- Patients are enrolled in a stable state. The EXACT is used to evaluate the effect of treatment on the symptomatic severity of medically treated events and the frequency of unreported symptom defined events.
- The E-RS is used to evaluate the effect of treatment on respiratory symptoms during non-exacerbating states.

A 12-week COPD treatment trial

- Patients are enrolled in a stable state. The E-RS is used to evaluate the effect of treatment on respiratory symptoms over the study period.
- The EXACT scoring algorithm is not used, or it serves as an exploratory endpoint to understand the effect of treatment on the frequency of symptom-defined events.

The EXACT and E-RS minimize investigator and subject burden by providing two validated uses for one diary.

- Assessment of COPD exacerbations via EXACT Total Score
- Quantification of respiratory symptoms in stable COPD using RS-Total and subscale scores

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Can the EXACT be used for estimating utility?

Dr. Jennifer Petrillo developed a preference-based scoring algorithm to estimate utilities of an exacerbation from a subset of items in the EXACT for use in cost-effectiveness models.

This scoring algorithm, known as the "EXACT-U" was developed according to NICE guidelines and there is evidence to suggest EXACT-U scores distinguish stable and acute COPD states, differentiate clinician-rated levels of exacerbation severity and are responsive to change. See **Petrillo and Cairns 2011** for more information.

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What are responder thresholds for the EXACT?

The 14-item EXACT quantifies the frequency, severity, and duration of unreported exacerbations of COPD and the severity of exacerbations seen in the clinic, urgent care, and around hospitalizations. Thus, the EXACT provides metrics for four exacerbation-related endpoints: Frequency, severity, and duration of unreported events and the symptom severity of reported COPD exacerbations.

The threshold for determining the presence of a symptom-defined event (worsening of the underlying condition) is based on both the magnitude and duration of score change: a 9 point increase (worsening) from the usual score (e.g., stable baseline) sustained for three days or a 12 point increase sustained for three days. So, 9 point changes are meaningful, and sustained increases of this magnitude are indicative of a symptom-defined exacerbation. An overview of the research supporting these values is included in the supplement of the paper published in **Leidy et al. 2014**.

Regarding day-to-day interpretation of the EXACT scores, if a patient reports an increase of 9 points, this would clearly be significant to the patient (and if sustained for three days, it would constitute an unreported symptom-defined exacerbation). Increases > 5 points may also be significant, however, the data suggest COPD patients can vary by 3-5 points on a day-to-day basis, suggesting this is "normal variability" (See Table 1 of **Leidy et al. 2014** – Information on SEM and Intra-individual variability during stable/baseline period across three trials). This variability does not control for other factors that may be measured or unmeasured in the study (e.g., seasonality).

Regarding thresholds for the four exacerbation-related endpoints, it is clear that fewer, milder, and shorter durations are preferred. To date, specific responder thresholds for unreported events (frequency, severity, duration) have not been tested. A reasonable responder threshold for severity of medically treated events is five points, although research is needed to test and document this proposition.

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What is the responder threshold for the E-RS:COPD?

The E-RS:COPD yields a total score and three subscale scores: Breathlessness, Cough & Sputum, Chest Symptoms. Responder thresholds were proposed in Leidy et al. 2014 and have been used successfully in randomized trials (e.g., Jones et al. 2016).

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Is there, and should there be, a perfect correspondence between health care resource utilization (HCRU) and symptom-based (EXACT) definitions of exacerbation?

No, nor should there be. The HCRU (medically treated event) definition of exacerbation is a dichotomous outcome based on the presence of a clinic visit or hospitalization and clinician-report of the event and change in treatment. The patient decides to seek care and is seen by the clinician who evaluates the patient and prescribes treatment (Event Occurred). A symptom-based definition of exacerbation using a daily diary is derived from a continuous variable tracking patient symptoms over time with a scoring threshold use to indicate a symptom-defined event occurred, independently of any patient action, with the event defined by sustained worsening of COPD symptoms beyond normal day-to-day variability (Mackay et al. 2018).

Several key points:

- The EXACT scoring threshold is used to identify unreported symptom-defined events (an Event Occurred). It is NOT used to validate or verify HCRU visits.
- To quantify symptom severity during HCRU events, the continuous EXACT scores are used, covering the full range of symptom experience, with higher scores indicating more severe symptoms.

Research has shown a strong relationship between continuous EXACT scores and HCRU events over time, with EXACT scores rising and falling with these events (**Leidy et al. 2014**; **Jones et al. 2014**).

The relationship between HCRU events and EXACT-defined events (threshold scoring) provides interesting insight into the nature of HCRU events. Research suggests that approximately 50% of HCRUs exceed the threshold of an EXACT-defined event (persistent increase in symptoms of at least 9 points); conversely, 50% do not reach the threshold used to identify unreported events (**Leidy et al. 2014**; **Jones et al. 2014**). Note that this does NOT mean EXACT scores did not rise; rather, it means scores did not reach the 9-point threshold. One should expect this result for many reasons, including:

- Patients choose to call or see their clinician for a variety of reasons, including clinician instructions, change in other health parameters, and timing (day of the week, holidays, etc.), all of which are not part of the symptomatic definition of exacerbation.
- Clinicians see patients and select treatments for a variety of reasons, including professional preferences, past experiences with a particular patient, comorbid conditions, family concerns, and/or the patient's reduced capacity for self-care or need for professional observation.

It is interesting to note that analyses of three independent trials showed that the correspondence between alternative indicators of patient worsening (airflow, rescue medication use) was equivalent or better for symptom (EXACT)-defined events than for HCRU events (**Leidy et al. 2014**).

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Are there logical inconsistencies in individual patient-report on items related to cough (i.e., items 2, 3, 4) and/or those related to breathlessness (i.e., items 7–11)?

No. A post-hoc analysis was conducted to address this question. Specifically, cross-tabulations were performed with data from the first validation study (N=410), deriving counts of logical inconsistencies across the 28-day study period. Results showed a very low percentage of logical inconsistencies (<0.6%), which remained low over time. These results were confirmed using data from two 3-month trials and one 6-month study. Data sources: **Leidy et al. 2010** and **Leidy et al. 2014**

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How should the EXACT be administered?

The EXACT was designed as an electronic patient-reported outcome (ePRO) to be completed on a handheld device (i.e., smart phone or tablet) each evening before bedtime. The diary takes less than three minutes to complete.

An EXACT ePRO Certification Program was developed to:

- Optimize consistency across devices and ePRO vendors
- Provide instrument users with a choice of informed ePRO vendors

Administering the EXACT or E-RS using paper-pen diary format is NOT recommended.

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What timelines should I consider when planning to administer the EXACT or E-RS in an international clinical trial?

There are two important time-limiting factors to consider — translations and device programming.

- For new translations, allow three to five months for this process.
- Plan for one to four months for device programming, IT validation, and uploading/formatting of the EXACT/E-RS in the selected languages.

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