Using Qualified PRO Measures in Drug Development
An Update on the EXACT and E-RS

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Introduction

Testing treatment effects in clinical trials requires outcome measures that are reliable, valid, and sensitive to change. To facilitate the use of appropriate and precise patient-reported outcome (PRO) measures in pharmaceutical trials, regulatory agencies in the United States (U.S.) and Europe have published guidelines covering specific therapeutic areas,[1-3] describing the use of PRO measures[4,5], and outlining procedures for qualifying drug development tools (DDTs).[6,7] The EXAcerbations of Chronic pulmonary disease Tool (EXACT®) and Evaluating Respiratory Symptoms scale (E-RS™) were the first tools to undergo the qualification review process and be qualified by both the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA). This paper describes the EXACT and E-RS and some of the insights gained through their use post-qualification.

The Exacerbations of Chronic Pulmonary Disease Tool (EXACT)

Many patients with chronic obstructive pulmonary disease (COPD) experience acute deteriorations of their condition, known as exacerbations, that are not only disconcerting to these individuals but can have significant short- and long-term health consequences. Understanding the risk factors and characteristic features of exacerbations are important areas of study, and reducing their frequency and severity are key treatment objectives of pharmaceutical sponsors and clinicians. The EXACT was developed to meet the need for a direct measure of patient-reported symptoms of exacerbation in clinical trials testing the effects of pharmaceutical agents on exacerbation frequency, severity, and duration.[8-11] This 14-item daily diary complements and extends information provided by traditional health care resource utilization (HCRU) data by standardizing the evaluation of symptoms around medically treated events. Using the unidimensional interval-level scale score produced by the EXACT, the symptom severity associated with events treated in the clinic or emergency room can be quantified in absolute terms (0 to 100, higher scores are worse) or the magnitude of change from baseline or stable state. Daily scores can also be used to evaluate changes leading up to and following events, including hospitalization.


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In addition to quantifying HCRU-associated events, the EXACT captures acute sustained worsenings of COPD that are not seen or treated by clinicians, yet adversely affect patient lives.[8,12-14] Because these events are not seen by a clinician, they are identified through a daily diary; in the case of the EXACT they are identified using a validated scoring threshold indicating an acute sustained worsening has occurred (9 points for 3 days, 12 points for 2 days). This yields data on frequency, severity, and duration of these symptom-defined events, again complementing and extending the information provided by HCRU-defined exacerbations.

The EXACT was developed to quantify exacerbation outcomes in trials testing the efficacy of therapies to treat acute exacerbations of COPD or prevent them from occurring, using retrospective data analyses for hypothesis testing. The measure was not designed for prospective use, such as signaling an upcoming exacerbation or prompting patients to call their clinician and seek care. The latter is not recommended in pharmaceutical trials because it could change patient diary response behavior and alter trial results. Licensed users of the EXACT choosing to try these alternate applications of the instrument are encouraged to test them and disclose that these are new uses of the instrument.

Qualification: On 9 January 2014, the FDA released their Draft Guidance for the EXACT[15] and on 13 April 2015, the EMA released their Draft Qualification Opinion for the EXACT and E-RS.[16]

The Evaluating Respiratory Symptoms (E-RS) in COPD Measure

The E-RS is a derivative instrument using the 11 respiratory symptom questions from the EXACT to quantify respiratory symptom severity in stable COPD.[17,18] During development, confirmatory factor analysis supported a second-order model with a general factor, representing respiratory symptom severity overall (E-RS Total), and three domains or subscales representing the three key respiratory symptoms of COPD: RS-Breathlessness, RS-Cough and Sputum, and RS-Chest Symptoms. E-RS scores were designed to serve as primary, secondary, or exploratory efficacy endpoints in clinical trials evaluating interventions to reduce the severity of respiratory symptoms of stable COPD. A step-down approach can be used, with the E-RS Total tested first, followed by the three subscales.

During the qualification process, the submitted name of this instrument was the EXAcerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms (E-RS), referencing its parent instrument. During the development of the qualification statement for this measure, the FDA requested a name change so the term "Exacerbation" would not appear in labeling related to symptoms of stable disease. To address this request, the name was changed to the "Evaluating Respiratory Symptoms" measure

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(retaining the E-RS acronym while avoiding the term exacerbation), adding "COPD" (E-RS:COPD) to specify the target population. All presentations and publications post 2016 (should) refer to this instrument as the Evaluating Respiratory Symptoms tool.

In any given study, the 14-item diary can be used either to evaluate exacerbations of COPD (EXACT scoring algorithm), respiratory symptoms in stable COPD (the 11-item E-RS:COPD scoring algorithm) or both.

Qualification: As noted above, the EMA released their Draft Qualification Opinion for the EXACT and E-RS on 13 April 2015[16] and on 8 March 2016 the FDA released their Draft Guidance for the E-RS.[19]

Use of the EXACT and E-RS:COPD Post-Qualification

The EXACT and E-RS have been widely used in clinical trials to measure treatment effects (40+ trials in clinicaltrials.gov), as well as in natural history and academic research (65+ academic licenses/studies), with more than 25 publications to date.[20] To protect the integrity of the instrument, Evidera licenses both measures and oversees and licenses all translations (now over 55). Licensing fees paid by for-profit organizations go to a research and development fund for these instruments and to facilitate licensing and free use by academic and not-for-profit investigators. The information below provides a high-level summary of some of the insight gained through research to date.

The EXACT

The EXACT has shown evidence of sensitivity to the effects of treatment on frequency of symptom-defined events, with patterns similar to those observed with HCRU frequency. For example, in the ATTAIN study, a 24-week international Phase III randomized, controlled clinical trial testing the efficacy of aclidinium for the maintenance treatment of COPD (N=828), a significant difference in exacerbation rates between each active treatment group and placebo for both HCRU and symptom (EXACT)-defined events was observed.[21] 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 (EXACT)-defined events and that these events were shorter and less severe (area under the curve) than events seen in patients receiving no calls.[22] 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.

The EXACT has also been used to better characterize symptom-defined events, their impact on patient outcomes, and patient treatment-seeking behavior phenotypes. Secondary analyses of the ATTAIN data showed patients experiencing unreported symptom-defined exacerbations had longer symptom-defined exacerbation recovery times, greater deterioration in lung function, and worse health status scores at the end of the study.[21]

Mackay and colleagues[23] showed that among symptom-defined exacerbations captured with the EXACT, patients with more severe stable disease (defined by history of exacerbations in the last year and airflow obstruction) were more likely to report events and receive treatment for symptom-defined exacerbations associated with smaller increases in symptom severity at event onset compared to patients with milder stable disease.[23] A secondary analysis of pooled data from two 12-week Phase II international randomized controlled trials using the EXACT to identify symptom-defined exacerbations found that patients who failed to recover from symptom-defined exacerbations (persistent worsening) had significantly lower EXACT scores at baseline and more gradual event onset compared with patients who recovered.[24] These findings suggest that patients with lower EXACT scores at baseline, and patients with more gradual symptom deterioration, may be less likely to report acute symptomatic events. Symptom-defined exacerbations with a more gradual onset may be more difficult for patients to identify as an acute worsening in their COPD health that is worth a health care visit for assessment and possible treatment. Results also suggest difficulty recovering from symptom-defined exacerbations leads to a decline in health status and increased levels of breathlessness and chest symptoms that may represent an early signal of disease progression.

There has been significant interest in incorporating digital instruments and wearable technologies as complementary endpoints in clinical trials. In a small, non-interventional study of 17 patients, Ehsan and colleagues[25] found a significant decrease in physical activity, measured through an activity monitor, during symptom (EXACT)-defined events that persisted for two weeks following symptomatic recovery. These events were also characterized by increased daytime sleepiness, decreased total sleep time, and decreased sleep efficiency (measured via actigraphy).[26]

Among the Challenges

A major challenge with the use and interpretation of the EXACT has been a misunderstanding of the relationship between symptom-defined and HCRU events. Data from

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clinical trials and observational studies have consistently shown a low concordance or "agreement" between these two types of events.[10,21,23] This is interesting and important information to help us better understand exacerbations, particularly those treated in the clinic, emergency room, or hospital. The low concordance is not a validity coefficient for either the EXACT or HCRU metric, but rather a function of threshold variability - the quantitative threshold required to identify unreported symptom-defined events, patients' qualitative threshold for seeking care, and clinician thresholds for diagnosis and treatment. Symptom-defined events are a sustained worsening in the patients underlying condition that are identified using a standardized, quantified score that exceeds normal day-to-day score variability. In contrast, HCRU events are clinic visits, driven by the patient's decision to seek care and diagnosed and treated by the clinician based on his/her judgement and practice setting. The HCRU event is observed and counted, however the patient and clinician behaviors related to that observed event are not standardized or quantified. Some patients are "less symptom tolerant" and seek care early, while others are more "tolerant" (or have other things to do) and decide not to seek care. Clinicians have different standards of diagnosis and treatment; health care systems have different standards for hospitalization (that could lead one to erroneously conclude that patients in some countries have more severe exacerbations when, in fact, this is due to admission policy). Symptom severity associated with HCRU events are highly variable, with milder HCRU events failing to meet the threshold for a symptom-defined event.[10,21] This simply indicates that some HCRU events are symptomatically mild, and that unreported events can be even more severe than those seen and treated. The EXACT offers data to better understand HCRU events, including the relationship between patient symptoms (magnitude, change, type), preferences, care-seeking behaviors, clinical assessment, and treatment, as well as insight into the day-to-day variability of symptoms outside the clinic setting.

The E-RS:COPD

The E-RS:COPD has been used successfully in a number of trials testing the effect of treatment on respiratory symptoms of COPD. In the ATTAIN study, statistically significant and clinically meaningful treatment effects were observed for the RS-Total score and each of the subscale scores.[27] Results of pooled data from the ATTAIN and AUGMENT Phase III trials comparing aclidinium bromide

and placebo also showed significant treatment effects for the RS-Total and subscale scores overall and by GOLD status.[27] Importantly, these results are referenced in the EMA Summary of Product Characteristics (SPC) for Duaklir Genuair, indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. "Duaklir Genuair improved daily symptoms of COPD such as 'breathlessness', 'chest symptoms', 'cough and sputum' (assessed by E-RS:COPD total score) (EMA Summary of product characteristics, pp. 10[28])." This was the first appearance of the E-RS:COPD in a label.

E-RS:COPD effects were also observed 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 bromide and tiotropium on respiratory symptoms versus placebo.[29]

A secondary analysis of pooled data from two Phase III, 24-week randomized, placebo-controlled trials of twice-daily aclidinium/formoterol (the ACLIFORM and AUGMENT studies), the efficacy of treatment compared to placebo or monotherapies in patients defined as less/more symptomatic using an RS-Total score ≥10/<10, respectively was conducted.[30] In more symptomatic patients, aclidinium/formoterol improved RS-Total score from baseline vs. placebo or both monotherapies.

The E-RS was used to evaluate respiratory symptom severity in the FULFIL study, a Phase III, 24-week randomized, double-blind, double-dummy, multicenter study comparing once-daily single inhaler triple therapy [fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI)] with twice-daily inhaled corticosteroid/long-acting β2-agonist therapy [budesonide/formoterol (BUD/FOR)] in patients with symptomatic COPD at risk of exacerbations.[31]

FF/UMEC/VI showed greater reductions from baseline in RS-Total and all subscale scores compared with BUD/FOR, with treatment differences statistically significant for each 4-week interval. The FF/UMEC/VI group exceeded the RS-Total responder threshold at 8 weeks compared to BUD/FOR and the RS-Breathlessness and RS-Cough and Sputum score changes which exceeded their responder thresholds by week 12.

New Uses for the E-RS – the E-RS:IPF

Thanks to the experiential knowledge and insight of 84 people with COPD during instrument development and content validation, and input from clinical and measurement experts, the E-RS covers the key respiratory symptoms experienced by people with COPD, with questions and response options easy for patients to read and rate. These symptoms (breathlessness, cough, sputum, and chest congestion) are not unique to COPD. The content, intuitive simplicity, and ease of patient use make the E-RS appealing as a PRO measure for other conditions affecting the respiratory system. An instrument cannot be transported from one target population to another without testing, however. Assurance is needed that the instrument is content valid and yields scores that are reliable, valid, responsive, and interpretable in the new target population.

There is qualitative and quantitative evidence to suggest the E-RS may be useful for trials of idiopathic pulmonary fibrosis (IPF).[32] As one might expect, the individual items comprising the E-RS map nicely to the IPF respiratory symptoms, however the structure of the measure and scoring are different. Unlike the E-RS:COPD, there is no total score. Rather, the E-RS:IPF has four scale scores corresponding to the key respiratory symptoms of IPF: breathlessness, cough, sputum, and chest symptoms, with any or all potential endpoints in clinical trials.[32]

A Perspective on EXACT and E-RS Qualification as Exploratory Endpoints

The FDA's qualification program for clinical outcome assessments and biomarkers facilitates discussion between instrument developers/advocacy teams and regulatory agencies to make certain interests are aligned. As the first PRO measures to be reviewed and approved under this evolving process, the EXACT and E-RS were both qualified as exploratory endpoints. Although initially disappointing, it became clear that the exploratory designation serves an interesting role for regulatory agencies and sponsors. By qualifying these instrument, the agencies acknowledged familiarity with the measures and agreed with the supporting evidence to date, including its content validity, reliability, quantitative validity, responsiveness and interpretation guidelines within the context of use described in the submission documents and outlined in the qualification. As the instruments are used by industry and academic scientists, evidence and understanding will continue to grow. Sponsors can talk with regulatory agencies about the use of the instrument(s) in their program(s) with this foundation. No need for sponsors to describe the measure(s) in detail or submit an instrument dossier. Discussions can proceed directly to the suitability and positioning of the measure(s) for their program based on the product profile, target population, stage of development, other proposed endpoints, and endpoint positioning. If the instruments are included in proof-of-concept or Phase II trials, these meetings can include a discussion of measurement properties and efficacy signals in their specific drug, target population, and trial designs to further inform conversations related to Phase III endpoint hierarchy and labeling claims. Agency decisions on the use and positioning of instruments qualified as exploratory endpoints, like the EXACT or E-RS, can be made on a case-by-case basis, informed by the unique elements of each case. Seen in this light, qualified measures like the EXACT and E-RS should be considered part of the drug development "tool box", ready for use in drug development programs as interests and needs arise.

Conclusions

When we started the EXACT journey a dozen years ago, it was clear the field needed a standardized method to quantify exacerbations of COPD to understand these important yet elusive events and their impact on health and quality of life. The journey has been filled with "firsts" and insight that accompanies exploration – first PRO consortium (thank you to all who participated; it was a pleasure!); first through the qualification process (submission pre-dated the guidance - thank you FDA colleagues for your interest, enthusiasm, and persistence!); first parallel PRO submission to the EMA (thank you EMA colleagues for your time, interest, and insight!); and, first qualified by both agencies (exploratory is a first step!).

Work on the EXACT led to the development of new symptom measures for studies of COPD and IPF. Our understanding of COPD exacerbations, symptom burden, and the effects of treatment on these patient experiences is growing as the measures are used in descriptive, natural history and interventional studies and results are shared through presentations and publications. Scientists and clinicians are asking new questions, approaching research in new ways, digging into data to uncover patterns and insight. May the journey continue. ■

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> Somewhere, something incredible is waiting to be known." – *Carl Sagan*

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> "It is not the strongest of the species that survive, nor the most intelligent, but the one most responsive to change." – *Charles Darwin*