Measuring health in pulmonary hypertension: emphasising the right end-point?

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emPHasis-10 addresses the unmet need for disease-specific quality of life instruments for pulmonary hypertension http://ow.ly/tdPDV

Pulmonary hypertension (PH) is a condition deriving from multiple aetiologies with the recent focus on Group 1 pulmonary arterial hypertension (PAH) and Group 4 chronic thromboembolic pulmonary hypertension (CTEPH) largely due to the surge of understanding in pathophysiology and resultant treatments available [1]. Both are a disease of the pulmonary circulation that is characterised by a progressive rise in pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR), with limited dysfunction of the left ventricle [2]. Symptoms manifest as patients' lose the ability to augment their cardiac output in the face of a fixed vascular resistance [3]. In addition, anxiety and depression disorders are highly prevalent in PAH and CTEPH patients and correlate with the patients' sense of wellness [4]. However, despite therapeutic options and overall improved outcomes, life expectancy is shortened [5, 6] and patients must face the myriad of issues that go along with a chronic debilitating fatal disease [7–9].

The definition of "good health" is not just the absence of disease but also incorporates emotional and physical security, a sense of contentment. The World Health Organization first formally acknowledged this concept in the 1952 proceedings, embracing the importance of "quality of life" (QoL) [10]. Health-related QoL (HRQoL) is a composite of physical, psychological and social domains of health seen as distinct qualities influenced by a person's perceptions or expectations [11]. It is important to realise that HRQoL has multiple components, a multidimensionality, representing numerous states of health, distinct from survival time [11]. Standardised metrics have been developed to quantitatively assess this abstract conceptualisation of well-being. The quantitative science of questionnaire development, however, needs to be balanced by the practicality of any measure. In practice, questionnaires need to be easily administered and scored. In addition, understanding what level of change is considered clinically meaningful is of critical importance. Although HRQoL outcomes usually correlate with standard objective measures at the population level, the extent to which a change in the "average score" can be translated to any given individual is often met with scepticism [12].

In this issue of the *European Respiratory Journal*, YORKE *et al.* [13] introduce a new PH-specific questionnaire, the emPHasis-10, a 10 item survey assessing "how PH affects" the patient's life. This study addresses an important, unmet need in the field of PH, for which disease-specific instruments are limited. To date, the only instrument developed specifically for PH is the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) [14–18]. Despite international validation, the CAMPHOR has certain attributes that have limited its widespread adoption. It is comprised of three separate scales, each of which

has its own response options, scoring and subdomains. While its measurement properties were carefully examined during the development process, its "real-world" performance in the hands of external investigators remains to be established. A recent study suggests that the CAMPHOR is predictive of clinical deterioration at diagnosis but is not predictive over time [19]. The development of a new instrument that can be quickly administered in a clinic setting and yields a single score has appeal, and provides researchers with greater choice in terms of study measures.

Although there is no universally accepted method for designing questionnaires, the overall approach used in the development of the emPHasis-10 follows the general practices commonly utilised by those in the field today; that is, qualitative interviewing to generate item content, cognitive testing of proposed items, item reduction, followed by an assessment of reliability, repeatability and concurrent validity. Moreover, the authors also employed modern psychometric techniques, specifically Rasch analysis, to assess item "fit" and "difficulty" with respect to the "ability" of the surveyed population. In general, development of the emPHasis-10 appears consistent with the basic principles outlined by the US Food and Drug Administration Guidance to Industry for Patient-Reported Outcomes [20], but ultimately its acceptability as a regulatory end-point in clinical trials remains to be determined.

No questionnaire is without limitations. Some behavioural researchers may argue that the breadth and depth of a patient's QoL cannot simply be reduced down to a single number derived from 10 questions. HRQoL, by definition, is inherently multidimensional, but conventional and modern psychometric techniques used to perform item reduction assume a one-dimensional construct. Such approaches can result in an instrument that has optimised statistical properties, but that does not guarantee an accurate/ valid assessment of the end-point it was intended to measure. Plus, with ongoing debate about current PH end-points and biomarkers as "true" surrogates of the disease for clinical practice and clinical trials, it is less clear how to assess the value of PH HRQoL with these comparators. In the debate between idealism and pragmatism, the developers of the emPHasis-10 have chosen the latter path, which some may argue is reductionist, but is reasonable given their goal of designing a tool that can be feasibly implemented within the demands of today's busy medical practice.

Although further work is required to determine its value in routine clinical practice, the emPHasis-10 holds promise as a new disease-specific measure for PH. Unlike other proprietary instruments, for which use can be restricted, development of the emPHasis-10 was funded by the Pulmonary Hypertension Association UK; consequently, "open access" to the instrument will be provided to clinical and academic communities. One potential advantage of such an approach will be not only to enhance the adoption this new instrument, but also to facilitate external validation of its value in clinical practice, and perhaps in clinical trials as well. Even if regulatory authorities never accept HRQoL as a primary end-point, payers are increasingly demanding it. As healthcare resources continue to become more constrained, costly new therapies and devices must demonstrate their value as agents of "good health". For PH specifically, satisfaction must be proved beyond just walking distance alone. With its emphasis on HRQoL in PH, emPHasis-10 may fulfil this role.

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