

Assessing Quality of Life in Patients with Common Variable Immunodeficiency: Why It Matters



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How do we, as health care providers, determine whether and how a patient has responded to a therapeutic intervention? What is a patient telling us when responding to the question “how are you doing?” A healthy therapeutic relationship is implicitly predicated on an alignment of goals by both the patient and the physician. Much to the frustration of both physicians and patients, the success of that relationship can be quite variable. As physicians we often look to objective measures of change in physiologic functions as indicators of response to therapy; these assessments are considered measurable and “clean.” Conversely, our patients are likely to report qualitative assessments, which may include recent symptoms, overall well-being, or perceived levels of physical, vocational, and social functioning. An example of the former is the asthma specialist who reviews peak-expiratory flow records or performs spirometry to assess improvement in lung function over time as evidence of clinical response to inhaled bronchodilators and corticosteroids, whereas the patient rarely reports interval changes in measured lung function or the number of eosinophils in a sputum sample since the last clinic visit. The patient will most often provide a qualitative assessment, in her or his own words, of change in symptoms over the intervening period of time, depending mostly on remembering events of the past few days, weeks, or perhaps even months. Some patients may give a quantitative response, such as the number of days of school or work missed or visits to the emergency department. As practicing clinicians, we learn to integrate objective and quantitative measures with the qualitative symptom reporting and anecdotes to form a clinical assessment (or global impression) of the patient’s medical condition, which leads to a subsequent diagnostic and therapeutic plan.

The past 2 decades have witnessed unprecedented progress in the development of novel therapeutics that stemmed from discoveries enabled by rapid technological advances in molecular biology and genetics. Translation of these discoveries into medicines can be arduous and expensive. Third-party payers

frequently demand that pharmaceutical companies demonstrate evidence of “clinical benefit” to determine whether to reimburse and if so, at what level. Increasingly, what is defined as clinical benefit is based not only on objective assessments of physiologic response but also on measures of patient-reported outcomes. To evaluate patient-centered outcomes properly, instruments that can reliably measure patient-reported symptoms, function, as well as assess quality of life need to be properly developed and validated in the specific populations of interest to ensure proper context of use and fit for purpose. Strong interest within the pharmaceutical industry and among academic investigators in such measures has led to the development of several generic instruments, such as the 36-item short form health survey¹⁻³ or the EuroQol five-dimensional questionnaire⁴⁻⁷ and increasingly, disease-specific patient-reported outcome instruments.

In 2009, the US Food and Drug Administration published the Patient-Reported Outcome (PRO) Measures Guidance for Industry (2009).⁸ This guidance outlines the processes and procedures for developing and validating such disease-specific PRO tools to be applied in the development of medicines or devices. Semi-structured patient interviews using words and phrases that patients can understand are used to elicit symptoms and impact on health-related quality of life (HRQOL), which is a multidimensional concept that includes domains related to physical, mental, emotional, and social functioning that focus on the effect that health status has on quality of life. All responses are specifically reported in the patients’ voice as the initial step. Once concept saturation is reached, items are developed along with appropriate response options and recall period. This is followed by the construction of a draft disease-specific conceptual framework of the PRO instrument, which aligns the items and domains. A second wave of interviews explores comprehension and understandability as well as relevance. The final testing is to establish the reliability, validity, and ability of the instrument to detect change, all of which are determined through an iterative process to further refine the instrument. The definitions of response must also be defined for the instruments to be considered appropriate for use in clinical practice or as outcome measures in the context of a clinical trial. These multiple steps are needed to ensure that the instrument will reproducibly capture the data that may be used to assess the effect a therapeutic intervention has on patient-centered outcomes such as disease symptoms, functioning, and quality of life (QOL).

In this issue of the *Journal of Allergy and Clinical Immunology—In Practice*, Quinti et al⁹ describe the development and early stages of validation of a QOL instrument, developed in and for patients with common variable immunodeficiency (CVID); the instrument is called the CVID_QoL. Given the costs associated with immunoglobulin replacement therapies and the burden these costs can

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Conflicts of interest: D. C. Adelman is employed by Aimmune Therapeutics. K. Howard is employed by ICON plc.

Received for publication September 23, 2016; accepted for publication September 26, 2016.

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J Allergy Clin Immunol Pract 2016;4:1180-1.
2213-2198

© 2016 American Academy of Allergy, Asthma & Immunology
<http://dx.doi.org/10.1016/j.jaip.2016.09.014>

put on patients and providers, properly developed and validated HRQOL instruments are an increasingly important component to assessing not only the value but also the success of the care we provide patients with CVID. The CVID_QoL was initially developed in 118 patients for the purpose of assessing the HRQOL of patients with CVID. The early stages of the validation process were undertaken at a single center and initially in a single language. This could create potential problems when using the measure in diseased patient populations beyond those involved in the development and validation processes if the population is not representative of the epidemiology of the overall target patient population. It is critically important that an instrument be able to provide interpretable data in the specific patient population. Each of the steps involved to define the content validity and psychometric properties must be repeated to ensure faithful translation, translatability, and cultural appropriateness; translatability and cultural adoption are of particular interest and importance to regulatory authorities. The sensitivity of the instrument to detect change in QOL over time may require further characterization for the instrument to be accepted by regulatory authorities for purposes of making claims to be included in the package insert of a particular drug. The CVID_QoL will have broader application, interest, and importance than solely for the purpose of drug development. Clinicians caring for patients with CVID will appreciate that the authors have appropriately developed an instrument that can help assess QOL as part of the clinical management of patients with CVID. Third-party payers, especially in Europe, are particularly interested in QOL assessments when considering reimbursement for drugs, even those that could be considered lifesaving.

As novel therapies emerge for other primary immunodeficiency disorders, development of additional age-appropriate, disease-specific QOL instruments will be needed not only to allow

clinicians and researchers to assess outcomes on individual patients but also to compare the similarities and differences that therapeutic interventions will have on the wide variety of disorders of human immunity for a specific group of patients' quality of life.

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