

A Systematic Method for Selecting Patient-Reported Outcome Measures in Diabetes Research

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To understand the true impact of treatment strategies in diabetes, it is important to look beyond just biomedical efficacy. The primary goal of diabetes treatment is to achieve near-normal blood glucose levels over the long term.¹ However, achieving good metabolic control requires full understanding, engagement, and commitment of the patient to the prescribed treatment strategy. Patients' experience can be adversely affected because of the direct effects of diabetes or its treatment, which can, in turn, affect clinical outcomes through such mediating factors as medication-taking behavior and adherence to lifestyle changes. Thus, treatment strategies for diabetes must seek to balance glycemic control against negative patient experiences, such as hypoglycemia symptoms and other effects that may adversely affect overall quality of life (QoL).² Although treatment efficacy is measured with biomarkers, examining patients' experiences requires health care providers to ask them directly about those experiences.³

Patients' experiences can be measured in a quantifiable and standardized manner in clinical research or practice by the administration and completion of patient-reported outcome measures (PROs), which encompass measurement of any aspect of a patient's health status that comes directly from the patient and is based on the patient's perception of a disease and its treatment(s).³ There are numerous PROs measuring a range of concepts, including perceived symptoms of high and low blood glucose, treatment satisfaction, health-related QoL (HRQL), health status, and weight changes.

Each concept represents a different aspect of an individual's thoughts and feelings about diabetes or its treatment. PROs may be used to establish treatment benefit, demonstrate no detriment where one may be assumed (e.g., anxiety associated with injectable agent initiation), explore patient perceptions of dosage levels, or understand the cost-effectiveness of an innovative therapy.

A U.K. Department of Health pilot study is currently exploring the use of PROs to measure national outcomes in individuals with diabetes. Both U.S. and European regulators have released guidance on the use of PROs in medical product development,^{3,4} highlighting the importance of these endpoints and outlining the scientific rigor that should be incorporated into the development and selection of PROs to allow meaningful outcomes. Although the European reflection paper (guidance document) focuses on HRQL, a specific PRO, the U.S. regulatory guidance provides discussion of PROs in general.

Despite the self-management nature of diabetes, much clinical research continues to neglect the patient perspective. Even where it is incorporated, systematic consideration is rarely given to the measurement strategy, leading to suboptimal capture of the relevant patient experiences and potential insensitivity to treatment effects. This editorial, therefore, aims to synthesize, build on, and bring a diabetes focus to regulatory guidance, to provide researchers with a succinct but systematic process for the selection of relevant patient-centric concepts and measures (PROs) in a

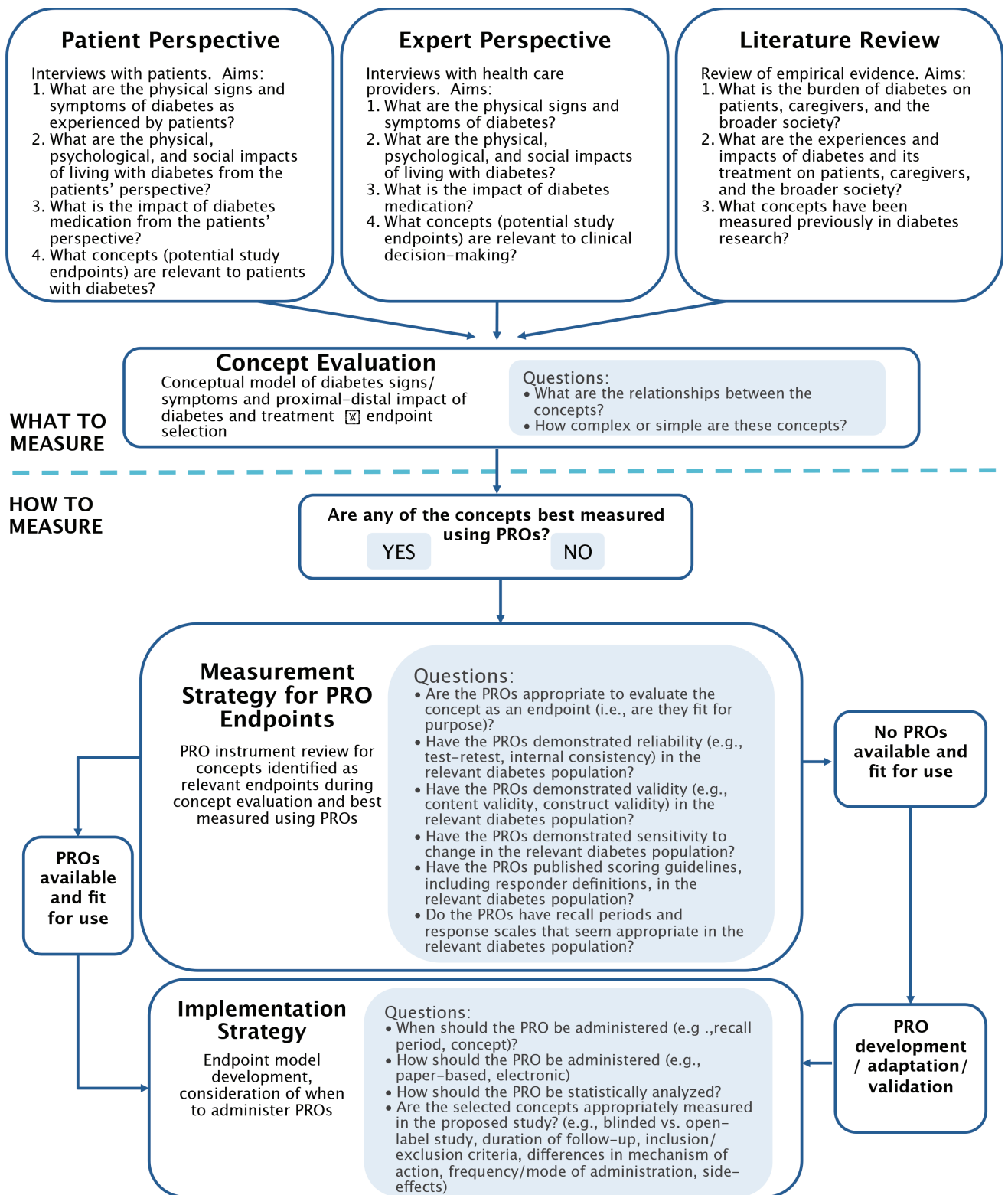


Figure 1. Selection of concepts for clinical research endpoints and selection of PROs for concept measurement.

diabetes research study, and to help users of trial data understand and critique PROs.

Figure 1 poses a series of questions to consider when selecting

PROs for endpoint measurement. There are two basic components to this process: identifying what to measure and determining how to measure it.

What to Measure
Identifying key patient perspectives and experiences to measure in a specific product development program is the first step in creating

Table 1. Factors Determining Whether a PRO Is “Fit for Purpose”

Measurement Property	Definition ³
Reliability	The ability of a PRO instrument to yield consistent, reproducible estimates of true treatment effect
<ul style="list-style-type: none"> • Test-retest reliability 	Stability of scores over time when no change is expected in the concept of interest
<ul style="list-style-type: none"> • Internal consistency reliability 	Extent to which items comprising a scale measure the same concept
<ul style="list-style-type: none"> • Inter-interviewer reliability 	Agreement among responses when a PRO is administered by ≥ 2 different interviewers (not self-completed by patients)
Validity	
<ul style="list-style-type: none"> • Content validity 	Evidence from qualitative research demonstrating that the PRO instrument measures the concept of interest relative to its intended measurement concept, population, and use
<ul style="list-style-type: none"> • Construct validity 	Evidence that relationships among items, domains, and concepts conform to logical relationships that should exist with other measures or characteristics of patients and patient groups
Ability to detect change	Evidence that a PRO instrument can identify differences in scores over time in individuals/groups that have changed with respect to the measurement concept. The identification of a responder definition (i.e., the amount of change required from baseline to be indicative of significant treatment benefit) is extremely helpful to HCPs in interpreting PRO concept(s)

a PRO strategy.⁵ A “disease model” or “conceptual model” provides a heuristic graphic that represents the relevant PRO concepts, such as symptoms, signs, and physical/social/emotional/occupational functioning, and the relationships among the concepts. A comprehensive conceptual model should be developed after a systematic review of the literature, as well as discussions with patients and health care professionals (HCPs). Obtaining information directly from patients is a crucial and often overlooked aspect of this process. Often, caregivers’ perspectives and broader societal views are also incorporated into conceptual models, and regulatory labels and payer perspectives are added for drug development research.

The researchers should then use this conceptual model to identify appropriate endpoints for their study. Important considerations include the complexity of measuring the concepts (e.g., perceived hypoglycemia is a unidimensional construct; QoL is a multidimensional and more complex concept), as well as whether the concept(s) of interest are best measured within a given study design (e.g., whether the study duration allows sufficient follow-up time for the concept of interest

to demonstrate meaningful change from baseline). The key objective at this stage is to identify patient experiences and perspectives that are most important for the population under study.

How to Measure

Once key patient experiences and perspectives have been identified and a conceptual model has been developed, appropriate measurement strategies are considered. Researchers commonly use PROs based on what has been used in past studies or according to the instrument name,⁶ rather than carefully evaluating an instrument’s content and administration details in the unique trial context. This leads to inappropriate selection of PROs, misinterpretation of data, and flawed conclusions,³ which can delay regulatory review and publication of data. If PROs are not optimally capturing the relevant patient experiences, the measure may also be insensitive to treatment effects, leading to null findings.

For a PRO instrument to be considered “fit for purpose” in a specific program, it must capture the key patient experiences identified in the conceptual model and demonstrate reliability, validity, and ability to detect change in the population of

interest (Table 1). If no instrument is available that is fit for the purpose, a new instrument may be developed following standardized processes.^{3,4} Once PROs are identified or developed, consideration should be given to the most appropriate way to implement the PRO in the study, including frequency, platform, and mode of administration, as well as how to analyze the data. For example, measuring symptom intensity and frequency may require short recall intervals (e.g., 24 hours) to capture variability in patient experience and avoid recall error.

Conclusion

Treatment requires a progressive and multifactorial approach that addresses the clinical and psychosocial aspects of living with diabetes. Therefore, patients’ perspective regarding their illness and treatments is increasingly acknowledged as a key consideration in diabetes health care decisions. Examining patients’ perspective and experiences in clinical trials assists HCPs in making decisions in clinical practice that are “respectful of, and responsive to, individual patient preferences, needs, and values”⁷ and allows them to understand likely medication-taking behavior in the real world.^{7,8}

The mission of *Diabetes Spectrum* is “to assist HCPs in the development of strategies to individualize treatment and diabetes self-management education for improved QoL and diabetes control.”⁹ Although there are no universally accepted specific definitions of QoL, there is general consensus that QoL is multidimensional, including physical, psychological, and social aspects,¹⁰ thereby sharing a common basis with the World Health Organization’s definition of health.¹¹ This article provides researchers with a systematic process for selecting and interpreting relevant patient-centric concepts and measures, including QoL, in a diabetes research study. This will help to ensure that PRO data are meaningful and to minimize measurement error, which, in turn, will simplify interpretation and help us better understand how patients experience diabetes, its treatment in clinical research specifically, and health care in general.

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