Patient-reported outcome measures in inflammatory bowel disease

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Patient-reported outcome measures (PROMs) are increasingly used in both research and clinical health settings. With the recent development of United States Food and Drug Administration guidance on PROMs, more attention is being devoted to their role and importance in health care. Several methodological challenges in the development, validation and implementation of PROMs must be resolved to ensure their appropriate utilization and interpretation. The present review discusses recent developments and updates in PROMs, with specific focus on the area of inflammatory bowel disease.

Key Words: *HRQoL; IBD; PROMs*

Les mesures de résultats déclarés par le patient en cas de maladie inflammatoire de l'intestin

Les mesures de résultats déclarés par le patient (MRDP) sont de plus en plus utilisées dans les milieux de recherche et les milieux cliniques. Depuis les directives récentes de la *Food and Drug Administration* des États-Unis sur le sujet, on s'intéresse davantage au rôle et à l'importance de ces mesures dans les soins. Il faut résoudre plusieurs problèmes méthodologiques liés à l'élaboration, à la validation et à la mise en œuvre des MRDP pour en assurer l'utilisation et l'interprétation adéquates. La présente analyse traite des récents ajouts et mises à jour aux MRDP, particulièrement les maladies inflammatoires de l'intestin.

Patient-reported outcome (PRO) measures (PROMs) are measures of the outcome of treatment and disease management that are reported directly by the patient or the caregiver. They highlight patients' experience with a disease and its treatment, including thoughts, impressions, perceptions and attitudes (1).

These outcomes may include symptoms, health/functional status, health-related quality of life (HRQoL), satisfaction with treatment and outcomes, and perceptions of the humanity of care through short, self-completed questionnaires most commonly used to measure patients' symptoms, functional status or HRQoL before and after an intervention (1-4). PRO instruments can be used in risk management programs because they are tools that measure the benefits and risks of exposure to pharmaceutical products from the patient's perspective. Clinical measures of improvement in some disease states may not necessarily correlate with improvements in a patient's ability to perform daily activities (5).

This category of health outcome measurement was developed following a significant global shift in the philosophy and understanding of health care and how it is measured. It is important to distinguish PROMs from patient-reported experience measures, which focus on aspects of the humanity of care such as being treated with dignity or being kept waiting (6).

Several thousand generic and disease-specific PROMs have emerged. Generic PROMs usually focus on general aspects (eg, mobility, ability to self-care). A single PROM can be comprised of numerous scales and domains (3,4).

Initially, PROMs were meant to be an additional outcome for clinical trials. However, over the years, PROMs have become a target to collect in several health care systems to help with better administration and planning of health services (7).

The first nationwide application of PROMs in clinical care was in the United Kingdom (UK) in 2008 in a voluntary audit of mastectomy and breast reconstruction, followed in April 2009 by a mandatory audit of all providers of hip and knee replacement, groin hernia repair and varicose vein surgery (8). Since April 2009, the National Health Service in the UK became the first health system in the world to advocate routinely collecting PROMs (4).

In 2006, the United States Food and Drug Administration (FDA) published new guidelines recommending PROMs to be used as end points in clinical trials. It was recommended that "the use of PRO instruments is part of a general movement toward the idea that the patient, properly queried, is the best source of information about how he or she feels" (9). These guidelines recommended a systematic cascade or cycle for creating a PRO instrument, which usually entails several important steps including item generation, selection of a method of administration, recall period and response scales (9). Any PRO instrument must be evaluated for validity, reliability and its ability to detect a meaningful change. The guidance also described how sponsors of new drugs or devices can use study results measured by PRO instruments to support claims on labels or the advertising of approved products (9).

A Patient-Centered Outcomes Research Institute (PCORI) has been created in the United States to support research that can produce answers generated through using rigorous, valid, patient-centred methods (10). The PCORI has adopted the following mission statement to guide their work: "help people make informed health care decisions, and improves health care delivery and outcomes, by producing and promoting high-integrity, evidence-based information that comes from research guided by patients, caregivers, and the broader healthcare community" (11).

PATIENTS' VIEWS OR CLINICIANS' VIEWS

Although many physicians are questioning the objectivity of PROMs in clinical practice and how patients may be affected by many other confounders when they complete PROM questionnaires, many other health care workers believe in incorporating patients' feedback and recognize the benefits of PROMs (12,13).

The skepticism of those who are opposed is based on the belief that only physicians can objectively recognize improvement of symptoms and subsequent improvement in quality of life (QoL).

In contrast, those who advocate for routine use of PROMs in health care are appreciative of how patients welcome being involved, and this may have significant health benefits in itself. Patient response rates are invariably better than those of clinicians, which may be

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explained by the fact that a patient has to complete only one questionnaire, whereas a clinician must complete a questionnaire for every patient. Moreover, to a large extent, PROMs avoid observer bias, which is inevitable if physicians are assessing their own practice (3).

Considering patients' views increases public accountability of health services and health care professionals; assists physicians to provide better and more patient-centred care; assesses and compares the quality of providers; and provides data for evaluating different practices (3). Whether these data are confounded by many other factors remain a matter of debate. These confounders include how and where the interview/survey is being conducted, how patients feel about health care providers including their own physicians, patients' socioeconomic status, cultural background and patients' health comorbidities (13).

PROMs IN CLINICAL TRIALS

Outcome selection and reporting in clinical trials can be a challenging task. Heterogeneity and lack of validation of outcomes measured across different studies for the same disorder or therapy could compromise synthesis of high-quality evidence (13). Several items of PROMs can be ill-defined depending on how the survey is designed (structured versus semistructured or nonstructured) (13-15); consequently, reporting the outcome can be difficult. A proposed solution to this problem is the development of core outcome sets (COSs). COSs are an agreed minimum set of outcome domains to be measured and reported in all trials of a particular treatment or condition (ie, standardization of a minimum set of outcomes that can be measured across all the studies for the same disease or treatment) (14). This should significantly reduce outcome reporting bias (15,16). Currently, however, there is no consensus in several disciplines on what these COSs should be.

PROMs IN INFLAMMATORY BOWEL DISEASE

Several questionnaire and survey tools, including HRQoL tools, examining views and feedback of patients with inflammatory bowel disease (IBD) have been developed over the years. Several examples include Inflammatory Bowel Disease Stress Index (IBDSI), Inflammatory Bowel Disease Questionnaire (IBDQ-32), Rating Form of IBD Patient Concerns (RFIPC), Cleveland Global Quality of Life (Faszio Score), Inflammatory Bowel Disease Quality of Life Questionnaire (IBDQOL), Inflammatory Bowel Disease Questionnaire – short form (IBDQ-9), Short Inflammatory Bowel Disease Questionnaire and Work Productivity and Activity Impairment: Crohn's Disease (WPAI: CD) (17-25) (Table 1).

Many of these tools have been used primarily in the research setting and are frequently used as end points for clinical trials in IBD. Several examples include reporting significant improvement of HRQoL in patients with IBD treated with several biologics (26-35). Both generic and disease-specific tools were used in these studies including the EQ-5D (26,30-33).

Nonetheless, until recently, the term 'PROMs' has not been formally used to describe these tools. On the other hand, very few studies have developed their own PROMs based on previous similar tools, patients' feedback and expert opinion.

A recent study by Kappelman et al (36), used the Patient-Reported Outcomes Measurement Information System (PROMIS) initiative of the National Institutes of Health, which was developed to address, investigate and promote implementation of PROMs among patients with chronic disease (37,38). In this study, the investigators performed cross-sectional and longitudinal analyses using an Internet cohort of adults with IBD to evaluate the performance PROMIS measures in relation to validated activity indexes and disease-specific HRQoL (36). They built their own PROMs questionnaire based on previous literature, investigators' experience and patients' feedback. The main domains included were anxiety, depression, fatigue, sleep disturbance, satisfaction with social role and pain interference. They used the Short IBD Questionnaire (24) to measure HRQoL. Disease activity was assessed using the Short Crohn's Disease Activity Index (SCDAI) for Crohn's disease (CD) (39) and the Simple Clinical Colitis Activity Index (SCCAI) for ulcerative colitis and indeterminate colitis (40). More than 10,000 patients with IBD were able to complete PRO testing. In the cross-sectional part of the study, and compared with the general population, IBD patients in this cohort reported more depression, anxiety, fatigue, sleep disturbance and pain interference; they also had less social satisfaction. In each PROMIS domain, there was worse functioning with increased disease activity and worsening Short IBD Questionnaire scores. Longitudinal analyses showed improved PROMIS scores with improved disease activity and worsening PROMIS scores with worsening disease. Based, on these results, the authors concluded that the use of PROMs should advance patient-centred outcomes research in IBD (36).

TABLE 1
Characteristics of inflammatory bowel disease (IBD)-specific patient-reported outcome measures (PROMs) used in adult patients with IBD

PROMs	Outcome measured	Items, n
Inflammatory Bowel Disease Stress Index (IBDSI) (17)	Overall life satisfaction, worries about health, relationships, sexuality, body image, recreation and psychosomatic symptomatology	8
Inflammatory Bowel Disease Questionnaire (IBDQ)-32 (18)	Quality of life	32
Rating Form of IBD Patient Concerns (RFIPC) (19)	Concerns associated with IBD and treatments	25
Cleveland Global Quality of Life (Faszio Score) (CGQL) (20)	Quality of life after pouch surgery	3
Inflammatory Bowel Disease Quality of Life Questionnaire (IBDQOL) (21)	Quality of life	36
Inflammatory Bowel Disease Questionnaire- short form (IBDQ)-9 (22,23)	Quality of life	9
Short Inflammatory Bowel Disease Questionnaire (SIBDQ) (24)	Quality of life	10
Work Productivity and Activity Impairment: Crohn's Disease (PAI:CD) (25)	Work and activity impairment	6

In a study from Norway (41) that used the term 'PROMs', Jelsness-Jørgensen et al (42) used the Short Form 36 (SF-36), Inflammatory Bowel Disease Questionnaire (N-IBDQ) (43) and the Rating Form of IBD Patient Concerns (RFIPC) (16) instruments as PROMs at baseline and after one year to examine the impact of conventional versus nurse-led follow-up on PROMs of 140 patients with IBD (41). Conventional follow-up was described as regular visits to a clinic that was operated by experienced consultant gastroenterologists. Nurse-led follow-up was performed in the form of three monthly visits to a clinic that was led by an IBD nurse. Periods of hospitalization, surgery and number of relapses were also recorded at baseline and during follow-up. There was no significant difference in any of the study outcomes, except for a shorter interval from the start of a relapse to starting treatment in the nurse-led follow-up group (41).

In a small group of patients with CD, Dur et al (44) examined determinants of health (DH) that are most important to patients and explored which DH(s) were covered by commonly used PROMs for CD (44). They found that social support, self-efficacy, job satisfaction and occupational balance were the most meaningful DHs for patients with CD. While social support and self-efficacy were covered by several PROMs, such as the Inflammatory Bowel Disease – Self Efficacy Scale (IBD-SES), job satisfaction, occupational balance, secondary gain from illness, sense of coherence, vocational gratification and work-life balance are not covered by any of the 18 identified PROMs (44).

PROMs AND INTERNATIONAL CLASSIFICATION OF FUNCTIONING, DISABILITY AND HEALTH IN IBD

The WHO's International Classification of Functioning, Disability and Health (ICF) has been used worldwide for many different goals (45-47). The ICF is a generic classification for functionality and has been used for evaluating functional outcomes in other chronic disorders (eg, stroke) (48). It provides a unified, holistic and standardized language to describe health, disease and disease consequences. It also connects, through several domains, disease-related disability with other factors that may influence heath conditions including social, personal and environmental factors (49,50).

Several investigators have suggested linking measurements of health status in patients with IBD and the ICF (45,51,52). In a recent systematic review by Achleitner et al (45), who were trying to create a link between several IBD-related PROMs and ICF, they defined PROMs as outcome measures in which patients respond to a number of standardized questions asked in a paper-pencil format. The items of the identified PROMs were linked to the ICF. The authors identified 46 studies reporting the use of IBD-specific PROMs. Of note was that these studies did not use the term 'PROMs' for these specific tools; however, these questionnaires were mainly addressing QoL for patients with IBD (16-24). Nearly 70% of the 129 items identified could be linked to specific categories of the ICF (45). However, none of those already existing IBD PROMs contained all items that could be linked to ICF (45). Consequently, there is room to create and validate new PROMs that involve all necessary ICF-based items. This tool can be used for clinical and research purposes.

Peyrin-Biroulet et al (53) performed a literature search investigating disability evaluation in IBD in relation to ICF. Although the several available tools for QoL measurement in IBD capture some aspects of functioning, it was obvious that disability was poorly investigated in the IBD literature. Moreover, compared with other chronic diseases, such as rheumatoid arthritis (RA), the consequences of disability in the management of IBD was underestimated. The authors recommended identifying ICF COSs for IBD that were already implemented in other chronic diseases such as depression and obesity. In addition, and similar to Achleitner et al (45), they also recommended the development of a validated tool including all aspects of limitations of functions in patients with IBD that can be used for both clinical practice and research purposes (46). This tool should be considered to be under the umbrella of PROMs, and should be designed to consider the different personal and environmental factors for individual patients with IBD.

Hence, the international IBD disability index (IBD-DI) was developed as a result of the collaborative work of several investigators (The IPNIC group) (52). The index was developed through several steps including four preparatory studies and is currently being validated (53-55). ICF IBD-DI consists of 19 categories assessed through 28 questions covering the five domains of overall health, body function (seven categories), body structures (two categories), activity participation (five categories) and environmental factors (five categories) (52). The IBD-DI was specifically designed to exclude the use of any questions that examine patients' subjective coping and feelings (53,55). It addresses the extent of disability and limitations in several areas such as sleep, work, social events and exacerbating effects of medication, food, family and health care professionals. Similar to other ICF scores, positive scores were proportional to absence of limitations and good functioning, while negative scores were indicative of greater disability. Scores from each question were combined into domain totals and a final composite score representative of the overall degree of disability ranging from −80 (maximum degree of disability) to 22 (no disability) with '0' as the anticipated point of neutrality. Scores of severe, moderate, mild and minimal disability correlated with the ability to work <50%, 50% to 75%, 76% to 99% and 100% of work hours in the previous week (53,55).

In a validation study, Leong et al (55) measured IBD-DI, IBD-Q and WPA:I in an adult cohort with IBD. They also examined disease-related clinical outcomes, including CDAI, in those with CD (75 patients) and partial Mayo score in patients with ulcerative colitis (41 patients); they also recruited 50 healthy controls. IBD-DI significantly correlated with CDAI, partial Mayo score and IBD-Q. IBD-DI was the only outcome predictive of unemployment status.

PROMs IN OTHER DISCIPLINES

Cancer care

Several PROMs have been used in both clinical care and research involving cancer patients (56-64). In the most widely cited model of PRO measurement, Wilson and Cleary (59) highlighted an interesting, unique perception of PROs in the form of different 'levels' of PROs along a scale with regard to their 'proximal' (symptoms) versus 'distal' (overall QoL) relationship to the disease or treatment involved (59). The model indicated that more distal PROs were subject to greater mediation by personal and environmental factors than were more proximal PROs. The most distal outcome, overall QoL, was affected not only by health status but also by nonmedical factors (eg, bereavement, financial stress, environmental factors). Intermediate levels of PROMs are available as health-related or disease-specific QoL measures, which limit assessment to the impacts of health in general or a particular condition (58,59).

Soreide and Soreide (60) emphasized the increasing importance of PROMs in addition to the classical outcomes for clinical patient-centred decision making in patients with cancer.

Three main approaches to measuring PROMs in patients with cancer have been suggested. One is the generic approach to health status measurement that allows comparison across different health conditions (61). The second approach is the cancer-generic approach, which is more specific to patients with any cancer, regardless of type (62-64). The third is more focused to the specific cancer subtype (65,66).

PROMIS is also developing measures of self-reported health domains specifically targeted to cancer, such as sleep/wake function, sexual function, cognitive function and the psychosocial impacts of the illness experience (ie, stress response and coping, shifts in self-concept, social interactions and spirituality) (67). Future directions include reviewing the current PROMs in oncology to ensure continuing validity (58).

RA

Standardization of disease assessment in RA have been formulated through the Outcome Measures in Rheumatology Clinical Trials (OMERACT) meetings, leading to a 'core set' of eight outcomes as an international standard in RA clinical trials (68,69). Interestingly, these outcomes did not include fatigue, which is an integral part of RA experienced by almost all patients (70,71). Nicklin et al (72) developed draft PROMs not only to measure fatigue in patients with RA but also to develop the wording for it in a way that patients can understand and express. Fatigue descriptors included 'exhausted', 'tired', 'drained', 'lethargic', etc. Nonetheless, this set of PROMs has not yet been fully evaluated for validity or reliability (72). This study highlighted the importance of collaboration with patients to develop PROMs.

In their systematic review to appraise PROMs that focussed on RA of the foot, Walmsley et al (73) identified 11 PROMs that were utilized in this context; however, only one was disease specific. Examples of nondisease-specific PROMs would include the Foot Function Index (74), The Manchester Foot Pain and Disability Questionnaire (75), The Podiatry Health Questionnaire (76), The Bristol Foot Score (77), The Foot Health Status Questionnaire (78) and The Rowan Foot Pain Assessment Questionnaire (79). The disease-specific PROM was The Juvenile Arthritis Foot Disability Index (80). The review concluded that there was a need to develop an RA-disease and foot-specific PROM with a greater emphasis on cognitive pretesting methods and patient preference-based qualities (73).

Asthma

A recent inquiry from the UK identified several concerns regarding outcome measures in patients with allergy (81). Worth et al (82) are currently conducting a systematic review to identify validated generic

and disease-specific PROMs for asthma and related allergic conditions in adults and children. Blanco-Aparicio et al (83) preformed a prospective cohort study that included 108 adult patients with asthma. Patients were asked to complete a survey to determine the ability of brief specific HRQoL questionnaires to predict emergency department visits and hospitalizations in patients with asthma. They used the AQ20, which is a specific questionnaire validated for patients with asthma (84). They also used chronic obstructive pulmonary disease-specific questionnaires in another group of patients with chronic obstructive pulmonary disease (85,86). The AQ20 predicted exacerbations in asthma during the first year of follow-up but not during the second year (83).

The Living with Asthma Questionnaire is a validated asthma-specific QoL instrument for assessing patients' own subjective experiences of asthma. The scale has 68 items and covers 11 domains of asthma experience. They were developed from extensive interactions with patients with asthma (87).

Diabetes

A diabetes QoL (DQoL) instrument has been developed and validated in patients (both adolescents and adults) with type 1 diabetes (88). The DQoL is a multiple-choice assessment tool with four primary scales that includes 46 core items. These scales are satisfaction, impact, diabetes worry, social/vocational worry. This tool does not identify specific types of treatment or self-monitoring. Consequently, it can be used for patients using different methods of diabetes management (88). However, it has been recently identified that currently there are no PROMs that are strongly associated with variations in therapeutic strategies of diabetes (89). Moreover, PROMs are poorly utilized in diabetes care (89).

Surgery

Several generic and disease-specific PROMs have been used in patients who have undergone surgeries. Generic PROMs include EQ-5D and EQ-VAS (90-93). Examples of surgery-specific PROMs include Aberdeen Varicose Vein Questionnaire (AVVQ), Oxford Hip Score (OHS) and Oxford Knee Score (OKS) (93-96).

PEDIATRIC CARE

Children are not small adults. Interviewing children and adolescents requires knowledge of their specific cognitive, linguistic, social, cultural and developmental characteristics to better understand their perspective (97,98). Developing the knowledge in advance of key words the children use, for example, by asking parents, will allow the interviewer to quickly connect with the child. Parental interviews should provide information about the child's history as well as clarify each parent's view of the child. Questions asked to children should be simple and precise (98). Careful attention should be devoted to the use of age-appropriate language throughout the interview (99). These issues must be taken into consideration when health care providers plan and develop pediatric-specific PROMs and assess HRQoL. Several validated tools have been developed for several pediatric diseases.

In the area of pediatric IBD, generic and disease-specific instruments have been developed, validated and utilized in many settings. Generic tools include the Pediatric Quality of Life Inventory (PedsQL), which examined HRQoL in children with IBD and compared them with healthy peers and with children with other chronic diseases (100-103). Disease-specific tools include the IMPACT questionnaire, which measures six domains including bowel-related symptoms, systematic symptoms, functionality including social interaction, body image, emotional aspects and treatment-related concerns (104,105).

Other disease-specific instruments include the TNO-AZL Children's Quality of Life questionnaire (TACQOL), which includes seven domains (106), and IMPACT II (NL), which includes six domains (107).

A recent systematic review recently examined the available literature that investigated psychosocial functioning and HRQoL in children and young adults with IBD and identified 12 studies that included >5000 children and young adults (790 with IBD, <18 years of age) and fulfilled its inclusion criteria (108). Several studies examined HRQoL (106,107,109,110) but only one study was a prospective longitudinal study using IMPACT III instrument (110). Overall, and despite concerns about design and methodological flaws in several of those studies, HRQoL appeared to be lower in children and young adults with IBD (108).

In an attempt to develop a self-efficacy scale for children with IBD (111), a recent pediatric study followed the FDA cycle for developing PROMs (9). The investigators initially conducted a survey in the form of semistructured questionnaire to obtain the input of patients attending a pediatric gastroenterology clinic. Self-efficacy themes related to disease management were reviewed and followed by arranging a consensus panel of gastroenterologists and psychologists to review the initially constructed items. These specific items were then reviewed and adjusted by a panel of participants for content and understandability using cognitive interview methods. This eventually resulted in four domains that include a three-item self-efficacy scale (112). Validation studies are needed before this scale can be widely used (112).

PROMs have been developing with promising results in other areas of pediatrics and child care including children with mental health problems, eye problems and obesity (113-115).

FINAL REMARKS

In a recent Canadian survey (116), 52% of Canadians believed that the current health system needs fundamental changes and 10% believed that the system needs to be completely rebuilt. These challenges are not unique to Canada but occur across the world (117).

Many Canadian health care leaders were interviewed seeking their views on the challenges that the system is currently facing, especially with regard to quality improvement (118). The results of these interviews highlighted the need for engaging physicians and patients in quality agenda. One of the themes identified in this survey was the need to commit to measurement and reporting on performance and quality outcomes. Quality measurements and indicators are crucial for health care improvement. PROMs can add unique aspects of quality and performance measurement. Moreover, they can inform health care providers on issues related inequities in health status. National surveys, such as the Canadian Community Health Survey, can be utilized to provide meaningful PROMs.

Under the Excellent Care for All Act, The Ontario government has legalized the performance of yearly surveys for patients' satisfaction. The results of these surveys should be used to guide health care providers in improving the quality of care. However, there is a need for development, validation and implementation of quality indicators that can be linked to improved outcomes (119).

On the other hand, several health care providers are debating whether patient-satisfaction scores are linked to improvement in overall outcomes (120). A recent study showed that increased patient satisfaction was associated with health care-related costs and higher overall mortality (121). The authors speculated that the cause of their conclusion may be related to the fact that there is currently an increasing utilization of discretionary care (medical management for which there is no proven benefit) with higher chances of overtreatment and iatrogenic harm, an explanation that has been addressed previously (121,122).

Several questions related to PROMs and their use, including those for IBD, still require answers as to the best way to define patient satisfaction, how to develop them and whether FDA guidelines must be followed in development, how to objectively measure it and whether the improvement is truly beneficial (120). Although developing the IBD-DI is an important step, it remains unclear whether it will help in answering these questions, and how practical its routine use in clinical and research setting will be.

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