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Evaluating Health-related Quality of Life (HRQoL) Scales for Rare Diseases from a Quality of Life (QoL) Perspective

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Abstract

Although rare diseases concern a small fragment of the population, they collectively affect about 4% of the general population. The well-being of patients with rare diseases has long been overlooked, but several scales now measure their health-related quality of life (HRQoL), enabling targeted cures and interventions. However, not all scales are equally efficient at measuring key aspects of quality of life of patients. In the present study, we evaluate health related quality of life (HRQoL) scales for rare diseases from the perspective of the social science-driven field of quality of life (QOL). Using the method of Booyesen to evaluate social indicators, we review eleven scales frequently used in the case of rare diseases (CFQ, CFQoL, DLQI, MOS, PLC, QLI, SF-12, SF-36, SIP, Skindex, TAAQOL) and map what is measured and what is not. Key findings are that scales are overly focused on output-based specific indicators, lack flexibility, and miss a holistic view of quality of life. We suggest improvements such as incorporating more generic items, including input indicators, targeting general well-being, and involving patients in the development of questions.

Keywords: Rare diseases, HRQoL, QOL, well-being, scales, evaluation

1. Introduction

Rare diseases¹ include a wide and diverse group of life-threatening and handicapping diseases, often chronic and incurable. Although each disease affects only a small number of individuals, the population which suffers from one rare disease is paradoxically high (300 million people worldwide, cf. Nguengang Wakap et al. 2021). About 80% of rare diseases are genetic and thus frequently begin in early childhood (Bogart and Irvin 2017).

Historical context

Since the rise of chronic diseases in the mid-20th century, the shift from a care provided in hospitals to a care provided outside hospitals, the shift from cure to disease management, biological measures such as survival were no longer appropriate, so that more attention has been paid to the way patients lived with their diseases and their well-being. According to Armstrong (2009), in the 1970s, “a rhetoric emerged that stressed a new goal for medicine, that of improving health-related quality of life” (HRQoL) (p.103). The concept of quality of life literally “colonized” modern medicine (see Armstrong and Caldwell 2004) as it provided a solution to assess the quality of care given to a patient, which was both “a legitimate clinical goal and an ethical right” (p.366). However, although the biomedical field uses extensively the term “quality of life”, it became clear that there are large differences (epistemological, theoretical, methodological) in the way this term is used in the field of

¹ Rare diseases are diseases that affect a small percentage of the population. The thresholds are different according to the country or the region. In the European Union, rare diseases should affect not more than 1 in 2000 persons. In the USA, they should affect less than 200'000 patients in the country.

QOL, i.e. quality of life perceived from the field of social sciences, and HRQoL, i.e. quality of life as considered within the medical field (Michalos 2004).

The field of QOL can be divided into three main substreams whose objective is to measure hedonic, evaluative and eudaimonic well-being. Except for eudaimonic well-being, which is a rather autonomous subfield based on multidimensional measures, the vast majority of quality of life studies focus on unidimensional measures of well-being such as life satisfaction, life evaluation or emotions. Because it is mainly constituted by social scientists, the main focus has been the general population in order to provide advice to policy makers to maximize well-being among the population. As such, it has produced little in the field of clinical research, and virtually no studies from the field of QOL has focused on rare diseases apart from a few exceptions (Bryson et al. 2020).

Since the rise of HRQoL in the 1970s, over 1,000 instruments adapted to different conditions were developed (see in Karimi & Brazier 2016). However, while the scientific literature covered prevalent diseases (cancer, renal disease, heart disease, ...) it addressed only lately rare diseases. This was firstly due to the scarce prevalence of cases in each rare disease, which failed to meet the numerical prerequisite required by the quantitative paradigm of HRQoL instruments, but also to the fact that rare diseases tended to be under-investigated until recently. As Huyard (2009) puts it, the term 'rare diseases' was "hardly meaningful" before the 1970s when it appeared in the United States in the 1980's in the USA and a couple of decades later in Europe (see in Cohen and Biesecker 2010).

Current challenges

Living with a rare disease affects dimensions of life that go way beyond mere physical considerations, with social, emotional and psychological features being impacted as well, hereby affecting all domains of well-being (Veenhoven 2007, Bryson et al 2020). Admittedly, measuring the quality of life of patients with rare diseases should reflect its multidimensionality and possibly provide insights that can lead to better treatments and interventions. Patients with rare diseases report poorer health-related quality of life (HRQoL) than the general population but also compared to people living with chronic but prevalent conditions (Aymé, Kole and Groft 2008). Part of the reasons is that patients feel they lack proper advice from their medical advisor due to fact that health-related quality of life is not assessed adequately and few rare diseases have effective treatments or cures (Cohen & Biesecker 2010). HRQoL indicators should “enable professional decision-making based on relevant, personal and holistic information about patients” (Miron Canelo, p.3). Also, the well-being of patients is mostly hidden as many measures are based on the perspective of medical staff. According to Cohen & Biesecker (2010), “the medical literature remains limited in fully representing the perspective of those affected with these conditions” (p.1137). Therefore, a robust evaluation of the current tools for measuring quality of life of patients with rare diseases is lacking.

In the latest review on quality of life of patients with rare disease (targeting articles that were 1) original research of 2) individuals affected with rare genetic conditions 3) the goal of which was to describe QoL and/or predictors), 18 scales are included, with 7 for children only (Cohen and Biesecker 2010). As we are interested in the whole population, we keep

the scales that are not restricted to children or adolescents. This leaves us with 11 scales that are frequently used in research papers to assess the quality of life of patients with rare diseases: Cystic Fibrosis questionnaire (CFQ), Cystic Fibrosis Quality of Life Questionnaire (CFQoL), Dermatology Life Quality Index (DLQI), Medical Outcomes Study General Health Survey (MOS), Profile of Quality of Life in the Chronically Ill (PLC), Quality of Life Index (QLI), Medical Outcomes Study Short Form 12 (SF-12), Medical Outcomes Study Short Form 36 (SF-36), Sickness Impact Profile (SIP), Skin Diseases Quality of Life Index (Skindex), TNO-AZL Adult Quality of Life (TAAQOL). Although the review dates from 2011, after looking at the publications on Pubmed since then, no particular scale that has emerged in the last decade for rare diseases, except for isolated initiatives (see e.g. Koto et al. 2022). We do not evaluate the families of PROMIS assessment as they do not represent a particular scale and raises questions on their potential for rare diseases (see Whittall, Meregaglia and Nicod (2021)) but discuss directly in the findings the possibilities they offer in measuring QOL.

Study objectives

Although there are multiple attempts to question the validity of well-being from a medical perspective (HRQoL), these tools have never been questioned in depth from the perspective of QOL. This matters as medical practitioners tend to be focused on the effectiveness of treatments and overlook well-being, which social scientists typically consider. Thus, the insights of QOL can offer an insightful mirror. In this paper, we assess the quality of existing scales for rare diseases by using insights from the field of QOL, namely the method of Booyesen (2002), often used in evaluating social indicators (e.g. Croes and Vermeulen 2016, Del Rio et al. 2021, Brulé 2022, Karasev et al. 2022). This way, we can

bring a unique contribution to the evaluation of HRQoL scales for patients with rare diseases.

2. Existing generic and specific scales

In this section, we present the eleven scales for rare diseases used for the general population of individuals with rare diseases (i.e. children-only related scales are excluded). These are CFQoL, CFQ, DLQI, MOS, PLC, QLI, SF-12, SF-36, SIP, Skindex and TAAQOL. These are presented in Table 1.

Table 1 about here

Cystic Fibrosis Questionnaire (CFQ) is a disease-specific scale for adults with cystic issues (Henry et al. 1997, Quittner et al. 2002, Wenninger et al. 2003). It has three modules (health related quality of life (HRQoL), symptoms and overall health perception). There are nine dimensions for HRQoL (Physical Functioning, Vitality, Emotional state, Social limitations, Role Limitations/School Performance, Embarrassment, Body Image, Eating Disturbances, Treatment Constraints), three symptom scales (Respiratory, Digestive, Weight) and one health perception scale.

Cystic Fibrosis Quality of Life (CFQoL) is the questionnaire developed by Gee et al. (2000) on quality of life of patients with cystic fibrosis. It comprises nine dimensions (physical functioning, social functioning, treatment issues, chest symptoms, emotional responses, concerns for the future, interpersonal relationships, body image, career concerns)².

² There are slight differences between two versions of the scale, with emotional responses absent from CFQoL1 and Relationships at work excluded from CFQoL2.

Dermatology Life Quality Index (DLQI) was the first dermatology-specific quality of life questionnaire (see in Finlay and Khan 1994). The DLQI consists of 10 questions concerning patients' perception of the impact of skin diseases on different aspects of their health-related quality of life over the last week. These questions cover daily sensations, impediment in pursuing daily activities and effect of treatment.

Medical Outcomes Study General Health Survey (MOS) was designed by Stewart, Hays and Ware (1988). It comprises six dimensions (physical functioning, role functioning, social functioning, mental health, health perceptions, pain).

Profile of Quality of Life in the Chronically Ill (PLC) is a standardized, self-administered survey assessing HRQoL of patients with chronic diseases developed by Siegrist, Hernandez-Mejia and Fernandez-Lopez (2000). It comprises a generic part, as well as disease-specific and a treatment-specific part.

Skinindex is an index dedicated to assessing the impact of skin diseases on quality of life. It was developed by Chren et al. (1996). It comprises two dimensions (physical and psychosocial) divided in 8 subdimensions (cognitive, social, discomfort, limitations, depression, fear, embarrassment, and anger).

The Quality of Life Index (QLI) covers several dimensions of quality of life of patients (daily living activities, work or principal activities, health, outlook over life and support). Each dimension is covered by one item. Originally aimed to be filled by health professionals, it is also designed to be assessed by the respondent as well as significant others of the patient (Spitzer 1987).

The SF-36 is one of the most used tools. It is a questionnaire meant to assess patients' own view of their health and well-being. It comprises 8 dimensions (limitation in social activities due to health problems, limitation in social activities due to physical problems,

limitation in social activities due to emotional problems, bodily pain, mental health, limitation in role activities due to emotional issues, vitality, general health perception (see Ware and Sherbourne 1992). There is also a general question asking for a general assessment of one's health and comparison with one year ago. Two versions of the questionnaire exist, a standard with a 4-week recall period and an acute one, with a one week recall period.

SF-12 was the most used for assessment of clinical outcomes in the field of HRQoL (see in Miron Carnelo 2021). The SF-12 is a shortened version of the SF-36. It has the same eight dimensions but fewer questions. It was designed for the Medical Outcomes Study (MOS). Patients fill out the questionnaire which is then scored by medical doctors or practitioners.

The Sickness Impact Profile (SIP) was designed to measure the impact of illness on behaviors (Bergner et al. 1981). It has 3 dimensions (psychosocial, physical and other impairments), 12 sub-dimensions (sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care and movement, social interaction, alertness behavior, emotional behavior, and communication) and 136 items.

TNO-AZL Adult Quality of Life (TAAQOL) is a questionnaire developed by the Dutch technical institution TNO (Toegepast Natuurwetenschappelijk Onderzoek) and the Leiden University Medical Centre (Fekkes et al. 2001). It consists of 45 questions divided into 12 domains (gross motor functioning, fine motor functioning, pain, sleeping, cognitive functioning, social functioning, daily activities, sexual activity, vitality, happiness, depressive moods, and aggressiveness). In this scale, each item is weighted by the problem it represents for the person. For instance, a question on how much did one struggle to walk up the stairs is weighted against how much did that matter for the person.

3.Evaluation of the scales of HRQoL for patients with rare diseases

Evaluation of existing scales is a must-do in order to reflect upon the distance between latent variables and measured variables. It is regularly done in the fields of HRQoL (see e.g. Miron Canelo et al. 2021, Fryback et al. 2010, Hand 2016, Salde et al. 2018, Whittal et al. 2021) and QOL (see e.g. Zou, Schimmack and Gere 2013, Facchinetti and Siletti 2022, Brulé 2022). However, rare diseases bring specific barriers to traditional validation methods, also in the case of selecting health measurement instruments (COSMIN). As for HRQoL in the case of rare diseases, “reliability as well as content, criterion, and construct validity, and also responsiveness should be taken into account in selecting the instrument to be used assessing individuals with rare diseases” (Rajmil, Perestelo-Porez and Herdman 2010, p.251). Miron-Canelo et al. (2021) use validity, reliability, discriminatory power, internal consistency and strength of recommendation. Although the fields are different, the criteria used in the field of QOL are about similar, articulated around validity and reliability concerns. There are several methods as well in field of QOL. Ivan and Mercy (2014) use five criteria: relevance (attractiveness, responsiveness), accuracy and reliability, timeliness and continuity, comparability, clarity (easiness in understanding, communicability). For Verdugo et al. (2012), indicators in the field of QOL of handicapped person should reflect “what people want in their lives, are culturally sensitive, are related to current and future policy issues, are those that the individual (or service provider) has some control over, and can be used for quality improvement purposes” (p.23). The perspective of QOL is to look not only at the effectiveness of treatments but what matters for the well-being of patients. Validity, reliability and sensitivity to changes are presented in table 2 below.

Table 2 about here

A look at the QOL and HRQoL literature make it possible to find others sets of criteria. In this paper, we use the method of Booyesen (2002) to review existing scales in the field of HRQoL. It is articulated around 7 criteria: content, technique and method, comparative application, focus, clarity and simplicity, availability and flexibility. There are several reasons to select this method. First, it enables a combination of descriptive as well as evaluating criteria. Second, some of the criteria such as clarity, availability and focus provide a powerful heuristic framework in our case. Third, it includes the criterion “flexibility” which is important in the domain of rare diseases as many diseases cover very limited number of people and thus require some suppleness in order to navigate with these limits. Fourth, which is also a consequence of the former criteria, it has been used in the assessment of indicators in various fields and contexts (e.g. Croes and Vermeulen 2016, Del Rio et al. 2021, Brulé 2022, Karasev et al. 2022).

Some criteria are usable as such, whereas others may be influenced by the original field in which the scale was developed (cross-national comparison of development). This is the case for flexibility and availability. Both are meant for cross-national indexes, the first one for the easiness to replace questions or items and the second one for availability of the data across countries. In order to use them, we need to recontextualize them in the field of patients with rare diseases. The rest of the indicators are all usable as they were originally designed. We present them all below in the context of the present study.

Content is a descriptive criterion in which dimensions and subdimensions of the scales are presented. *Technique and method* is a more detailed descriptive criterion composed of several subcriteria. In this category, the way the various items were selected is presented

(whether they were based on the literature, experts, patients, how the items were measured based on ordinal/cardinal/dichotomic indicators, the length of Likert scale (1-4, 1-7, 1-10...), how the different dimensions, subdimensions and items were weighed, how they were aggregated (arithmetic, geometric), how the validity was assessed (item analysis, external validity). *Comparative application* aims at understanding what the scale intends to measure and compare (intrapersonal, intragroup, interpersonal differences). *Focus* is based on whether the index (and the indicators) rely on input (what are the conditions for health-related quality of life of the patient, such as the frequency of visit of family or medical staff) or output perspectives (what are the results of the health-related quality of life of the patient, i.e. such as difficulty to climb the stairs). *Clarity and simplicity* is a way to evaluate how clear, simple and readable is the scale in relation to what it is meant to evaluate. We consider it is totally clear and simple (***) if the items are well integrated with the objective and if the number of items is limited, partly clear and simple (**) if the integration between the objective and the items are not clear or if the number of items is high and not clear and simple (*) if the objective and the items are not well connected and the number of items is too high. For *availability of the data*, originally meant for availability of the data at the national level, we use it in the sense of availability of the questionnaire, as some of the questionnaires are non-available, some are available at a fee and some are freely available. For *flexibility*, we look at the degree of variability that is made possible by the scales, be it by including a disease-specific part on top of a generic one or by including weights that the respondents can use to stick as closely as possible to their experience. We consider it is highly flexible (***) when items for a specific rare disease could be chosen or added and low flexibility (*) was given when only generic questionnaires were available. There was no in-between situations.

The assessment of the 11 scales according to the seven criteria is presented in table 3 below.

Table 3 about here

4.Discussion

Assessing the quality of existing scales for patients with rare diseases leads to different points of discussion. The perspective of QOL studies make it possible to place special emphasis on the overall well-being of patients. We explore below the tensions between disease-specificity and genericity, input and output, and item-specific or integrative assessments, the place of the patient in the questionnaire, before taking some epistemological reflections. We finish by providing key recommendations to measure the well-being of patients with rare diseases. The main hrqol measures are compared to key measures of qol (life satisfaction, life evaluation, affective measures) in Table 4.

Table 4 about here

Disease-specific vs generic

Because rare diseases pose a practical problem, due to the low numbers of cases each represents, it is hard to imagine a specific scale for each of the thousands of rare diseases that have been mapped. Still, there is an agreement that most rare diseases lack disease-specific items that would enable to understand better patients' experience (see Arends, Hollak and Biegstraaten (2015), IRDiRC (2016)). Thus, balancing feasibility and specificity can be done by a compromise between some degree of "genericity" and some degree of adaptability. To go beyond common dilemma between generic assessment applicable to

most situations but imprecise for health care purposes and specific assessment, which is more precise but that miss a degree of integration, Lenderking et al. (2021) suggest a few strategies to adapt to the needs of the specific disease: use of item banks, adapting existing measures, adaptive methods of content validity assessment and updating existing content validity evidence. We have seen that scales such as the PLC, which uses 40 generic questions and 10 to 20 disease-specific or treatment-specific items, enable that flexibility for diseases while most scales do not enable any flexibility.

Input vs output

Input and output indicators are one classical way to make sense of the focal of the indicators, whether it is on the efforts made (input) or on the outcome (output) (see e.g. Land 1983, Maggino 2017). In certain cases, for instance to measure the effectiveness of charity programmes or in the corporate sector, a distinction is made between output, outcome and impact (see e.g. UNDP 2009), which we don't do here, as it is less relevant in our cases.

In the context of scales of rare diseases, most scales are using output indicators in order to observe for instance, the impediments or the emotions due to the disease (for instance "I am angered by my health condition" or "I am embarrassed by my skin condition" for Skindex). In a few cases, there are questions that are not specific to the illness, i.e. about the emotions in general or social questions such as having a job or not, that can be considered as much as an input for quality of life or as an output due to the illness ("I am not working at all" or "I often act irritable toward my work associates" in the Sickness Impact Profile). It is common to note that some items can be both an input and an output such as for instance the case of literacy in development programmes which is at the same time an

output and an input for further development (Booyesen 2002). Looking at the scale of HRQoL for rare diseases, the almost complete focus on output indicators we have observed in these eleven scales should be at the very minimum questioned, because HRQoL is multidimensional and asking a respondent to relate a certain emotional state to the illness or a certain social situation to the illness is anything but obvious. As researchers in quality of life know all too well, respondents are able to know how good they feel but are not always aware of the reasons for it. According to Michalos (2004), “giving people the first word to assess the overall quality of their own lives does not imply that each person’s word is always the only, best or final word, or that such first words are in principle incorrigible” (p.34).

Also, in an attempt to externalize preexisting problems, maybe a respondent could be tempted to attribute to the illness a situation that has little to do it but rather to personality or other aspects not related to health. Therefore, it might be more prudent to combine impediment-specific questions and more general input indicators that can be further linked to the conditions of respondents in order to determine if yes or no, people with a given disease suffer statistically more or not than the rest of the population of the disease to meet people, find a job, have intimate relationships, etc. Using more input would enable comparative applications and not only descriptive applications of a certain group. This also entails that to enable comparative applications, there is a need for available data at the national level. However, we have seen that data for the general population was only available for the SF-12 and SF-36 scales. In the rest of the cases, there are essentially no data available on the general population for comparative purposes. This is the goal of Patient-Reported Outcomes Measurement Information System (PROMIS), which aim at measuring quality of life of the general population and to link it to any specific disease,

although, admittedly, it does not serve as a silver bullet for assessment of quality of life for patients with rare diseases (Aartsma-Rus et al. 2016, Slade et al. 2018).

Item-specific or integrative questions

Many of the assessments of quality of life of patients with rare diseases are based on specific impediments due to the illness or certain aspects of the daily life due to the illness. Pooling different diseases together through PROMs is a way to gather knowledge of scattered observations in a sensible way (Whittal, Meregaglia and Nicod 2021). However, mixing together general observations and disease specific questions is no guarantee for successfully measuring quality of life of the patients. Most scales “fail to encompass a more comprehensive and subjective self-assessment” (Cohen & Biesecker (2010), p.9) and miss more general dimensions of quality of life, such as social participation as well as integrative assessment. Although the focus on health could indicate that medical aspects are enough, the recent extension of the conceptualization of health (with well-being, social dimensions, environmental aspects, agency, see e.g. Huber et al. 2011) is an indication that researchers must extend the purely medical frame that was used before to assess health-related quality of life of patients. In that sense, the field of QOL, despite the many divergences that exist within, has much to offer and includes almost systematically measures with some degree of evaluative assessment on one’s life as a whole, which is mostly absent from the scales for rare diseases. Although the assessment of Booyesen (2002) shows that most scales are based on output measures, they are still not integrative measures as meant in the field of QOL such as life satisfaction or life evaluation. This might be due to the different scales, where assessing health-related quality of life is meant for immediate micro-interventions whereas QOL is meant for instruction policymakers for long term, macro changes. This might also be due to the fact that the development of HRQoL instruments involved a

pragmatic attempt to capture the impact of diseases without much attention to what quality of life actually meant (see e.g. Armstrong et al. 2007). Although it might not be possible to directly act upon items of life satisfaction and live evaluation, these make it possible to have a general evaluation of the respondent's satisfaction with the current condition, and on the long run, to understand which items matter and which ones matter less. As stated by Cohen & Biesecker, "evidence demonstrates that factors beyond the physical manifestations of the disease, such as psychological well-being, coping, and illness perceptions, influence QoL and may serve as potent targets for intervention" (p.1136). This means that one does not only have to cure physical problems but also emotional issues and the agency of the patient (Hubert et al. 2011) so an integrative assessment is relevant for practitioners. As a matter of fact, some researchers in the field of HRQoL look into more integrative measures used by social indicators researchers (see Hörnquist 1990, Raphael et al. 1996). Without sticking to general measures only, which would prevent practitioners from acting on some aspects, integrative measures provide a quite stable helicopter view of the general feeling of the well-being of respondents and the potential effectiveness of interventions. Indicators often face contradicting objectives such as local relevance and comparability, consistency versus reactivity or providing the most precise view of the situation without being a burden for the respondents. Any researcher designing a questionnaire feels the urge to ask as many questions as possible to scan the camera obscura of the respondents but any human being filling a questionnaire quickly faces a fatigue when the questionnaire is too long. This represents a common tension where no exact response exists and must be discussed on a case-by-case basis. The question on the tradeoffs between unidimensionality and multidimensionality has often been asked within quality of life studies (Beckie and Hayduk 1997, OECD 2013). Whereas quality of life of

patients with rare diseases seem to lead to multidimensional indexes, too many questions, on top of leading to a higher dropout can also lead to a too specific contextualization, thus preventing any comparison at a larger scale. Additionally, comparisons between diseases become cumbersome, as specific symptoms and domains are often unique to one condition. This is also true in the way the questions are framed. For instance, an item such as “I go out as much as usual even though I have this skincondition” (Skindex) is not transferable to other cases whereas “I am doing fewer social activities with groups of people” (SIP) can be used across different diseases. This is also true for an item such as “Over the last week, has your skin prevented you from working or studying?” (Dermatological Life Quality Index) which could be transferred to other sickness if a more generic tone about the illness was chosen.

The patient at the center of the intervention

In several cases, patients were left out of the design and, sometimes, evaluation of their HRQoL, not all of which for reasons of disability. As in the case of PROMs, the patients are not always central and sometimes not even included. Most of the questionnaires were based on interviewing a panel of experts after an *ad hoc* literature review and patients were rarely interviewed, apart from a few scales (e.g. Dermatology Life Quality Index (DLQI), Cystic Fibrosis questionnaire (CFQ)). Also, for certain scales such as the Quality of Life Index, patients do not fill directly the questionnaires which are filled by the health professionals in charge of the patient. The patients' agency is taken away in the case of cognitive, communication or physical impairment, in which case survey can be replaced or questionnaire filling/answering must be done by a caregiver or an observation from a closely related person. But in other non-extreme cases, the direct involvement of the patients seems desirable (see e.g. Nord et al. 2001, Bogart et al. 2022).

Flexibility of the questionnaire is also a way to put the patient at the center of the questionnaire, by for instance relating the impediment with the subjective evaluation of it. A critique of Cohen and Biesecker (2010) is that “generic scales measure status (i.e., level of impairment or satisfaction) in the various domains of QoL, without assessing importance of each domain. This is a crucial weakness because it overlooks the relative meaning of the various components of QoL to each individual. In effect, by asking only about status, this imposes an objective standard of ideal QoL” (p.1140)³. Some scales such as the TAAQOL enable to ask respondents certain impediments (walk up the stairs, cut paper with scissors, bend over) and how much they are bothered by it. This provides an objective and subjective evaluation of it, quite in line with what researchers in the field of QOL studies would differentiate, that is the objective situation and the evaluation of it (see e.g. Veenhoven 2000, Maggino 2015). This enables not to force certain respondents to wonder about things they would not otherwise ask themselves (see Bourdieu 1994). In that sense, flexibility of the questionnaire is one way to give back agency to the respondents.

Epistemology

The field of HRQoL and the field of QOL have surprisingly little to do with each other, apart from the names (see e.g. Michalos 2004, Miron-Canelo et al. 2021). They are characterized by different epistemes, different disciplines (medical sciences versus social sciences) and different scales. Within the HRQoL paradigm, it seems common that “people make distinctions between some part of life that is influenced by health, and some other parts of life that are not so influenced” (Anderson and Burckhardt 1999, p.300), a distinction that is absent in the field of QOL (although other divisions certainly exist, e.g. objective/subjective,

³ This was stated earlier by Ferrans(1996), “different people value different things... there is no single QoL for all people with the same life condition” (p295).

macro/micro, unidimensionality/multidimensionality, ordinality/cardinality... (Maggino 2015, Brulé and Maggino 2017)). It is likely that the border between these health-related parts of life and non-health related parts of life is somewhat artificial and that respondents confound their quality of life with their health, or at least include the latter in the former, an inclusion which is commonly done in the field of QOL and even among certain HRQoL practitioners. For instance, Fletcher, Hunt and Bulpitt (1987) admit that “the concept of quality of life encompasses many components: cultural and political values as well as more tangible measures such as living and educational standards and freedom from disease” (p. 557). Measuring the quality of life of patients with rare diseases goes beyond mere physical aspects, and many of the current measures have lot to gain from integrating some of the insights of the social indicators movement and the field of QOL.

5. Concluding remarks to improve the measurement of the well-being of patients with rare diseases

The well-being of patients with rare diseases still largely stems from the field of health and therefore carries the light of practitioners, somewhat lacking the perspective of social sciences. In this study, we have assessed the quality of eleven scales used to measure the quality of life of patients with rare diseases. Although they typically suffer from structural weaknesses, they also each hold a fragment of the good practices observed in the field of QOL studies (combination input/output, personalization, flexibility, etc.). The evaluation of the well-being of patients can be improved by including input indicators, by using some degree of genericity in order to tackle issues due to small populations, by including integrative questions and by involving the patients in the selection of the items. By adopting these recommendations, the assessment of HRQoL of patients with rare diseases can be

significantly improved, leading to better-targeted interventions and enhanced patient well-being.

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Table 1: HrQoL measures for rare diseases

Instrument	Acronym	Primary Domains	Target Population	Focus	Type of Measure
Cystic Fibrosis Questionnaire	CFQ	Physical, emotional, social functioning	Cystic Fibrosis patients	Disease-specific QoL	Disease-specific
Cystic Fibrosis Quality of Life	CFQoL	Physical, emotional, treatment burden	Cystic Fibrosis patients	Disease-specific QoL	Disease-specific
Dermatology Life Quality Index	DLQI	Symptoms, daily activities, treatment	Dermatology patients	Impact of skin diseases on QoL	Disease-specific
Medical Outcomes Study	MOS	Physical, mental health, social role	General population and patients	General health and QoL	Generic
Pediatric Liver Conditions QoL	PLC	Physical health, emotional, social	Pediatric liver patients	Disease-specific QoL	Disease-specific

Quality of Life Index	QLI	Health, psychological, social, economic	General population	Overall QoL and well-being	Generic
12-Item Short Form Health Survey	SF-12	Physical and mental health	General population	General health status	Generic
36-Item Short Form Health Survey	SF-36	Physical, mental health, vitality, pain	General population	Broad health status measurement	Generic
Sickness Impact Profile	SIP	Physical, mental, social functioning	General population, health studies	Functional status and sickness impact	Generic
Skindex	Skindex	Symptoms, emotions, functioning	Dermatology patients	Dermatology-specific QoL	Disease-specific
TAAQOL (The Amsterdam Health-Related Quality of Life)	TAAQOL	Physical, emotional, cognitive, social	General population	Health-related QoL	Generic

Table 2: reliability, validity and sensitivity

Instrument	Reliability	Validity	Sensitivity to Change
Cystic Fibrosis Quality of Life (CFQoL)	Cronbach's alpha = 0.72 - 0.92; test-retest r = 0.74 - 0.96	Good discriminant and criterion validity for cystic fibrosis	High sensitivity to clinical status changes
Cystic Fibrosis Questionnaire (CFQ)	Cronbach's alpha = 0.67 - 0.94; test-retest r = 0.45 - 0.90	Strong construct validity; convergent with SF-36 on similar domains	High sensitivity, particularly in clinical trials and for monitoring disease progression
Dermatology Life Quality Index (DLQI)	Cronbach's alpha = 0.82, test-retest r = 0.99	Good construct and concurrent validity with other skin-specific measures	Moderate, especially for clinical improvements
Medical Outcomes Study (MOS)	Test-retest reliability r = 0.85 - 0.90	Strong convergent and criterion validity	High in clinical populations
Profile of Quality of Life in the Chronically Ill (PLC)	High internal consistency reported, reliability > 0.80	Criterion validity supported in chronic illness settings	Moderate for chronic disease management
Quality of Life Index (QLI)	Reliability varies with population; generally high consistency	Good construct validity across general and specific domains	Moderate to high, sensitive in health and social domains
12-Item Short Form Health Survey (SF-12)	Cronbach's alpha generally > 0.70	Good construct validity, derived from SF-36	Moderate sensitivity
36-Item Short Form Health Survey (SF-36)	Cronbach's alpha > 0.80 for most scales	Strong construct and criterion validity	Moderate to high
Sickness Impact Profile (SIP)	Test-retest reliability r = 0.92, internal consistency r = 0.94	Strong construct and criterion validity across conditions	High sensitivity for detecting minor health changes
Skindex	Cronbach's alpha = 0.76 - 0.86	Strong construct and criterion validity, specific to dermatology	High in clinical practice
The Amsterdam Health-Related Quality of Life (TAAQOL)	Cronbach's alpha range: 0.70 - 0.90	Good construct validity, convergent with SF-36	High sensitivity to changes in health

Table 3: evaluation of hrqol measures

	TAAQOL	Profile of Quality of Life in the Chronically Ill (PLC)	Medical Outcomes Study General Health Survey (MOS)	Dermatology Life Quality Index (DLQI)
content	12 dimensions (Gross motor functioning, Fine Motor functioning, Cognition, Sleep, Pain, Social contacts, Daily activities, Sex, Vitality, Happiness, Depressive mood, anger)	6 dimensions (physical, psychological, social, positive moods, negative mood, social well-being) + listings of symptom (diseases specific)	6 dimensions (physical functioning, role functioning, social functioning, mental health, health perceptions)	6 dimensions (feelings, daily activities, leisure, work/school, personal relationships, treatment)
technique and method				
selection	literature plus discussions with experts	literature plus discussions with experts	patients survey	patients survey
	ordinal (verbal 1-4)	Ordinal (0-4)	ordinal (verbal 1-3, 1-5, 1-6)	ordinal 0-3 (not at all-a lot)
scaling of index	0-100	0-4	0-100	0-30
weighting	equal weight + personal weight	equal	Equal	equal
aggregation	At the dimension level	At the dimension level	Arithmetic	arithmetic
validity	item analysis/external validation	external validation	item analysis/external validation	external validation

	intragroup (clinical trials, evaluative or	intragroup (clinical trials, evaluative or		
comparative application	descriptive studies)	descriptive studies)	intergroup	interpersonal, intergroup
focus	output	output	Output	Output
clarity and simplicity	**	***	**	**
availability	Non-available	Non-available	Available	Available
flexibility of the				
questionnaire	*** (weight for the importance of the item)	*** (disease specific, treatment specific)	*	** (not relevant item)

Table 3 (continued)

	Cystic Fibrosis Quality of Life			
	Cystic Fibrosis questionnaire (CFQ)	questionnaire (CFQoL)	Skindex	Sickness Impact Profile
content	3 dimensions (quality of life, school, work, or daily activities, symptom difficulties), 12 subdimensions (physical functioning, role, vitality, emotional functioning, social, body image, eating disturbances, treatment burden, health perceptions, weight, respiratory symptoms, digestive symptoms)	9 subdimensions (physical functioning, emotional functioning, social functioning, future concerns, treatment burden, interpersonal relationships, chest symptoms, body image, career issues)	2 dimensions (physical, psychosocial) , 8 subdimensions (cognitive, social, depression, fear, embarrassment, anger, discomfort, limitations)	12 dimensions (sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care and movement, social interaction, alertness behavior, emotional behavior, and communication)
	technique and method	theory, interviews of patients and specialists	theory, ad hoc	survey
selection	ordinal 1-4 verbal (a lot of difficulty/some difficulty/A little difficulty/no difficulty, always/often/sometimes/never,...)	ordinal 1-6 verbal (all of the time-never/strongly disagree-strongly agree)	ordinal 1-5 verbal (never, rarely, sometimes, often, all the time) and 1-6 verbal (strongly disagree to strongly agree), standardized to 0-100	dichotomous (Yes/no)
	scaling of items			

scaling of index	0-100	0-100	0-100	0-100
weighting	Equal	equal	equal	equal
aggregation	aggregated at the subdimension level, no	aggregated at the subdimension	aggregated at the subdimension level,	3 scores (psychosocial, physical, and other
	global aggregation	level, no global aggregation	no global aggregation	impairment)
validity	item analysis/external validation	item analysis/external validation	item analysis/external validation	item analysis/external validation
comparative				
application	Intergroup	intergroup	intrapersonal, interpersonal	intergroup
focus	Output	output	output	output
clarity and simplicity	**	**	**	**
availability	Available	available	available under fee	available under fee
flexibility of the				
questionnaire	*	*	*	*

Table 3 (continued)

Quality of Life Index

SF 36

SF12

		8 dimensions (vitality, physical functioning, physical limitations, emotional limitations, social functioning, bodily pain, general and mental health) (36 items)	8 dimensions (vitality, physical functioning, physical and emotional limitations, social functioning, bodily pain, general and mental health) (12 items)
Content	5 dimensions (health, activity, daily living, outlook and support)		
technique and method			
selection	Survey	ad hoc, theory	ad hoc, theory
scaling of items	ordinal (0-2)	ordinal, dichotomic	ordinal, dichotomic
scaling of index	0-10	0-100 for each dimension	0-100 for each dimension
weighting	Equal	equal	equal
aggregation	arithmetic	none	none
validity	item analysis/external validation	item analysis/external validation	item analysis/external validation
comparative application	interpersonal	intergroup	intergroup
Focus	Output	input/output	input/output
clarity and simplicity	***	***	***

availability	non-available	available	available
flexibility	*	*	*

Table 4: summary of Hrql and main qol measures

Instrument	Acronym	Primary Domains	Target Population	Focus	Type of Measure
Cystic Fibrosis Questionnaire	CFQ	Physical, emotional, social functioning	Cystic Fibrosis patients	Disease-specific QoL	Disease-specific

Cystic Fibrosis Quality of Life	CFQoL	Physical, emotional, treatment burden	Cystic Fibrosis patients	Disease-specific QoL	Disease-specific
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Pediatric Liver Conditions QoL	PLC	Physical health, emotional, social	Pediatric liver patients	Disease-specific QoL	Disease-specific
Quality of Life Index	QLI	Health, psychological, social, economic	General population	Overall QoL and well-being	Generic
12-Item Short Form Health Survey	SF-12	Physical and mental health	General population	General health status	Generic

36-Item Short Form Health Survey	SF-36	Physical, mental health, vitality, pain	General population	Broad health status measurement	Generic
Sickness Impact Profile	SIP	Physical, mental, social functioning	General population, health studies	Functional status and sickness impact	Generic
Skindex	Skindex	Symptoms, emotions, functioning	Dermatology patients	Dermatology-specific QoL	Disease-specific
TAAQOL (The Amsterdam Health-Related Quality of Life)	TAAQOL	Physical, emotional, cognitive, social	General population	Health-related QoL	Generic
Life Evaluation	N/A	Overall satisfaction with life	General population	Global life satisfaction	Well-being/life satisfaction
Life Satisfaction	N/A	Satisfaction with various life domains	General population	Overall satisfaction in life domains	Well-being/life satisfaction

Affective Measures	N/A	Positive and negative affect	General population	Emotional well-being	Affective well-being
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