

## Chapter XV

# MEASURING QUALITY OF LIFE IN CLINICAL RESEARCH

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The relative failure of objective indicators (mortality, morbidity) to account for certain benefits of medicine, or surgery, has led the medical community to develop subjective indicators such as quality of life.

Quality of life (QOL) is a judgment criterion. This criterion can be used in all types of study: case-control, cohort, therapeutic trial, etc. But it must be justified. The interpretation of the results depends on it. There are two approaches to QOL, one general defined by the WHO, "an individual's perception of their place in life, in the context of the culture and value system in which they live and in relationship with one's objectives, expectations, standards and concerns", the other more specific to the medical field, known as health-related QOL "The health-related quality of life is the value attributed to the length of life according to disabilities, functional level, perceptions and social opportunities modified by disease, injury, treatment or health policy"

To measure a person's QOL in a clinical research context, it is usual to use a questionnaire. This will be developed according to the objectives of the study, the population studied and the concept of QOL chosen. A self-questionnaire is always preferable when the situation allows it. It must be easy to apply, validated in a population of healthy subjects, and have recognized metrological qualities.

Despite these precautions, there are many biases in interpretation. The interpretation of the results will be all the more accurate if the upstream reflection has been thorough.

## I- INTRODUCTION

The relative failure of objective indicators (mortality, morbidity) to account for certain benefits of medicine or surgery has led the medical community to develop subjective indicators such as QOL in order to consider the existence of a another reality.

Medicine now takes into account the individual as a whole and not only in his somatic aspects. The sole opinion of medico-surgical experts in the medical assessment is no longer sufficient. The concept of QOL establishes a more humanistic approach to medicine, by modifying the doctor's view of his relationship with the patient. He forgets his classic position of subject supposed to know by accepting to focus his attention on the strictly subjective points of view that an individual has of himself, of his current situation, of his handicap, of his expectations and of his goals in life [1]. Medical concerns have evolved, medicine now

addresses both the thinking subject (suffering, anxious) and the living subject (whose body is sick) [2] [3]. Medicine must allow the patient to live longer, in good health, and satisfied with his life.

Multiple measurement tools, validated or not, are being developed with the aim of providing reliable, specific and reproducible assessments. At present, when designing a clinical research protocol, it becomes essential to add a QOL questionnaire as a guarantee of the interest shown to the patient. But this systematic attitude is of little value. Whether the QOL is the main criterion for evaluating the efficacy of a treatment, or one of the secondary criteria, in all cases its meaning and the interpretation of the results depend on multiple factors, in particular the relevance the tool used and the conceptual framework of QOL chosen.

## **2- WHAT IS QUALITY OF LIFE?**

### **A- General concept of quality of life**

There is no universal definition of QOL; each using their own terminology. QOL is subjective, dynamic and influenced by the environmental context. Like happiness or sadness, when we use this term, everyone understands it, everyone having their own definition. The meaning of this concept is intuitive, spontaneous and specific to each person.

A first approach is represented by the person's feelings about their own existence. This is, in particular, his satisfaction in the different areas of his life; variable domains according to the ages of life. These different domains cover “the wide range of dimensions of human experience from those associated with the necessities of life to those associated with a sense of fulfillment, success and personal happiness” [4].

A second approach defines QOL as the difference between an individual's expectations and their present situation. With in addition, in the case of the child and the adolescent, the expectations of the parents which may be different from those of the child. For many North American authors, quality of life can be broken down into "being" (what we are), "becoming" (what we are going to wants to become), and “belonging” (how one feels integrated into a group of belonging or society: notions of adaptation, social acceptance, belonging) [5]. D.Curran [6] evokes the ability of human beings to adapt their personal expectations to what they perceive as compatible with their condition. These adaptations allow people with difficult living conditions to acquire a sense of suitable QOL [7]. Thus each individual, according to his history, his current situation and his personal journey, can perceive a life situation as allowing an excellent or a deplorable QOL. The judgment of a doctor on the QOL of his patient is then made impossible. Several studies confirm this hypothesis, comparing the estimation of the QOL by the doctor, and by the patient himself: the patient often considers himself much more satisfied with his life than his doctor judges. [8][9].

These approaches both make it possible to affirm that the person concerned is alone capable of evaluating his own QOL: "the perception that an individual has of his place in existence, in the context of the culture and the system of values in which it lives, and in relation to its goals, expectations, standards and concerns"[10].

This WHO definition is thus organized around three main dimensions: the physical or physiological dimension, the mental or psychological dimension and the social or environmental dimension.

**The physical dimension** is approached from the angle of subjective data. It is not a question of measuring a functional score or a degree of disability, but the way in which the subject perceives and expresses his physical dependence and certain symptoms such as pain or fatigue.

**The psychological dimension** explores the mental state (depression, self-esteem, personality structures) expressed by the subject in his answers to the questioning.

**Social and family interactions** constitute the third dimension of the QOL concept. In adults, unlike children, one of the major components of this last dimension is represented by socio-economic status.

### **B- Health-related quality of life concept**

If the QOL is defined as the evaluation of the satisfaction and well-being of the individual in the different areas of his life, the QOL related to health or Health Related Quality Of Life (HRQOL) is then considered as a sub -area of this multidimensional concept. Its measurement is concentrated on aspects directly related to the state of health. "Health-related quality of life is the value that is attributed to the length of life according to handicaps, functional level, perceptions and social opportunities modified by illness, injury, treatment or health policies.» [12].

When we measure the QOL of the subject suffering from a very debilitating disease, we are in fact measuring his QOL related to his health, as the disease is at the heart of the subject's existence.

Definitions of health-related QOL found in the literature often include functional status and state of health. Even if it is certain that QOL, function and health are linked, this does not mean that they are interchangeable [11]. To illustrate this point, we will cite the Sickness Impact Profile (SIP)[28]. This questionnaire includes 136 items divided into three dimensions: the physical dimension (ambulation, body care, movement, mobility), the psychosocial dimension (social interactions, emotional behavior, communication) and the last dimension grouping together independent sub-dimensions (sleep, meals, work, housework, hobbies). In the case of patients with a motor impairment, with this questionnaire, we measure the functional independence, the incapacities, the difficulties of daily life, but not the QOL of the subject. We obtain the opinion of the subject on objective data of his life far from the notion of QOL as defined by the WHO. We get information about what the person is capable of doing, but much less about how they feel.

## **III- QOL MEASUREMENT**

Measuring "consists of (establishing) rules for assigning numbers to objects and representing quantities of attributes" [13]. The fact of wanting to quantify or measure a qualitative value seems suspect at first glance. Bergson, in 1889, [14] was already wondering about the desire of doctors, to make psychology "scientific", to reduce the qualitative to the

quantitative. He opposed the desire of doctors to pass off "perceptions of magnitude for magnitudes of perception". The concept of QOL is by definition outside the spectrum of quantity, since it can be defined as what makes the essence of life. The precedence of quality over quantity is not called into question by the desire to measure this QOL. This is the only way the medical world has found to measure the gain or loss of well-being caused by therapeutic interventions. We must measure the QOL of our patients based on the opinion of the patients, that is to say on purely subjective criteria. To convert the QOL of a patient into numerical data, we can reason by considering that well-being has several components or dimensions and that within each dimension, it admits the plus and the minus. In other words, within each dimension, there are degrees in the quality of functioning that make it possible to specify the QOL of the individual. We then convert quality into quantity using standardized questionnaires whose quantified patient responses in terms of satisfaction will constitute our QOL profile or quantified index. These measures combine subjective valuations with descriptive elements and are called composite measures.

To measure a person's QOL in a clinical research context, it is usual to use QOL questionnaires. We could evaluate the QOL, by asking a person to estimate their level of QOL, on a scale of 1 to 10. First, the result obtained would only be global, imprecise and difficult to interpret. Indeed, how to interpret an evaluation of QOL at 4.3? Moreover, faced with such a question, the subject's response is quick, without in-depth reflection on his existence and his feelings. The fact of using questionnaires with sub-dimensions allows the subject to progress in the analysis of the different facets of his life. The information obtained is more precise, we then obtain scores by dimension, within which each question can also be interpreted.

We can also approach the QOL of a group of individuals very differently using econometric (utility) measures or using the QALY (Quality Adjusted Life Years) indicator, i.e. the number of years of life gained adjusted for the quality of life (related to health) (see chapter X). This indicator is an attempt to objectively estimate the QOL without taking into account the direct opinion of those concerned. The QALY index is usually used to evaluate several medical therapies, by comparing the years of survival they offer, "adjusted" by a judgment of the quality of this survival. This method makes it possible to study the impact of certain morbid states and to compare the cost-benefit of certain interventions which prolong life at the cost of secondary effects or physical sequelae, psychological and/or social consequences. These measures allow healthcare professionals to justify certain therapeutic choices [15]. They are not interested in the feelings of the patient in his individuality, but try to estimate at the level of a group of patients the impact of a therapeutic intervention and this, for the sake of rationalization of care and public health policy.

#### **IV- CHOOSING A QOL QUESTIONNAIRE FOR A CLINICAL RESEARCH PROJECT**

Whether the QOL is the main or secondary endpoint of the study, its conceptual delimitation in the population studied must be specified according to the objectives pursued by the study. And this choice must be justified in the protocol. Thus the questionnaire will be chosen according to the objectives of the study, the population studied and the concept of QOL chosen.

## **A- Generic or specific questionnaire**

There are two types of QOL questionnaires, generic questionnaires and specific questionnaires. Generic questionnaires are developed from questionnaires developed for the general population. They can never give a detailed account of the specificity of each pathology addressed, but make it possible to compare the results of several studies on different populations. They are insensitive to changes in health status. On the contrary, specific questionnaires assess “the part of health, well-being or quality of life that is primarily affected by the pathology in question” [13]. The instrument can be specific to a given pathology or a given population. A specific instrument may contradict the data provided by a generic instrument insofar as the generic instrument cannot take into account the particularities of the population studied.

For example, for a therapeutic trial concerning the evaluation of a new insulin pen in a population of diabetic children, if one plans to measure the QOL, the most suitable questionnaire is a specific questionnaire for diabetic children in connection with the specific aspects of the disease (constraint of injections 3 times a day, relationship to other children, etc.). The specific tool has all its value in this case because it addresses all facets of the child's QOL in relation to his diabetes.

## **B- Self-questionnaire versus hetero-questionnaire**

As a general rule, self-assessment is the subject of consensus [16]. The person himself is the best placed to assess his own QOL. The QOL of a deficient or chronically ill subject should not be assessed by an able-bodied individual [16]. The evaluator's projection of his own benchmarks of a quality life distorts his assessment of the QOL of a deficient or sick subject. If for a valid subject, the fact of being able to walk is often inherent to a quality life, the reasoning of a deficient subject is often very different.

Concerning the evaluation of QOL, all medical and paramedical personnel underestimate the patient's QOL compared to their own evaluation [16] [17]. In the context of neuromuscular diseases, for Abresch et al. [18], ventilation in patients with Duchenne muscular dystrophy was only able to develop when we began to take an interest in the patient's opinion to guide therapeutic choices. Physicians judging the QOL of patients with muscular dystrophy to be very affected, tended not to offer any treatment that could have prolonged their life. Gibson [19] also reported that one of the reasons why physicians did not recommend ventilatory assistance to patients with muscular dystrophy was that they considered their QOL to be poor.

In children, the validity and reproducibility of self-assessment of their QOL have long been called into question; parents and caregivers were considered better able to describe the child's QOL [20] [21] [22]. However, adults' judgments about the child's emotions are based on their interpretations of the child's behavior, which constitutes an additional bias to this measure. In addition, one of the risks of hetero-evaluation in children is not to take into account elements that are relevant for the child but misunderstood or underestimated by those around them. While the adult often perceives hospitalization as a negative health event, some children see it as a mark of courage, linked to a sense of self-esteem. Certainly, health professionals and parents can provide valuable assessment of a child's psychological and physical functioning. But we also need to question the value of an adult's judgment about how the child feels and about their own perceptions of well-being.

Finally, the ideal respondent, as with adults, should be children. From the age of 8, it seems that self-assessment is reliable, but it is still necessary to use a validated questionnaire adapted to this population.

But sometimes because of very young age, impaired cognitive abilities, or behavioral problems, this self-assessment is impossible. Hetero-evaluation remains the only alternative if we want to measure the QOL of patients.

### **C- Easy-to-apply questionnaire adapted to the study population**

The questionnaire must be a pragmatic and easily applicable tool in the population studied. In case of difficulty concentrating, especially in children, it should not be too long. The items in the questionnaire must be easily understood by patients, avoiding double negatives, for example. The questioning must be oriented according to the population studied on important areas of QOL, areas that vary according to the patient's age, sex and condition. For example, in adults, questions about financial resources may be important [23]. In adolescents, the questionnaire must contain items on the body and its acceptance, on the relationship with parents, which constitute pivotal elements of QOL at this age. In a population with impaired motor skills, it will be necessary to ensure the absence of items directly related to motor function.

Finally, the possible feelings of devaluation engendered by the QOL questionnaires in the patient should not be underestimated. Ideally, the questionnaires should contain both negative items such as “have you been stressed; depressed; easily discouraged.....” and “positive” QOL items such as “are you happy; satisfied with your life; surrounded by your friends.... ”. Thus patients are not only questioned about what is wrong, but also about what brings them well-being.

The criteria for judging the acceptability of the questionnaire in the population are the response time to the questionnaire, the number of refusals to participate, compliance (number of items filled in on all the items).

### **D- A questionnaire with good metrological qualities.**

A good measurement tool must satisfy certain metrological qualities to be considered relevant: its sensitivity to change, its reliability and its validity. These different properties are analyzed during the validation study of a QOL questionnaire.

These validation studies are long and expensive, but they are a must before using a tool in a clinical trial.

The questionnaires are subject to copyright, so they cannot be modified or translated without the authorization of the author. In the case of a tool translated into another language, you must first check that the translation was done according to a rigorous methodology: linguistic validation. Then check that the translation has retained the satisfactory metrological qualities of the tool.

### **1- Faithfulness:**

Reliability is the capacity of the questionnaire to behave reliably and therefore to measure the QOL in a reproducible way. Intra-rater reliability or reproducibility indicates the consistency of measurements. It is defined by the stability of the result during the repeated measurements, the state of the subject remaining stable during this period of time. It is to be linked to the notion of measurement precision. Inter-rater reliability is studied by carrying out an independent assessment by two observers at the same time. In the case of qualitative measurement such as QOL, the reliability of the different measurements will be evaluated by the concordance coefficient Kappa (which applies to qualitative judgments).

### **2- Internal consistency:**

Crombach's alpha coefficient assesses the internal consistency of a set of items corresponding to a clinical dimension; i.e. the strength of the inter-correlations between items of the same dimension. The items of each dimension must form a coherent whole. The more the items are linked together, the closer the alpha coefficient is to 1. In practice, the internal consistency must be quite high ( $\alpha > 0.70-0.80$ ), but the coefficient must not be too close to 1 because this means that several items are redundant.

### **3- Validity:**

The validity or relevance of a tool is its ability to properly measure what it is supposed to measure.

Validity has many facets. **Face validity** represents the subjective judgment (function of the user) taking into account the visible aspects of the scale in a superficial way: the length of the questionnaire, the wording of the items, the response methods, etc. **Content validity** (also called specificity) concerns the relevance of the content of the tool established by expert judgement. It judges whether the questions selected represent all the facets of the concept to be measured. The selection of the items retained to compose the tool must have been carried out by a team made up of medical experts, patients and psychologists. **The validity against criterion** (criterion validity) represents the measurement of the intensity of the statistical link existing between the measurement carried out by the scale studied and the measurement carried out by an existing scale considered as the reference. Finally, **the validity of the construct** (construct validity) is affirmed as successive experiments confirm the theoretical hypotheses put forward during the design of the scale.

### **4- Sensitivity to change**

An instrument is said to be sensitive to change if it is able to accurately measure the plus or minus variations of the measured phenomenon. It must allow a sufficiently detailed classification of individuals and be able to identify clinically perceptible variations. A tool is sensitive if it measures the phenomenon studied with sufficient finesse to distinguish individuals or groups of individuals. Sensitivity to change is important since it makes it possible to evaluate the evolution of the disease with the possible effects of the therapies.

### **5- Overall score or QOL profile**

Only the homogeneity of the questions will allow the establishment of an overall score or QOL index. If the different dimensions are not homogeneous, we will obtain a score per dimension and a QOL profile more than an overall index. Some questionnaires such as the CHQ (Child Health Questionnaire) [24] for example will only provide a QOL profile while

others such as the VSP-A (Vécu Santé Perçu par l'Adolescent, *Adolescent Perceived Health-Real Life*) [25] will authorize the establishment of an overall QOL index out of 100.

## **V- BIASES IN THE INTERPRETATION OF RESULTS**

The QOL is a judgment criterion that can be used in all types of study: descriptive, case-control, cohort, therapeutic trial....

In the case of a descriptive study, the QOL of the patients is measured at a time  $t$  as an additional measure making it possible to better define the population. The question is whether in this specific population due to an acute condition, long-term treatment or a chronic condition, the QOL of patients is significantly different from the general population. It is not a question of interpreting QOL measurements according to their value, because there is no QOL standard. For the interpretation of a QOL measurement in a given population, we must have results in a so-called reference population.

In the case of a case-control study, the interpretation is easier because the comparison is made with the control population.

Finally, in cohort studies and therapeutic trials, the notion of sensitivity to change comes into play because several QOL measurements are taken at different intervals. The questions asked may concern the evolution of the QOL of patients with a chronic disease over time and the impact of therapy on this evolution.

### **A- Interpretation bias related to the very concept of QOL**

There is no QOL standard. In most cases, the questionnaires make it possible to calculate a score by dimension, or even an overall score if the homogeneity of the questionnaire allows it. These scores are often transformed linearly on a scale ranging from 0 to 100, with 100 indicating the "most favorable" QOL and 0 the "least favorable" QOL. How to interpret a score of 85 for example? Can we say for example that the patient has a good QOL since he is in the maximum quarter of the results, but could we not also say that his QOL is not perfect since it does not reach 100%? This type of interpretation is not necessary, because to interpret a QOL score, it is necessary to have data on a reference population matched at least on age and sex. For example, if QOL is assessed in children, the key period of adolescence is tricky to interpret. Indeed, it has been shown in healthy adolescents that, if their evaluation of QOL was poor, it is ultimately that they were doing rather well by adopting an attitude of opposition specific to this age [4]. Without the reference to a population of healthy children, the interpretation of the results would have been erroneous.

In the case of a cohort study or a therapeutic trial, the biases are even greater. If between two QOL measurements framing a therapeutic intervention, for example, a significant increase in QOL is measured, the causal link will be evoked but difficult to confirm. Because what happened in the lives of these patients in this interval, they got married, found a job that fulfilled them, or perhaps they lost a close person, so many factors that are difficult to control in a therapeutic trial apart from an individual interview with a psychologist. This is not to call into question the usefulness of the QOL questionnaire in clinical research, but only to relativize certain conclusions, and to underline the caution with which the results must be interpreted. For example, in a study on the impact of implementing non-invasive ventilation in patients with muscular dystrophy, Young et al. [26] conclude that ventilation has a positive



effect on patients' QOL because the QOL remains stable after initiation of NIV, whereas the authors postulated that the QOL should deteriorate with the progression of the pathology. Here is an example of a very questionable conclusion, because nothing proved that in the absence of this ventilation the QOL of these patients would have deteriorated [27].

## **B- Bias related to QOL measurement**

### **1- Lack of sensitivity to change**

The use of a QOL measure that is not sensitive to change may explain the lack of significance of a comparison test. Concluding therapeutic ineffectiveness would then be a mistake. This is all the more so if the QOL is one of the secondary endpoints for which the expected progression thanks to the treatment has not been taken into account in the calculation of the sample size.

### **2- Concept of the questionnaire not adapted to the question asked**

The interest of the study may be called into question depending on the choice of a generic scale or a specific scale or a health-related QOL scale; for example what would be the interest to use a QOL scale in which we would take into account the functional capacities of movement in the evaluation of a population of patients with a motor disability?

If this study included a comparison with a general population, we would know the result immediately. If this study was testing the effectiveness of a therapy on function, wouldn't it have been more relevant to use a motor function measurement scale?

## **CONCLUSION**

The notion of QOL appears as a multidimensional concept, with variable definitions depending on the evaluator and the objectives of the evaluation. A person's QOL cannot be equated with the absence of objective symptoms. It appears that the best evaluation of the QOL in clinical research is that using a questionnaire:

- for which the concept of QOL has been perfectly defined,
- which has good metrological qualities,
- which is addressed directly to the patient, so as not to miss elements that are unknown or underestimated by those around them.

However, QOL profiles or indexes must be interpreted with great caution, the well-being felt by a person throughout his or her life cannot be reduced to a few figures, however precise and valid they may be. Such an evaluation cannot be conceived without an interview with the patient allowing to identify his history and his family and social environment in order to apprehend areas inaccessible by a standardized questioning.

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