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# What is quality of life?

- **Quality of life (QoL)** is a ubiquitous concept that has different philosophical, political and health-related definitions.
- **Health-related QoL (HRQoL)** includes the physical, functional, social and emotional well-being of an individual.
- HRQoL is a **patient-reported outcome** usually measured with carefully designed and validated instruments such as **questionnaires** or **semi-structured interview schedules**.
- These assessments are increasingly important when **evaluating the benefits and harms of new treatments** being tested in clinical trials.
- They can also be used via **touch screen technology** to help monitor the impact of disease and its treatment on individual patients in the clinic.

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## What is quality of life?

### Introduction

**Quality of life (QoL)** can be defined in many ways, making its measurement and incorporation into scientific study difficult. As illness and its treatment affect the psychological, social and economic well-being, as well as the biological integrity, of individuals, any definition should be all encompassing while allowing individual components to be delineated. This allows the impact of different disease states or interventions on overall or specific aspects of QoL to be determined. Box 1 shows the core domains or components of multidimensional **health-related QoL (HRQoL)**. Sometimes studies employ a questionnaire that measures only one construct, in other words it is unidimensional, such as a pain (brief pain inventory [BPI])<sup>1</sup> or anxiety inventory (Spielberger state/trait anxiety inventory [STAI]).<sup>2</sup> It is preferable that each of the scales within a multidimensional **questionnaire** is shown to be unidimensional, meaning it can be analysed or used as a stand-alone assessment.

The majority of this article will focus on QoL within a cancer setting, as oncology has generated some of the most productive research in medicine for the development and utilisation of QoL measures.<sup>3</sup>

### Primary reasons for measuring QoL

The primary purpose of any cancer treatment is to improve the quality of patients' lives, hopefully by curing the disease but also by

ameliorating the worst symptoms for as long a period as is possible. Avoidance of iatrogenic harm, namely side-effects and other adverse events of treatment, is also imperative. Every clinician, therefore, will make implicit, subjective judgements about QoL when treating a patient. Unfortunately very few clinicians make explicit, objective assessments about QoL using validated tools and instruments. Formal assessment of QoL is now a mandatory requirement in most clinical trials but scepticism about its true value means that outside a trial setting most clinicians depend on informal appraisal, believing clinical judgement to be superior to formal assessment. In the past, routine usage was limited by the perception that available tests were too time-consuming to use or difficult to score and interpret, but modern technology challenges this argument, as will be described later.

Measurements of tumour volume and serum tumour markers are typical examples of the primary parameters of response to treatment. However, improvements in such measures can produce little, if any, noticeable benefit for the patient or may be associated with a decline in QoL if the side-effect profile of treatment is high. Sometimes the outcome of clinical trials reveals only modest differences between treatments and in such circumstances QoL can be a helpful outcome. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA)

#### Box 1. Core components of multidimensional HRQoL assessment

- Physical
- Functional
- Psychological/emotional
- Social/occupational

#### Box 2. Ways HRQoL can improve patient care

- Widening the parameters of benefit
- Indicating a need for supportive interventions
- As a prognostic indicator
- Aiding decision-making
- Informing resource allocation and healthcare policy

now often require QoL or patient-reported outcome (PRO) information before licensing novel anticancer drugs and have issued guidance as to which instruments can be used.<sup>4,5</sup> (The Medicines and Healthcare products Regulatory Agency in the UK works closely with both the FDA and EMEA).

There are many ways in which measurement of QoL can help improve patient care and outcomes (Box 2).

## Methods in which HRQoL can improve patient care

### Widening the parameters of benefit

In many situations; for example, when chemotherapy is given for palliation in advanced cancer, QoL is arguably the sole criterion of efficacy. Conventional parameters such as response, disease-free intervals and survival may be less relevant.

For example, survival in non-small cell lung cancer may be only a few months and, although meta-analyses have shown that chemotherapy produces a modest extension of life compared with best supportive care, some clinicians are reluctant to offer chemotherapy as treatment side-effects may negate any survival gains. Clinical trials incorporating QoL assessments can provide more information and help clarify the relative harms and benefits of palliative chemotherapy, and aid patient decisions when survival gains are small.

Some treatment side-effects; for example, pain and emotional effects, can only be determined by the patient. Physiological measures and clinician-reported outcomes often present a poor reflection of how a patient feels or indeed functions. Sometimes even the patients' relatives and closest carers are unable to offer accurate proxy judgements about these QoL domains, although in some cases, when the patient may be too ill to complete forms, there may be no alternative.

### Indicating a need for supportive interventions

Therapies of proven efficacy almost always have unwanted side-effects which may be severe enough for a doctor to reduce optimal dosing schedules or for patients to stop adhering to the recommended dose.

Systematic QoL assessments help delineate these side-effects and their temporal nature. This can assist in determining the types of supportive interventions that may be needed to ameliorate the worst side-effects. For example, hand and nail problems are common with taxane therapy; however, research has shown that wearing specially designed frozen gloves during administration of chemotherapy can prevent or minimise the impact of this distressing side-effect.

The benefit:harm ratios of non-pharmacological treatments such as intensity-modulated radiotherapy or intraoperative radiotherapy may well reveal different side-effects from those found with external beam radiotherapy and therefore necessitate different ameliorative interventions.

### QoL as a prognostic indicator

It is well known that patients with a good QoL at the start of treatment fare better than those with a poorer baseline score, but there is also an increasing body of literature in various cancers demonstrating the utility of QoL as an effective prognostic indicator.<sup>3</sup> PROs have been shown to be stronger predictors of survival than computed tomography scans in patients with liver metastases associated with colorectal cancer. In these patients, assessment of QoL has been shown to provide a better estimate of survival than measurement of tumour size.<sup>6</sup> Given the uncertainty and controversy that surrounds the use of expensive agents towards the end of life which might be causing toxicity with only modest therapeutic gains, it would seem reasonable to use patients' QoL to aid end-of-life treatment decisions. Finally, QoL could be used as a surrogate endpoint for survival in clinical trials.

### Decision-making

Some novel therapies convey, at best, only modest benefits that are outweighed by the impact of side-effects; others may have demonstrably better efficacy but a challenging side-effect profile. When different treatment options are available patients and doctors need to discuss these potential harms and benefits. This is only really possible if there has been a systematic collection of such data using reliable PROs.

Occasionally QoL studies offer surprising or counter-intuitive information about the impact of treatment on patients. An example being the first randomised trial designed to determine the psychological benefits of breast-conserving surgery and radiotherapy compared with mastectomy. Surprisingly, breast-sparing operations did not convey psychosexual benefits, probably due to the fact that women still had to confront the fact that they had a life-threatening disease.<sup>7</sup>

Patients are now often counselled and offered choice given that trials show no survival advantage over the very different surgical policies and similar rates of psychological morbidity and sexual dysfunction.<sup>8</sup>

In early breast cancer, additional adjuvant hormonal treatment for at least two years reduces the risk of cancer recurrence and death. Hormonal treatments have different side-effect profiles and may affect a woman's choice of treatment. Anastrozole has fewer vasomotor complaints than are reported with other aromatase inhibitors, but has some disadvantages in terms of arthralgia, vaginal dryness and sexual dysfunction.<sup>9</sup> This type of comprehensive collection of PROs allows patients to make informed and individualised decisions on the most appropriate treatment and any required supportive interventions.

### **Resource allocation and healthcare policy**

All healthcare systems have to confront the economic reality of a finite budget and infinite demands. Utility-based measures include the health utilities index (HUI) and the popular EuroQoL (EQ-5D), which are used to generate **quality-adjusted life-years (QALYs)**. QALYs are utilised by health economists to calculate the cost-utility of different interventions. Policy makers may set certain QALY thresholds. The use of these thresholds by regulatory bodies when making decisions regarding NHS payments for treatments is controversial; indeed, QALYs have many limitations, including the undervaluing of life in old age and towards the end of life (see *What is a QALY?*<sup>10</sup> for further discussion).

Sometimes patients are denied supportive drug treatments on the grounds of cost, but if QoL data are available, the benefits that

accrue from their provision are useful and powerful arguments. Nausea and vomiting (N&V) was previously one of the most debilitating and QoL-reducing side-effects of chemotherapy. Drugs such as metoclopramide were ineffective for many patients, especially those on high-dose regimens; indeed, N&V could become a dose-limiting side-effect leading to some patients abandoning treatment or developing anticipatory N&V. The use of 5-hydroxytryptamine 3 antagonists, such as ondansetron, was initially restricted to only those patients on the most emetogenic therapy due to their costs; however, QoL data showed that the financial costs were small when considered alongside the patient burden of unremitting N&V.<sup>11</sup>

### **Design and development**

It is also important to consider how to measure HRQoL scientifically. Measurement of PROs has recently become much more sophisticated. The development process is now more structured and QoL tools are rigorously tested to ensure that they are reliable, valid and responsive to change. The constructs and structure of the best instruments, such as the generic short form 36 (SF-36),<sup>12</sup> the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30<sup>13</sup> and the Functional Assessment of Chronic Illness Therapy (FACIT) system<sup>14</sup> (Box 3), have been through years of development and modification. There are few reasons for developing any new tools, although refinement of existing resources and development of additional items, modules or subscales is needed if there is insufficient coverage of novel treatments or of the specific disease being examined.

Oncology has produced the most important disease-specific HRQoL tools. The EORTC QLQ-C30<sup>13</sup> and the Functional Assessment of Cancer Therapy – General (FACT-G)<sup>15</sup> have both undergone an extraordinary amount of rigorous design, development and validation, and testing as shown in Box 4.

The best HRQoL systems have clearly defined rules and procedures for the development of additional items, ensuring a

## Box 3. Examples of well-regarded HRQoL instruments

### Generic instruments

- SF-36 (short form 36)
- FACIT (Functional Assessment of Chronic Illness Therapy)

### Cancer-specific instruments

- EORTC QLQ-C30 with tumour-specific modules
- FACT-G with tumour and treatment-specific subscales

## Box 4. The development of FACT-G

1. Cancer patients and oncology physicians and nurses generated a list of potential items.
2. Psychologists conducted a structured interview with patients, which began with open-ended prompt to report as many factors as possible which impact on QoL, followed by more focused questions on different aspects of QoL.
3. Oncologists reviewed the patient-generated list and added any other items they felt necessary.
4. A group of 90 patients ranked the 137 items using a Likert scale (1 = little / no importance; 4 = very important) and only those rated 'very' or 'extremely important' were retained.
5. Oncologists, nurses and psychologists reviewed this list and eliminated any redundant items.
6. The final list of 38 items was reviewed to ensure reasonable content and coverage.
7. The final phase involved the piloting of different response modes and rewording of ambiguous items.

consistency of measurement and permitting comparison with data already collected. To ensure consistency, all HRQoL systems should have manuals with instructions for administration, for the imputation of any missing data and for scoring, as well as hints about the interpretation of results. The better systems will also include examples of the endpoints or statistical outcomes that should be used to determine clinically important changes or differences between groups.

## Most frequently used questionnaires

Frequency of use does not necessarily mean the best or most appropriate use, and there are many publications purporting to measure HRQoL that have not in fact employed instruments with robust psychometrics or valid collection methods. HRQoL should be a PRO and not a measure judged by a healthcare professional or similar. For example, many

past publications claiming to report on QoL have in fact used the Karnofsky Performance Scale (KPS). This was originally developed to determine nursing requirements and is a rating scale completed by a physician. An assessment scale such as this would no longer be acceptable as a valid HRQoL instrument.<sup>16</sup>

### SF-36

Arguably the most important and frequently used generic HRQoL assessment is the SF-36. This multi-purpose, short-form health survey is comprised of 36 questions which provide an eight-scale profile of functional health and well-being scores (physical function, role function, bodily pain, general health, vitality, social functioning, emotional well-being and mental health) as well as composite physical and mental health summary measures, and a preference-based HUI.

The SF-36 has been used in literally thousands of general and specific population surveys, permitting comparison of the relative

burden of diseases, and differentiating the health benefits or harms of diverse treatments. The respondent burden is not great but an even shorter validated version, the SF-12, comprised of 12 items, is also available. The instrument has been translated using backwards and forwards methodology into approximately 50 languages.

## FACT-G

FACT-G is part of the FACIT system.<sup>17</sup> This widely used instrument has undergone many modifications; version IV currently comprises 26 items. It is very similar in principle to the EORTC QLQ-C30 having a general questionnaire to which either tumour- or disease-specific and treatment-specific subscales or modules can be added.

## Choosing an instrument

The choice of instrument depends very much on the reason for measurement and the primary concepts of interest. A study looking at a new analgesic for the relief of arthritis may require a specific instrument to measure pain perception; for example, the BPI, or a disease-specific instrument such as the Arthritis Impact Measurement Scales (AIMS),<sup>18</sup> or a more generic instrument such as the SF-36 to evaluate the impact of pain on other aspects of QoL and compare across other conditions where the analgesic was also indicated or licensed. When examining the impact of a specialist nurse counselling service, a good anxiety or depression scale might be more appropriate. The key issues when choosing a test are to review the instrument for coverage of items of interest and to ensure that it is valid and reliable.

A useful website to consult is [www.proqolid.org](http://www.proqolid.org), a collaborative project

between the Information Resources Centre of the Mapi Research Institute, France and Dr Marcello Tamburini, Istituto Nazionale Tumori, Italy. The Quality of Life Instruments Database (QOLID) contains detailed information on over 1,000 PRO questionnaires.

## Difficulties in analysis and interpretation

Box 5 shows that one of the many arguments against incorporating QoL assessment either in clinical trials or more often in routine clinics is that the analysis and interpretation of data is too complex. Although this may previously have been true, considerable work has been performed to establish the minimally important differences that would constitute a real change in scores as well as clinically meaningful differences that might prompt a change in management.

## New technologies

One of the most important research areas over the past few years has been development of automated collection of questionnaire PROs via **touch screens**<sup>19</sup> and **smart pens** that can be used easily in the clinic setting and not just within a clinical trial. Research has shown that patients, even those not part of the IT generation, are comfortable using them. Talking touch screens have also been used successfully with illiterate patients.

## Conclusion

PROs, of which HRQoL is one of the most important, have overcome many of the barriers and objections to their use. There are excellent instruments available with robust

### Box 5. Barriers to using PROs in a research setting or clinical setting

- Too time-consuming
- Lack of a good questionnaire
- Doctors' perception that their experience is sufficient to assess QoL
- No one to score and analyse data
- Difficult to interpret data

psychometric properties and increasing evidence that they are more reliable indicators of the positive and negative impact of disease and treatment than clinical opinion or even some more traditional objective measures, and so complement other assessments. The challenge remains to encourage more clinicians to use them outside of the clinical trial setting.

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## Useful link

EORTC: <http://groups.eortc.be/qol/index.htm>

## Further reading

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