1

Introduction

Summary

A key methodology for the evaluation of therapies is the randomised controlled trial (RCT). These clinical trials have traditionally considered relatively objective clinical outcome measures, such as cure, biological response to treatment, or survival. More recently, investigators and patients alike have argued that subjective indicators should also be considered. These subjective indicators are often regarded as indicators of quality of life. They comprise a variety of measurement scales, such as emotional functioning (including anxiety and depression), physical functioning, social functioning, pain, fatigue, other symptoms and toxicity. A large number of questionnaires, or instruments, have been developed for quality of life assessment and have been used in a wide variety of circumstances. This book is concerned with the development, analysis and interpretation of data from these quality of life instruments.

1.1 Patient-reported outcomes

This book adopts a broad definition of quality of life, and discusses the design, application and use of single- and multi-item, subjective, measurement scales. This encompasses not just ‘overall quality of life’ but also the symptoms and side effects that may or may not reflect – or affect – quality of life. Some researchers prefer to emphasise that we are only interested in health aspects, as in health-related quality of life (HRQoL or HRQL), while others are now adopting patient-reported outcomes (PROs) as the description, because that term indicates interest in a whole host of outcomes, such as pain, fatigue, depression through to physical symptoms, such as nausea and vomiting. But not all subjects are ‘patients’ who are ill; it is also suggested that PRO could mean person-reported outcome. Health outcomes assessment has also been proposed, which avoids specifying the respondent: for young children and for the cognitively impaired we use proxy assessment. And for many years some questionnaires have focused on health status or self-reported health (SRH), with considerable overlap with quality of life.

In this book we shall use the now well-established term quality of life, and its common abbreviation QoL. By that, we include general questions such as ‘How good is your overall quality of life?’ or ‘How do you rate your overall health?’ that represent ‘global assessments; dimensions such as pain or fatigue; symptoms such
as headaches or skin irritation; function, such as social and role functioning; issues, such as body image or existential beliefs; and so on. Mostly, we shall assume the respondent is the patient or person whose experience we are interested in (self-report), but it could be a proxy.

The measurement issues for all these outcomes are similar. Should we use single- or multi-item scales? Content and construct validity – are we measuring what we intend? Sensitivity, reliability, responsiveness – is the assessment statistically adequate? How should such assessments be incorporated into clinical trials? And how do we analyse, report and interpret the results?

1.2 What is quality of life?

Quality of life (QoL) is an ill-defined term. The World Health Organization (WHO, 1948) declares health to be ‘a state of complete physical, mental and social well-being, and not merely the absence of disease’. Many other definitions of both ‘health’ and ‘quality of life’ have been attempted, often linking the two and, for QoL, frequently emphasising components of happiness and satisfaction with life. In the absence of any universally accepted definition, some investigators argue that most people, in the Western world at least, are familiar with the expression ‘quality of life’ and have an intuitive understanding of what it comprises.

However, it is clear that ‘QoL’ means different things to different people, and takes on different meanings according to the area of application. To a town planner, for example, it might represent access to green space and other facilities. In the context of clinical trials we are rarely interested in QoL in such a broad sense, and instead are concerned only with evaluating those aspects that are affected by disease or treatment for disease. This may sometimes be extended to include indirect consequences of disease, such as unemployment or financial difficulties. To distinguish between QoL in its more general sense and the requirements of clinical medicine and clinical trials the term health-related quality of life (HRQoL) is frequently used in order to remove ambiguity.

Health-related QoL is still a loose definition. What aspects of QoL should be included? It is generally agreed that the relevant aspects may vary from study to study but can include general health, physical functioning, physical symptoms and toxicity, emotional functioning, cognitive functioning, role functioning, social well-being and functioning, sexual functioning and existential issues. In the absence of any agreed formal definition of QoL, most investigators circumvent the issues by describing what they mean by QoL, and then letting the items (questions) in their questionnaire speak for themselves. Thus some questionnaires focus upon the relatively objective signs such as patient-reported toxicity, and in effect define the relevant aspects of QoL as being, for their purposes, limited to treatment toxicity. Other investigators argue that what matters most is the impact of toxicity, and therefore their questionnaires place greater emphasis upon psychological aspects, such as anxiety and depression. Yet others try to allow for spiritual issues, ability to cope with illness, and satisfaction with life.
functioning; issues, we shall assume the stated in (self-report).

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organization (WHO, social well-being, of both 'health' and of QoL, frequently
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and treatment consequences of QoL clinical trials to remove

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1.3 HISTORICAL DEVELOPMENT

Some QoL instruments focus upon a single concept, such as emotional functioning. Other instruments regard these individual concepts as aspects, or dimensions, of QoL, and therefore include items relating to several concepts. Although there is disagreement about what components should be evaluated, most investigators agree that a number of the above dimensions should be included in QoL questionnaires, and that QoL is a multidimensional construct. Because there are so many potential dimensions, it is impractical to try to assess all these concepts simultaneously in one instrument. Most instruments intended for health-status assessment include at least some items that focus upon physical, emotional and social functioning. For example, if emotional functioning is accepted as being one aspect of QoL that should be investigated, several questions could evaluate anxiety, tension, irritability, depression and so on. Thus instruments may contain many items. Although a single global question such as 'How would you rate your overall quality of life?' is a useful adjunct to multi-item instruments, global questions are often regarded as too vague and non-specific to be used on their own. Most of the general questionnaires that we describe include one or more global questions alongside a number of other items covering specific issues. Some instruments place greater emphasis upon the concept of global questions, and the EQ-5D questionnaire (Appendix E4) asks a parsimonious five questions before using a single global question that enquires about 'your health'. Even more extreme is the Perceived Adjustment to Chronic Illness Scale (PACIS) described by Härny et al. (1993). This instrument consists of a single, carefully phrased question that is a global indicator of coping and adjustment: 'How much effort does it cost you to cope with your illness?' This takes responses ranging between 'No effort at all' and 'A great deal of effort'.

One unifying and non-controversial theme throughout all the approaches is that the concepts forming these dimensions can be assessed only by subjective measures, and that they should be evaluated by asking the patient. Proxy assessments, by a relative or other close observer, are usually employed only if the patient is unable to make a coherent response, for example those who are very young, very old, severely ill or have mental impairment. Furthermore, many of these individual concepts—such as emotional functioning and fatigue—lack a formal, agreed definition that is universally understood by patients. In many cases the problem is compounded by language differences, and some concepts do not readily translate to other tongues. There are also cultural differences regarding the importance of the issues. Single-item questions on these aspects of QoL, as for global questions about overall QoL, are likely to be ambiguous and unreliable. Therefore it is usual to develop questionnaires that consist of multi-item measurement scales for each concept.

1.3 Historical development

One of the earliest references that impinges upon a definition of QoL appears in the Nichomachean Ethics, in which Aristotle (384–322 BC) notes: 'Both the multitude and persons of refinement ...conceive “the good life” or “doing well” to be the same
thing as "being happy". But what constitutes happiness is a matter of dispute ...some
say one thing and some another, indeed very often the same man says different things at
different times: when he falls sick he thinks health is happiness, when he is poor,
wealth'. The Greek *ευδαιμονία* is commonly translated as 'happiness' although
Harris Rackham, the translator that we cite, noted in 1926 that a more accurate
rendering would embrace 'well-being', with Aristotle denoting by *ευδαιμονία* both
a state of feeling and a kind of activity. In modern parlance this is assuredly quality
of life. Although the term 'quality of life' did not exist in the Greek language of 2000
years ago, Aristotle clearly appreciated that QoL not only means different things to
different people but also varies according to a person's current situation. Quality of
life was rarely mentioned until the twentieth century, although one early commentator
on the subject noted that happiness could be sacrificed for QoL: 'Life at its noblest
leaves mere happiness far behind; and indeed cannot endure it ...Happiness is not
the object of life: life has no object: it is an end in itself; and courage consists in the
readiness to sacrifice happiness for an intenser quality of life' (Shaw, 1900). It would
appear that by this time 'quality of life' had become a familiar term that did not
require further explanation. Specific mention of QoL in relation to patients' health
came much later. The influential WHO 1948 definition of health cited above was
one of the earliest statements recognising and stressing the importance of the three
dimensions – physical, mental and social – in the context of disease.

One of the first instruments that broadened the assessment of patients beyond phys-
iological and clinical examination was the Karnofsky Performance Scale proposed in
1947 (Karnofsky and Burchenal, 1947) for use in clinical settings. This is a simple
scale ranging from 0 for 'dead' to 100 indicating 'normal, no complaints, no evidence
of disease'. Healthcare staff make the assessment. Over the years, it has led to a
number of other scales for functional ability, physical functioning and activities of
daily living (ADL), such as the Barthel Index. Although these questionnaires are
still sometimes described as QoL instruments, they capture only one aspect of it and
provide an inadequate representation of patients' overall well-being and QoL.

The next generation of questionnaires, in the late 1970s and early 1980s, that quan-
tified health status were used for the general evaluation of health. These instruments
focused on physical functioning, physical and psychological symptoms, impact of
illness, perceived distress and life satisfaction. Examples of such instruments include
the Sickness Impact Profile (SIP) and the Nottingham Health Profile (NHP). Although
these instruments are frequently described as QoL questionnaires, their authors neither
designed them nor claimed them as QoL instruments.

Meanwhile, Prietman and Baum (1976) were adapting linear analogue self-
assessment (LASA) methods to assess QoL in breast cancer patients. The LASA
approach, which is also sometimes called a visual analogue scale (VAS), provides a
10 cm line, with the ends labelled with words describing the extremes of a condition.
The patient is asked to mark the point along the line that corresponds with their
feelings. An example of a LASA scale is contained in the EQ-5D (Appendix E4).
Prietman and Baum measured a variety of subjective effects, including well-being,
mood, anxiety, activity, pain, social activities and the patient's opinion as to 'Is the treatment helping?'

Much of the development of QoL instruments has built upon these early attempts, although newer instruments emphasise more strongly subjective aspects, such as emotional, role, social and cognitive functioning. Frequently, one or more general or global questions concerning overall QoL are included. However, despite a shift to the inclusion of psychological and social aspects, these instruments continue to link QoL to the functional capacity. Thus, if a patient is unable to achieve full physical, psychological or social functioning, it is assumed that their QoL is poorer. Although this may in general seem a reasonable assumption, it can lead to theoretical problems. In particular, many forms of functioning, especially physical functioning, may be regarded as causal variables that can be expected to change or affect a patient's QoL but do not necessarily reflect the true level of their QoL (see Section 2.11).

For example, a patient may have a poor QoL irrespective of whether their physical functioning is impaired; this might arise because of other factors, such as pain. Therefore scales measuring functional status assess only whether there are problems that may cause distress to the patient or impair their QoL; these scales do not necessarily indicate the patient's QoL. Despite these reservations, most instruments continue to focus on health status, functional status and checklists of symptoms. For clinical purposes this may be logical since, when comparing treatments, the clinician is most concerned with the differences in the symptoms and side effects due to the various therapies, and the impact of these differences upon QoL.

A number of other theoretical models for QoL have been proposed. The expectations model of Calman (1984) suggests that individuals have aims and goals in life and that QoL is a measure of the difference between the hopes and expectations of the individual and the individual's present experience. It is concerned with the difference between perceived goals and actual goals. The gap may be narrowed by improving the function of a patient or by modifying their expectations. Instruments such as the Schedule for Evaluation of Individual Quality of Life (SEI-QoL) and the Patient Generated Index (PGI), described in Section 1.7, use Calman's expectations model as a conceptual basis and provide the facility to incorporate personal values.

The needs model relates QoL to the ability and capacity of patients to satisfy certain human needs. QoL is at its highest when all needs are fulfilled, and at its lowest when few needs are satisfied. Needs include such aspects as identity, status, self-esteem, affection, love, security, enjoyment, creativity, food, sleep, pain avoidance and activity. Hunt and McKenna (1992) use this model to generate several QoL measures. Somewhat related is the reintegration to normal living model that has also been regarded as an approach to assessing QoL. Reintegration means the ability to do what one has to do or wants to do, but it does not mean being free of disease or symptoms.

Other definitions or indicators of QoL that have been suggested are personal well-being and satisfaction with life. The impact of illness on social, emotional, occupational and family domains emphasises the illness aspect. The existential approach notes that preferences are not fixed and are both individual and vary over time – as was recognised so long ago by Aristotle. Having a 'positive approach to life' can give
Life high quality, regardless of the medical condition. Therefore it can be important to assess existential beliefs and also coping. A patient’s perception of their QoL can be altered by influencing their existential beliefs or by helping them to cope better. The existential model of QoL leads to the inclusion of such items as pleasure in life and positive outlook on life.

Patient-preference measures differ from other models of QoL in that they explicitly incorporate weights that reflect the importance that patients attach to specific dimensions. Different states and dimensions are compared against each other, to establish a ranking in terms of their value or in terms of patients’ preferences of one state over another. These and other utility measure approaches to QoL assessment are derived from decision-making theory and are frequently employed in any economic evaluations of treatments.

Thus there is continuing philosophical debate about the meaning of QoL and about what should be measured. Perhaps the simplest and most pragmatic view is that all of these concepts reflect issues that are of fundamental importance to patients’ well-being. They are all worth investigating and quantifying.

1.4 Why measure quality of life?

There are several reasons why QoL assessments may be included in RCTs, and it is important to distinguish between them as the nature of the measurements, and the questionnaires that are employed, will depend upon the objectives of the trial. Perhaps the most obvious reason is in order to compare the study treatments, in which case it is important to identify those aspects of QoL that may be affected by the therapy. These include both benefits, as may be sought in palliative trials that are expected to improve QoL, and negative changes, such as toxicity and any side effects of therapy.

Clinical trials of treatment with curative intent

Many clinical trial organisations have now introduced the assessment of QoL as being a standard part of new trials. An obvious reason for the emphasis towards QoL as an important endpoint is that treatment of fatal diseases can, and often does, result in limited gains in cure or prolonged survival. With some notable exceptions, little improvement has been seen in patients with major cancer diagnoses, HIV or AIDS. At the same time therapeutic interventions in these diseases frequently cause serious side effects and functional impairment.

There are numerous examples in which QoL assessments have had an unexpectedly important role in the interpretations and conclusions of RCTs, and it is perhaps surprising that it took so long for the relevance of QoL assessment to be appreciated. For example, one of the earlier randomised trials to include QoL assessment was by Coates et al. (1987), who reported that, contrary to their initial expectations,
it can be important of their QoL can to cope better. as pleasure in life that they explicitly to specific dimen- another, to establish the consequences of one state of QoL and about the importance to patients’ of QoL and about the approach is that important to QoL.

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1.4 WHY MEASURE QUALITY OF LIFE?

continuous as opposed to intermittent chemotherapy for advanced breast cancer not only prolonged survival but most importantly resulted in a superior QoL.

Similarly, other RCTs recognised that QoL may be the principal outcome of interest. For example, an RCT comparing three anti-hypertensive therapies conducted by Croog et al. (1986) demonstrated major differences in QoL, and the results of a cancer chemotherapy trial of Buccheri et al. (1989) suggest that small treatment benefits may be more than outweighed by the poorer QoL and cost of therapy. In extreme cases, the cure might be worse than the disease.

Example from the literature

Testa et al. (1993) describe an RCT evaluating hypertensive therapy in men. Two angiotensin-converting enzyme inhibitors, captopril and enalapril, were compared. In total, 379 active men with mild to moderate hypertension, aged 55 to 79, were randomised between the treatment arms. QoL was one of the main outcome measures. Several QoL scales were used, including an Overall QoL scale based on a mean score from 11 subscales.

In order to interpret the magnitude of the differences in QoL that were observed, stressful life events that produced an equivalent change in QoL scores were considered, and the responses to the Overall QoL scale were re-calibrated accordingly (see Chapter 18). Overall QoL scores shifted positively for captopril by 0.11 units, and negatively for enalapril by 0.11. Negative shifts of 0.11 corresponded to those encountered when there was ‘major change in work responsibility’, ‘in-law troubles’ or ‘mortgage foreclosure’. On the basis of these investigations, a clinically important change was deemed to be one between 0.1 and 0.2.

It was concluded that, although the therapies were indistinguishable in terms of clinical assessments of efficacy and safety, they produced substantial and different changes in QoL.

Clinical trials of treatment with palliative intent

One consequence of ageing societies is the corresponding increased prevalence of chronic diseases. The treatment outcome in such diseases cannot be cure but must relate to the improvement of the well-being of patients thus treated. The aim is to palliate symptoms, or to prolong the time without symptoms. Traditionally, clinical and not QoL outcomes have been the principal endpoints. For example, in an RCT of therapy for advanced oesophageal cancer, absence of dysphagia might have been the main outcome measure indicating success of therapy. Nowadays, in trials of palliative care, QoL is more frequently chosen as the outcome measure of choice.
Symptom relief is now recognised as but one aspect of palliative intervention, and a comprehensive assessment of QoL is often as important as an evaluation of symptoms.

**Example from the literature**

Bonkovsky *et al.* (1999) used the Medical Outcomes Study (MOS) SF-36 questionnaire with additional items to evaluate the benefit of therapy with interferon for patients with chronic hepatitis C. It was expected that most patients would have a normal lifespan. It had been shown that patients with hepatitis C have a clinically and socially important reduction in QoL, although it was unclear whether this results from the disease or its associated comorbidity.

The RCT recruited 642 patients, and an additional 750 healthy controls provided a baseline assessment. Patients had lower scores than the controls on all eight SF-36 scales, and these differences were considered clinically and socially relevant.

Between the randomised groups, those who sustained virological response to interferon experienced improvements in five of the eight SF-36 scales, and these improvements were clinically important and worthwhile. However, only 15% of patients obtained sustained virological response from the 24 weeks of interferon.

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**Example from the literature**

Fatigue, lethargy, anorexia, nausea and weakness are common in patients with advanced cancer. It had been widely believed at the time that progestagens, including megestrol acetate (MA), might have a useful function for the palliative treatment of advanced endocrine-insensitive tumours. Beller *et al.* (1997) report a double-blind RCT of 240 patients randomised to 12 weeks of high- or low-dose MA, or to matching placebo. Nutritional status was recorded, and QoL was measured using six LASA scales, at randomisation and after four, eight and 12 weeks.

Patients receiving MA reported substantially better appetite, mood and overall QoL than patients receiving placebo, with a larger benefit being seen for the higher dose. Table 1.1 shows the average change from the baseline at time of randomisation. No statistically significant differences were observed in the nutritional status measurements. Side effects of therapy were minor and did not differ across treatments.

The authors conclude that high-dose MA provides useful palliation for patients with endocrine-insensitive advanced cancer. It improves appetite,
mood and overall quality of life in these patients, although not through a direct effect on nutritional status.

Table 1.1  Average difference in QoL between baseline and subsequent weeks (Based on Beller et al., 1997)

<table>
<thead>
<tr>
<th>LASA scores</th>
<th>Placebo</th>
<th>Low dose MA</th>
<th>High dose MA</th>
<th>p-value (trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical well-being</td>
<td>5.8</td>
<td>6.5</td>
<td>13.9</td>
<td>0.13</td>
</tr>
<tr>
<td>Mood</td>
<td>-4.1</td>
<td>0.4</td>
<td>10.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Pain</td>
<td>-5.3</td>
<td>-6.9</td>
<td>1.9</td>
<td>0.13</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>-1.4</td>
<td>8.7</td>
<td>7.2</td>
<td>0.08</td>
</tr>
<tr>
<td>Appetite</td>
<td>9.7</td>
<td>17.0</td>
<td>31.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Overall QoL</td>
<td>-2.7</td>
<td>2.8</td>
<td>13.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Combined QoL measure</td>
<td>-2.1</td>
<td>2.4</td>
<td>12.3</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Improving symptom relief, care or rehabilitation

Traditionally, medicine has tended to concentrate upon symptom relief as an outcome measure. Studies using QoL instruments may reveal other issues that are equally or more important to patients. For example, in advanced oesophageal cancer, it has been found that many patients say that fatigue has a far greater impact upon their QoL than dyspnoea. Such a finding is contrary to traditional teaching, but has been replicated in various cancers.

**Example from the literature**

Smets et al. (1998) used the Multidimensional Fatigue Inventory (MFI-20, Appendix E14) to assess fatigue in 250 patients who were receiving radiotherapy with curative intent for various cancers. Patients rated their fatigue at fortnightly intervals during treatment and within two weeks after completion of radiotherapy.

There was a gradual increase in fatigue during radiotherapy and a decrease after completion of treatment. After treatment, 46% of the patients reported fatigue as being among the three symptoms causing most distress, and 40% reported having been tired throughout the treatment period.

Smets et al. conclude that there is a need to give preparatory information to new patients who are at risk of fatigue, and interventions including exercise

(Continued)
and psychotherapy may be beneficial. They also suggest that their results might be underestimates because the oldest and most tired patients were more inclined to refuse participation.

Rehabilitation programmes, too, have traditionally concentrated upon physical aspects of health, functioning and ability to perform ADLs; these physical aspects were most frequently evaluated by healthcare workers or other observers. Increasingly, patient-completed QoL assessment is now perceived as essential to the evaluation of successful rehabilitation. Problems revealed by questioning patients can lead to modifications and improvement in the programme, or alternatively may show that some methods offer little benefit.

**Example from the literature**

Results from several small trials had suggested that group therapy, counselling, relaxation therapy and psychoeducation might have a role in the rehabilitation of patients following acute myocardial infarction. Jones and West (1996) report an RCT that examined the impact of psychological rehabilitation after myocardial infarction. In this trial, 2328 patients were randomised between policies of no-intervention and intervention consisting of comprehensive rehabilitation with psychological therapy and opportunities for group and individual counselling. Patients were assessed both by interview and by questionnaires for anxiety and depression, state anxiety, expectations of future life, psychological well-being, sexual activity and functional disability.

At six months, 34% of patients receiving intervention had clinically significant levels of anxiety, compared with 32% of no-intervention patients. In both groups, 19% had clinically significant levels of depression. Differences for other domains were also minimal.

The authors conclude that rehabilitation programmes based upon psychological therapy, counselling, relaxation training and stress management seem to offer little objective benefit to myocardial infarction patients.

**Facilitating communication with patients**

Another reason for assessing QoL is to establish information about the range of problems that affect patients. In this case, the investigator may be less interested in whether there are treatment differences, and might even anticipate that both study arms will experience similar levels of some aspects of QoL. The aim is to collect information in a form that can be communicated to future patients, enabling them to
anticipate and understand the consequences of their illness and its treatment. Patients themselves often express the wish for more emphasis upon research into QoL issues, and seek insight into the concomitants of their disease and its treatment.

**Example from the literature**

The Dartmouth COOP, a primary care research network, developed nine pictorial Charts to measure patient function and QoL (Nelson et al., 1990). Each Chart has a five-point scale, is illustrated, and can be self- or office-staff administered. The Charts are used to measure patients’ overall physical functioning, emotional problems, daily activities, social activities, pain, overall health and QoL. The QoL item is presented as a ladder, and was later used in the QOLIE-89 instrument (Appendix E10, question 49).

Nelson et al. report results for over 2000 patients in four diverse clinical settings. Most clinicians and patients reported that the Charts were easy to use and provided a valuable tool. For nearly half of the patients in whom the Charts uncovered new information, changes in clinical management were initiated as a consequence.

It was concluded that the COOP Charts are practicable, reliable, valid, sensitive to the effects of disease and useful for measuring patient function quickly.

**Patient preferences**

Not only does a patient’s self-assessment often differ substantially from the judgement of their doctor or other healthcare staff, but patients’ preferences also seem to differ from those of other people. Many patients accept toxic chemotherapy for the prospect of minimal benefit in terms of probability of cure or prolongation of life, contrary to the expectations of medical staff. Therefore QoL should be measured from the patient’s perspective, using a patient-completed questionnaire.

**Example from the literature**

Slevin et al. (1990) asked 106 consecutive patients with solid tumours to complete questionnaires about their willingness to receive chemotherapy. They were told that the more-intensive regimen was likely to have considerable side effects and drawbacks, such as severe nausea and vomiting, hair loss, frequent tiredness and weakness, frequent use of drips and needles, admission

(Continued)
to hospital, decreased sexual interest and possible infertility. They were given different scenarios, such as (a) small (1%) chance of cure, (b) no cure, but chance of prolonging life by three months and (c) 1% chance of symptom relief only. All patients knew they were about to commence chemotherapy, and thus considered the questions seriously. Cancer nurses, general practitioners, radiotherapists, oncologists and sociodemographically matched controls were asked the same questions.

Table 1.2 shows the percentage of respondents that would accept chemotherapy under each scenario. There are major and consistent differences between the opinions of patients and the others, and also between the different healthcare staff.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Controls</th>
<th>Cancer Nurses</th>
<th>General Practitioners</th>
<th>Radiotherapists</th>
<th>Oncologists</th>
<th>Cancer Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>100</td>
<td>303</td>
<td>790</td>
<td>88</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td><strong>Cure (1%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive regimen</td>
<td>19</td>
<td>13</td>
<td>12</td>
<td>4</td>
<td>20</td>
<td>53</td>
</tr>
<tr>
<td>Mild regimen</td>
<td>35</td>
<td>39</td>
<td>44</td>
<td>27</td>
<td>52</td>
<td>57</td>
</tr>
<tr>
<td>Prolonging life by 3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive regimen</td>
<td>10</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>10</td>
<td>42</td>
</tr>
<tr>
<td>Mild regimen</td>
<td>25</td>
<td>25</td>
<td>27</td>
<td>13</td>
<td>45</td>
<td>33</td>
</tr>
<tr>
<td>Relief of symptoms (1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive regimen</td>
<td>10</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>7</td>
<td>43</td>
</tr>
<tr>
<td>Mild regimen</td>
<td>19</td>
<td>26</td>
<td>21</td>
<td>2</td>
<td>11</td>
<td>59</td>
</tr>
</tbody>
</table>

Slevin et al. comment that patients appear to regard a minute chance of possible benefit as worthwhile, whatever the cost. They conclude: ‘It may be that the only people who can evaluate such life and death decisions are those faced with them.’

These results have been closely replicated by others. For example, Lindley et al. (1998) examined QoL in 86 breast cancer patients, using the SF-36 and the Functional Living Index – Cancer (FLIC). They note that ‘the majority of patients indicated a willingness to accept six months of chemotherapy for small to modest potential benefit’.

**Late problems of psychosocial adaptation**

Cured patients and long-term survivors may have continuing problems long after their treatment is completed. These late problems may be overlooked, and QoL reported in such patients often gives results that are contrary to expectations.
Example from the literature

Bjordal et al. (1994b), in a study of long-term survivors from a trial of radiotherapy for head and neck cancer, unexpectedly found that the hypofractionated patients reported slightly better QoL than those who received conventional therapy. Hypofractionated patients had slightly better EORTC QLQ-C30 mean scores for role, social and emotional function and better overall QoL (Table 1.3), and reported less fatigue. However, both groups reported high levels of symptoms 7–11 years after their radiotherapy, such as dryness in the mouth and mucus production, and high levels of psychological distress (30% being clinical ‘cases’).

Table 1.3 Quality of life in head and neck cancer patients 7–11 years after curative treatment (Based on Bjordal et al., 1994b, and Bjordal and Kaasa, 1995)

<table>
<thead>
<tr>
<th></th>
<th>Conventional radiotherapy (n = 103)</th>
<th>Hypofractionated radiotherapy (n = 101)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EORTC QLQ-C30 Function scales (mean scores)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical function</td>
<td>74</td>
<td>79</td>
<td>NS</td>
</tr>
<tr>
<td>Role function</td>
<td>72</td>
<td>83</td>
<td>0.03</td>
</tr>
<tr>
<td>Social function</td>
<td>73</td>
<td>83</td>
<td>0.02</td>
</tr>
<tr>
<td>Emotional function</td>
<td>77</td>
<td>84</td>
<td>0.02</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>80</td>
<td>83</td>
<td>NS</td>
</tr>
<tr>
<td>Overall QoL</td>
<td>61</td>
<td>69</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>EORTC QLQ-C30 Symptom scales (mean scores)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>19</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32</td>
<td>25</td>
<td>0.04</td>
</tr>
<tr>
<td>Emesis</td>
<td>6</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td><strong>GHQ scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean score</td>
<td>20.8</td>
<td>19.7</td>
<td>NS</td>
</tr>
<tr>
<td>% cases</td>
<td>31%</td>
<td>32%</td>
<td>NS</td>
</tr>
</tbody>
</table>

The authors conclude that clinicians need to be aware of these problems and that some patients would benefit from social support or medication. It was proposed that the GHQ-20 could facilitate the screening for patients whose psychological distress might be treated.

Medical decision-making

QoL can be a predictor of treatment success, and several studies have found that factors such as overall QoL, physical well-being, mood and pain are of prognostic importance. For example, in cancer patients, pre-treatment assessments of QoL have
been shown to be strongly predictive of survival. On this basis, it is possible to argue, as do Coates et al. (1993), for the routine assessment of QoL in therapy trials.

It is not clear in these circumstances whether QoL scores reflect an early perception by the patient of disease progression or whether QoL status in some way influences the course of disease. If the former, the level of QoL is merely predictive of outcome. If it affects outcome, there could be potential to use improvement in QoL as an active form of therapy. Whatever the nature of the association, these findings underline the importance of evaluating QoL and using it when making medical decisions. Similar results have been observed in various disease areas. For example, Jenkins (1992) observed that pre-operative QoL partially predicts the recovery process in heart surgery patients. Changes in QoL scores during treatment have also been shown to have prognostic value.

Example from the literature

Coates et al. (1997) showed that patients' self-assessment of QoL is an important prognostic factor of survival in advanced cancer patients. Adult patients with advanced malignancy from 12 institutions in 10 countries completed the EORTC QLQ-C30 questionnaire. Baseline patient and disease characteristics were recorded.

Follow-up information was obtained on 656 patients, of whom 411 had died. In addition to age and performance status, the QLQ-C30 global QoL scale and the scales of physical, role, emotional, cognitive and social function were each predictive of subsequent survival duration. Table 1.4 shows the association of survival with the scores for overall physical condition (Q29) and overall quality of life (Q30). In this table, items Q29 and Q30 were each divided about their respective medians, and the hazard ratios show that patients with high scores were less likely to die than those below the median. For example, the hazard ratio of 0.89 for Q29 indicates that the rate of death in patients with high scores was only 89% of the death rate in those with low scores.

Table 1.4 Prognostic significance for survival of two single-item QoL scores in patients with cancer, after allowing for performance status and age (Based on Coates et al., 1997)

<table>
<thead>
<tr>
<th>QoL variable</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical condition (Q29)</td>
<td>0.89</td>
<td>0.82 to 0.96</td>
<td>0.003</td>
</tr>
<tr>
<td>Overall QoL (Q30)</td>
<td>0.87</td>
<td>0.80 to 0.94</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Coates et al. conclude that QoL scores carry prognostic information independent of other recorded factors.
1.5 Which clinical trials should assess quality of life?

It would be inappropriate to suggest that all RCTs, even in cancer, HIV or chronic diseases, should make a formal assessment of QoL. Clearly, there are situations where such information is not relevant. For example, when evaluating a potentially curative treatment that is not very likely to have adverse side effects, or if the treatments and side effects are similar in the various study arms, it might be unnecessary to make such assessment. However, many trial groups now insist that the investigators should at least consider the QoL implications and should positively justify not including the assessment of QoL.

When is QoL assessment a relevant endpoint? Gotay and Moore (1992) propose the following classification of trials for QoL purposes:

1. QoL may be the main endpoint. This is frequently true in palliative care, or when patients are seriously ill with incurable disease.
2. Treatments may be expected to be equivalent in efficacy, and a new treatment would be deemed preferable if it confers QoL benefits.
3. A new treatment may show a small benefit in cure rates or survival advantage, but this might be offset by QoL deterioration.
4. Treatments may differ considerably in their short-term efficacy, but if the overall failure rate is high then QoL issues should be considered.

Furthermore, despite the optimism of those who launch trials that seek a survival breakthrough, all too often completed trials show a limited survival advantage. Thus in these cases the relevance of QoL assessment has to be considered, since any gain in therapeutic efficacy would have to be weighed against possible negative effects pertaining to QoL.

1.6 How to measure quality of life

Ask the patient

Observers are poor judges of patients’ opinions. Many studies have shown that independent assessments by either healthcare professionals or patients’ relatives differ from the responses obtained when patients complete self-reported questionnaires. In some conditions observers appear to consistently overestimate QoL scores; in others, underestimate. There is general agreement that patients’ opinions vary considerably from the expectations of both staff and relatives. It has been suggested that observers tend to underestimate the impact of psychological aspects and tend to emphasise the importance of the more obvious symptoms. The impacts of pain, nausea and vomiting have all been reported as being underestimated. Expected symptoms and
toxicity tend to be accepted and hence ignored by clinical staff. Studies of nausea and vomiting in cancer patients receiving chemotherapy have found that doctors assume these symptoms are likely to occur and, as a consequence, often report only the more severe events. However, patients who are reported as having no problems may assert that they suffered quite a lot of vomiting (Fayers et al., 1991).

Observers frequently misjudge the absolute levels of both symptoms and general QoL. In addition, the patients’ willingness to trade QoL for possible cure may be misjudged. Many patients are willing to accept unpleasant or toxic therapy for seemingly modest benefits in terms of cure, although a few patients will refuse treatment even when there is a high chance of substantial gain. Physicians and nurses are more likely to say that they would be unwilling to accept the therapy for such small potential benefit. When patients with cancer choose between two treatments, if they believe their disease is likely to be cured they may be willing to accept a treatment that adversely affects their QoL.

Observers, including health professionals, may tend to base their opinions of overall QoL upon physical signs such as symptoms and toxicity. However, in many disease areas, conventional clinical outcomes have been shown to be poorly correlated with patients’ assessment of QoL. Thus, for example, in patients with asthma, Juniper et al. (1993) observed that correlations between clinical assessments and how patients felt and functioned in day-to-day activities were only modest.

Example from the literature

An early investigation conducted by Jachuk et al. (1982) into QoL concerned the effect of hypotensive drugs. Seventy-five patients with controlled hypertension each completed a questionnaire, as did a relative and doctor. A global summary question was included, about whether there was overall improvement, no change or deterioration.

As Table 1.5 shows, while the physicians assessed all patients as having improved, approximately half the patients thought there was no change or deterioration, and all but one patient was assessed by their relatives as having deteriorated. Patients attributed their deterioration as due to decline in energy.

<table>
<thead>
<tr>
<th></th>
<th>Improved</th>
<th>No change</th>
<th>Worse</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician</td>
<td>75</td>
<td>0</td>
<td>0</td>
<td>75</td>
</tr>
<tr>
<td>Patient</td>
<td>36</td>
<td>32</td>
<td>7</td>
<td>75</td>
</tr>
<tr>
<td>Relative</td>
<td>1</td>
<td>0</td>
<td>74</td>
<td>75</td>
</tr>
</tbody>
</table>
1.7 INSTRUMENTS

A large number of instruments have been developed for QoL assessment, and we provide a range of examples to illustrate some of the approaches used. Those reproduced (in the Appendix) have been chosen on the grounds of variety, to show particular features, and because these particular instruments are amongst the most widely used in clinical trials.

The aims and content of each instrument are described, together with an outline of the scoring procedures and any constructed multi-item scales. Most of the instruments use fairly simple forms of scoring, and the following basic procedure is usually used.

First, the successive levels of each categorical item are numbered increasingly. For example, a common scheme with four-category items is to grade responses such as 'not at all', 'a little', 'quite a bit' and 'very much' as being 0 to 3 respectively or, if preferred, 1 to 4, as it makes no difference after standardising the final scores. Second, when a scale contains multiple items, these are usually summed. Thus a four-item scale, with items scored 0 to 3, would yield a working score ranging from 0 to 12. Finally, the working score is usually standardised to a range of 0 to 100, and called the scale score. This enables different scales, possibly with different numbers of items and/or where the items have different numbers of categories, to be compared. In our example this would be achieved by multiplying by 100/12. We term this procedure the standard scoring method. A number of instruments are now advocating the use of T-scores, also called norm-based scoring, as described in Section 9.6.

Generic instruments

Some instruments are intended for general use, irrespective of the illness or condition of the patient. These generic questionnaires may often be applicable to healthy people, too. Some of the earliest ones were developed initially with population surveys in mind, although they were later applied in clinical trial settings.

There are many instruments that measure physical impairment, disability or handicap. Although commonly described as QoL scales, these instruments are better called...
measures of health status because they focus on physical symptoms. They emphasise the measurement of general health and make the implicit assumption that poorer health indicates poorer QoL. One weakness about this form of assessment is that different patients may react differently to similar levels of impairment. Many of the earlier questionnaires to some degree adopt this approach. We illustrate two of the more influential instruments, the SIP and the NHP. Some scales specifically address activities of daily living, and we describe the Barthel questionnaire.

Few of the early instruments had scales that examine the subjective non-physical aspects of QoL, such as emotional, social and existential issues. Newer instruments, however, emphasise these subjective aspects strongly, and also commonly include one or more questions that explicitly enquire about overall QoL. We illustrate this approach by the SF-36. More recently, some brief instruments that place even less emphasis upon physical functioning have been developed. Two such instruments are the EQ-5D, that is intended to be suitable for use with cost-utility analysis, and the SEIQoL, which allows patients to choose those aspects of QoL that they consider most important to themselves.

Sickness Impact Profile (SIP)

The SIP of Bergner et al. (1981) is a measure of perceived health status, as measured by its impact upon behaviour. Appendix E1 shows an extract of SIP – the full questionnaire takes 16 pages. It was designed for assessing new treatments and for evaluating health levels in the population, and is applicable across a wide range of types and severities of illness. The SIP consists of 136 items, and takes about 20 to 30 minutes to complete. The items describe everyday activities, and the respondents have to mark those activities they can accomplish and those statements they agree with. It may be either interviewer- or self-administered. Twelve main areas of dysfunction are covered, but there is no global question about overall health or QoL. It has been shown that the SIP is sensitive even to minor changes in morbidity. However, in line with its original design objectives, it emphasises the impact of health upon activities and behaviour, including social functioning, rather than on feelings and perceptions – although there are some items relating to emotional well-being.

The items are negatively worded, representing dysfunction. Data from a number of field studies were compared against assessments made by healthcare professionals and students, leading to 'scale values'. These scale values are used as weights when summing the individual items to obtain the scale score. The standard scoring method is used for each of the 12 dysfunction scales. Two higher-order dimensions, summarising physical and psychosocial domains respectively, are recognised and these are scored in a similar manner.

Nottingham Health Profile (NHP)

The NHP of Hunt et al. (1981) measures emotional, social and physical distress (Appendix E2). The NHP was influenced by the SIP, but asks about feelings and
emotions directly rather than by changes in behaviour. Thus, although the authors did not develop or claim it to be a QoL instrument, it does emphasise subjective aspects of health assessment. It was based upon the perceptions and the issues that were mentioned when patients were interviewed. When it was developed, the idea of asking patients about their feelings was a novel concept.

The version 2 contains 38 items in six sections, covering sleep, pain, emotional reactions, social isolation, physical mobility and energy level. Each question takes a yes/no answer. As with the SIP, each item reflects departures from normal, and items are weighted to reflect their importance. Earlier versions included seven statements about areas of life that may be affected by health, with the respondent indicating whether there has been any impact in those areas. These statements were less applicable to the elderly, unemployed, disabled or those on low income than are the other items, and are usually omitted. The NHP forms a profile of six scores corresponding to the different sections of the questionnaire, and there is no single summary index.

The NHP is short compared to the SIP, and is easy to complete. The wording is simple and easily understood. It is often used in population studies of general health evaluation and has been used in medical and non-medical settings. It is also frequently used in clinical trials, although it was not designed for that purpose. However, it tends to emphasise severe disease states and is perhaps less sensitive to minor – yet important – changes and differences in health state. The NHP assesses whether there are any health problems, but is not sufficiently specific to identify particular problems. Some items do not apply to hospitalised patients, and the developers do not recommend it for these patients. Its simplicity, while being for many purposes an advantage, means that it does not provide suitable coverage for the conditions that apply to patients in many clinical trials.

**Medical Outcomes Study 36-Item Short Form (SF-36)**

The SF-36 developed by Ware *et al.* (1993) evaluates general health status, and was intended to fill a gap between the much more lengthy questionnaires and other relatively coarse single-item measures (Appendix E3). It is designed to provide assessments involving generic health concepts that are not specific to any age, disease or treatment group. Emphasis is placed upon physical, social and emotional functioning. The SF-36 has become the most widely used of the general health-status measures. It can be either self-assessed or administered by a trained interviewer.

As the name implies, there are 36 questions addressing eight health concepts (simpler 12- and 8-question forms are also available). There are two summary measures: physical health and mental health. Physical health is divided into scales for physical functioning (10 items), role-physical (4), bodily pain (2) and general health (5). Mental health comprises scales for vitality (4 items), social functioning (2), role-emotional (3) and mental health (5). In addition, there is a general health transition question, which asks: ‘Compared to one year ago, how would you rate your general health now?’ There is also a global question about the respondent’s perception of their health: ‘In general, would
you say your health is: (excellent, very good, good, fair, poor)?” Most questions refer to the past four weeks, although some relate to the present. A few questions, such as those for role-physical, take yes/no responses, while some, such as the physical functioning items, have three categories (limited a lot, limited a little, not limited at all), and other items have five or six categories for responses.

The designers of the SF-36 selected, standardised and tested the items so that they can be scored using the standard scoring method. More recently, norm-based scoring has been advocated (see Section 9.6).

Most of the items appear broadly sensible. However, the physical functioning scale, in common with many similar scales, poses questions about interpretation. Questions ask whether your health limits you in ‘vigorous activities, such as running, lifting heavy objects, participating in strenuous sports’ or in ‘walking more than a mile’. It is not clear how those who never participate in such activities should respond – their health may be severely impaired, and yet they should respond ‘No, not limited at all’ and will therefore receive a score indicating better functioning than might be expected. Some of the alternative questionnaires therefore restrict physical functioning questions to activities that are expected to be applicable to everyone, while others, such as the Rotterdam Symptom Checklist (RSCL, described below), stress that the questions are hypothetical.

**EuroQol (EQ-5D)**

The EQ-5D of Brooks et al. (1996) is another general-purpose instrument, this time emphasising both simplicity and the multicountry aspects (Appendix E4). It takes about two minutes to complete but aims to capture physical, mental and social functioning, and is intended to be applicable over a wide range of health interventions. The EuroQol group, acknowledging its simplicity, recommend that it should be used alongside other instruments.

Five dimensions of QoL are recognised: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each of these is addressed by a simple three-category response scale. The principal EQ-5D question is represented by a 20 cm vertical VAS, scored from 0 to 100, on which the respondent should mark ‘your own health state today’, ranging from best imaginable health state to the worst imaginable health state. A single index is generated for all health states. Perhaps because of its simplicity, the EQ-5D has been less frequently used as the outcome measure for clinical trials. It has been used most widely for general healthcare evaluation, including cost-utility evaluation.

**Schedule for Evaluation of Individual Quality of Life (SEIQoL) and the Patient Generated Index (PGI)**

The SEIQoL (Hickey et al., 1996) and the PGI (Ruta et al., 1994) are examples of instruments that were developed to assess QoL from the individual’s perspective.
Most questions refer to a physical situation, such as the physical little, not limited at
the items so that they norm-based scoring
physical functioning about interpretation.

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walking more than
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instrument, this time index E4). It takes mental and social
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are examples of
ual's perspective.

The respondents can nominate areas of life that are particularly important to them,
and the current level of functioning in each of these areas is evaluated.

The procedure is as follows. First, the patient is invited to nominate the five most
important aspects of their quality of life. Most patients readily list five areas, but if
they find it difficult a standard list of prompts is used. Second, the patient is asked
to score each nominated item or aspect, according to its severity. The third and final
stage is to provide relative weights for the importance of each item.

The two instruments differ in the way they implement the second and third stages.
For the second stage, the PGI (Appendix E5) invites the patient to score their chosen
items using scales from 0, 'the worst you could imagine', to 10, 'exactly as you would
like to be'. The SEIQuoL offers a vertical VAS for each of their chosen areas, and
patients are asked to rate themselves on the scale between 'as good as can possibly
be' to 'as bad as can possibly be'. Each SEIQuoL scale generates a score between 0
and 100. At the third stage, the PGI asks patients to 'spend' a total of 10 imaginary
points to improve areas of their life. The SEIQuoL provides patients with a plastic
disc that consists of five overlapping segments; each segment can be rotated around the
central pivot, allowing its exposed size to be adjusted relative to the other segments.
The patient is asked: 'How do the five areas compare in importance to each other?'
This procedure generates five weights that sum to 100%. For both instruments, the
investigator calculates a score by multiplying the individual's self-rating in each of
their chosen areas by the relative weight that they assigned to it, and summing the
products over the five areas.

Both the SEIQuoL and the PGI recognise that sometimes seemingly trivial problems
may be of major significance to certain patients, while other issues that are thought
by observers to be important may in fact be considered unimportant.

Disease-specific instruments

Generic instruments, intended to cover a wide range of conditions, have the advantage
that scores from patients with various diseases may be compared against each other and
against the general population. On the other hand, these instruments fail to focus on the
issues of particular concern to patients with disease, and may often lack the sensitivity to
detect differences that arise as a consequence of treatment policies which are compared in
clinical trials. This has led to the development of disease-specific questionnaires. We
describe three contrasting questionnaires that are used in a single disease area – cancer –
and very different questionnaires that are widely used in epilepsy and asthma.

*European Organisation for Research and Treatment of Cancer (EORTC)*
*QLQ-C30*

The EORTC QLQ-C30 is a cancer-specific 30-item questionnaire (Aaronson *et al.*, 1993); see Appendix E6. The QLQ-C30 questionnaire was designed to be
multidimensional in structure, appropriate for self-administration and hence brief and easy to complete, applicable across a range of cultural settings and suitable for use in clinical trials of cancer therapy. It incorporates five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health-status/QoL scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and the perceived financial impact of the disease.

In the QLQ-C30 version 3.0 all items have response categories with four levels, from ‘not at all’ to ‘very much’, except the two items for overall physical condition and overall QoL, which use seven-point items ranging from ‘very poor’ to ‘excellent’. The standard scoring method is used. High scale scores represent high response levels, with high functional scale scores representing high/healthy levels of functioning, and high scores for symptom scales/items representing high levels of symptomatology/problems (Fayers et al., 2001).

The QLQ-C30 is available in a range of languages and has been widely used in multinational cancer clinical trials. It has been found to be sensitive to differences between patients, treatment effects and changes over time.

EORTC disease- or treatment-specific modules

The EORTC QLQ-C30 is an example of an instrument that is designed to be modular, with the core questionnaire evaluating those aspects of QoL which are likely to be relevant to a wide range of cancer patients. For each cancer site particular issues are often important, such as specific disease-related symptoms or aspects of morbidity that are consequences of specific forms of therapy. The QLQ-H&N35, described by Bjordal et al. (1999), is one of several modules that address additional issues (Appendix E7). This supplements the core QLQ-C30 with an additional 35 items for patients with head and neck cancer.

Functional Assessment of Cancer Therapy – General (FACT-G)

The Functional Assessment of Chronic Illness Therapy (FACT) Measurement System is a collection of QoL questionnaires targeting chronic illnesses. The core questionnaire, or FACT-G, was developed by Cella et al. (1993) and is a widely used cancer-specific instrument (Appendix E8). Similar to the EORTC QLQ-C30, the FACT questionnaires adopt a modular approach and so a number of supplementary modules specific to a tumour type, treatment or condition are available. Non-cancer-specific FACT questionnaires are also available for other diseases, such as HIV infection and multiple sclerosis.

The FACT-G version 4 contains 27 items arranged in subscales covering four dimensions of QoL: physical well-being, social/family well-being, emotional
and hence brief
and suitable for
ial scales (phys-
(fatigue, pain, and
ber of single items
nts (dyspnoea, loss
ed financial impact

is with four levels,
all physical condi-
‘very poor’ to
es represent high
h/healthy levels of
ing high levels of

en widely used in
itive to differences

ned to be modular,
ch are likely to be
articular issues are
pects of morbidity
T&N35, described
additional issues
ional 35 items for

erotterdam Symptom Checklist (RSCL)

The RSCL (de Haes et al., 1996) is another instrument that is intended for measuring
the QoL of cancer patients (Appendix E9). In the past the RSCL was used extensively
in European cancer clinical trials, although less so nowadays. It covers broadly similar
ground to the EORTC QLQ-C30 and has a similar number of questions. As its name
implies, greater emphasis is placed upon the symptoms and side effects that are
commonly experienced by cancer patients.

There are two features that are worthy of special note. First, the RSCL has an
introductory text explaining ‘for all symptoms mentioned, indicate to what extent you
have been bothered by it…’ This is in contrast to the QLQ-C30 and most other QoL
instruments, which merely inquire about the presence of symptoms. Thus one patient
might have ‘a little’ stomach ache but, when asked if it bothers them, might respond
‘not at all’; another might respond that the same ache bothers them ‘quite a bit’.

What is less clear is whether most patients read the questionnaire with sufficient care
to appreciate the subtle significance of the instructions. The second feature relates
to the ADL scale. Here, too, there are explicit instructions, stating: ‘We do not want
to know whether you actually do these, but only whether you are able to perform
them presently.’ Thus a patient might not ‘go shopping’ but is requested to indicate
whether they could if they wanted to. This is in marked contrast with the equivalent
scale on the SF-36 that not only asks about actual functioning but also includes some
strenuous tasks which are perhaps less likely to be applicable to the chronically ill.

The RSCL consists of 30 questions on four-point scales (‘not at all’, ‘a little’,
‘quite a bit’, ‘very much’), a question about activity level, and a global question about
‘your quality of life during the past week’ with seven categories. There are two main
scales – physical symptom distress and psychological distress – in addition to the scales for activity level and overall valuation. The standard scoring method is used.

**Quality of Life in Epilepsy (QOLIE-89)**

In contrast with the previous examples, the QOLIE-89 is a 13-page, 89-item questionnaire aimed at patients with epilepsy (Devinsky et al., 1995); Appendix E10 shows extracts. It is based upon a number of other instruments, in particular the SF-36, with additional items from other sources. It contains five questions concerning worry about seizures, and questions about specific ‘bothersome’ epilepsy-related limitations such as driving restrictions. Shorter versions with 31 and 10 items are available. The QOLIE-89 contains 17 multi-item scales that tap into a number of health concepts, including overall QoL, emotional well-being, role limitations owing to emotional support, social support, social isolation, energy/fatigue, seizure worry, health discouragement, attention/concentration, language, memory, physical function and health perceptions. An overall score is derived by weighting and summing the scale scores. There are also four composite scores representing issues related to epilepsy, cognition, mental health and physical health.

The QOLIE-89 has been developed and tested upon adults. Epilepsy is a serious problem for younger patients too, but children and adolescents experience very different problems from adults. Adolescents may be particularly concerned about problems of forming relationships with friends of the opposite sex, and anxious about possibilities of marriage and their dependence upon parents. Children may feel excluded from school or other activities, and may be teased by other children. Very young children may be unable to complete the questionnaire alone, and parents or others will have to assist. Thus QoL questionnaires intended for adults are unlikely to be satisfactory for younger age groups. One example of a generic QoL questionnaire that has been used for children with epilepsy is the 16-dimensional 16D, which Apajisalo et al. (1996) used in young adolescents aged 12–15, comparing normal children against patients with epilepsy. One interesting feature of the QOLIE-89 is that there are five questions about general QoL issues. Questions 1, 2, 3, 49 and 89 use various formats to enquire about health perceptions, overall QoL, overall health and change in health.

**Paediatric Asthma Quality of Life Questionnaire (PAQLQ)**

The PAQLQ developed by Juniper et al. (1996) has been designed to measure the problems that children between the ages of seven and 17 experience as a result of asthma; extracts from the self-administered version are shown in Appendix E11. The PAQLQ has 23 items relating to three dimensions, namely symptoms, activity limitations and emotional function. Items are scored from 1 to 7. Three of the activity questions are ‘individualised’, with the children identifying important activities at the
beginning of the study. There is a global question, in which children are asked to think about all the activities they did in the past week, and to indicate how much they were bothered by their asthma during these activities. The items reflecting each dimension are averaged, forming three summary scales that take values between 1 and 7.

Parents often have a poor perception of their child’s health-related QoL, and so it is important to ask the children themselves about their experiences. Since children may have difficulty in completing the self-administered questionnaire, Juniper et al. (1996) suggest using the interviewer-administered version, administered by a trained interviewer who has experience of working with children. Children may be strongly influenced by adults and by their surroundings, and so detailed guidelines and interviewing tips are provided. The PAQLQ has been tested in children aged between seven and 17 years, and has demonstrated good measurement properties in this age group.

Instruments for specific aspects of QoL.

The instruments described above purport to measure general QoL, and include at least one general question about overall QoL or health. In many clinical trials this may be adequate for treatment comparison, but sometimes the investigators will wish to explore particular issues in greater depth. We describe four instruments that are widely used in clinical trials to explore anxiety and depression, physical functioning, pain and fatigue. These domains of QoL are particularly important to patients with chronic or advanced diseases. Many other instruments are available, both for these areas and others. Additional examples are ‘coping’ (Hürny et al., 1993), ‘satisfaction’ (Baker and Intagliata, 1982), ‘existential beliefs’ (Salmon et al., 1996) and ‘self-esteem’ (Rosenberg, 1965). Since these questionnaires evaluate specific aspects of QoL, in order for a patient assessment to be called ‘quality of life’ these instruments would normally be used in conjunction with more general questionnaires.

Hospital Anxiety and Depression Scale (HADS)

The HADS was developed by Zigmond and Snith (1983) and was initially intended as a clinical screening tool to detect anxiety and depression (Appendix E12). It has become widely used in clinical trials for a wide range of conditions, including arthritis, bowel dysfunction, cancer, dental phobia, osteoporosis and stroke. The HADS consists of 14 questions that are completed by the patients. Each question uses a four-point scale. Seven of these questions were designed to address anxiety, and the other seven depression. The HADS deliberately excludes items that may be associated with emotional or physical impairment, such as dizziness and headaches; it emphasises the psychological signs or consequences of anxiety and depression.

Two particular features of the HADS are interesting from the point of view of scale design. The questions addressing anxiety and depression alternate (odd and
even items, respectively), and half of the questions are worded positively and half negatively (for example, ‘I feel cheerful’ and ‘I get sudden feelings of panic’).

Each item is scored 0 to 3, where 3 represents the state associated with the most anxiety or depression. The items are summed after suitable ordering, yielding two subscales ranging from 0 to 21. Based upon psychiatric diagnosis, HADS ratings of 11 or more are regarded as definite cases that would normally require therapy; ratings of 7 or less are non-cases; those scoring 8 to 10 are doubtful cases that are usually referred for further psychiatric assessment.

Another widely used instrument is the Beck Depression Inventory (BDI) (Beck et al., 1961), which measures existence and severity of depression. It can be either self-rated or administered orally and emphasises cognitive rather than affective symptoms.

**McGill Pain Questionnaire (MPQ)**

The MPQ is one of the most widely used tests for the measurement of pain (Melzack, 1975). The full version has 20 main groups of items, each with between two and six adjectives as response categories, such as flickering, quivering, pulsing, throbbing, beating, pounding. It takes five to 15 minutes to complete. Based upon a literature search of terms used to describe pain, the MPQ uses a list of descriptive words that the subject ticks. The words are chosen from three classes of descriptors – sensory (such as temporal, spatial, pressure, thermal), affective (such as tension, fear) and evaluative (such as intensity, experience of pain). There is a six-point intensity scale for present pain, from no pain through to excruciating pain. Three major measures are derived: a pain rating index using numerical scoring, the number of descriptive words chosen, and the value from the pain intensity scale. Pain-rating index scores can be calculated either across all items or for three major psychological dimensions, called sensory – discriminative, motivational – affective and cognitive – evaluative.

The short version, termed the SF-MPQ (Melzack, 1987), is shown in Appendix E13. It has 15 items that are graded by the respondent from none (0) through to severe (3). There is also a 10 cm VAS, ranging from ‘no pain’ through to ‘worst possible pain’, and the same six-point intensity scale as in the full version. It takes two to five minutes to complete. Each description carries a weight that corresponds to severity of pain. This leads to a summary score that ranges from 0 (‘no pain’) to 5 (‘excruciating pain’). The SF-MPQ has subscales for affective and sensory components of pain, as well as a total score.

Pain is a complicated and controversial area for assessment, although some of the problems serve to illustrate general issues in QoL assessment. For example, the Zung (1983) self-rating Pain and Distress Scale measures physical and emotional distress caused by pain, rather than severity of pain itself. This recognises that severity of pain, either as indicated by pain stimuli or by the subject’s verbal description, may result in different levels of distress in different patients. One level of pain stimulus may produce varying levels of suffering, as determined by reactions and emotions, in different patients. Also, pain thresholds can vary. Another issue to be considered
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when assessing pain is that analgesics can often control pain very effectively. Should one be making an allowance for increasing dosages of, say, opiates when evaluating levels of pain? In some studies it may be appropriate to measure 'uncontrolled pain', in which case one might argue that it is irrelevant to enquire about analgesics. On the other hand, high doses of analgesics can be accompanied by disadvantages.

**Multidimensional Fatigue Inventory (MFI)**

The MFI of Smets *et al.* (1995) is a 20-item self-report instrument designed to measure fatigue (Appendix E14). It covers five dimensions, each of four items: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity. There are equal numbers of positively and negatively worded statements, to counter possible response bias, and the respondent must indicate to what extent the particular statement applies to him or her. The five-point items take responses between 'yes, that is true' and 'no, that is not true', and are scored 1 to 5, where 5 corresponds to highest fatigue. The five scale scores are calculated by simple summation.

Four of the scales appear to be highly correlated, with mental fatigue behaving differently from the others. This suggests that there may be one or two underlying dimensions for fatigue. However, for descriptive purposes, and for a better understanding of what fatigue entails in different populations, the authors suggest that the separate dimensions be retained and that the five scales should not be combined. If a global score is required, the general fatigue scale should be used.

**Barthel Index of Disability (BI)**

Disability scales were among the earliest attempts to evaluate issues that may be regarded as related to QoL. They are still commonly employed, but mainly as a simple indication of one aspect of the patient's overall QoL. The BI (Mahoney and Barthel, 1965) was developed to measure disability, and is one of the most commonly used of the class of scales known as ADL scales. ADL scales focus upon a range of mobility, domestic and self-care tasks, and ignore issues such as pain, emotions and social functioning. The assumption is that a lower ADL score implies a lower QoL.

The BI is used to assess functional dependency before and after treatment, and to indicate the amount of nursing care that is required. It has been used widely for assessing rehabilitation outcome and stroke disability, and has been included in clinical trials. Unlike any of the other scales that we have described, it need not be completed by the patient personally but is more intended for administration by a nurse, physiotherapist or doctor concerned with the patient's care. It therefore provides an interesting contrast against the subjective self-assessment that has been adopted by many of the more recent measures. The BI examines the ability to perform normal or expected activities. Ten activities are assessed, each with two or three response categories, scored 5, 10 or 15; items are left blank and scored 0 when patients fail
to meet the defined criteria. Overall scores range for 0 (highest dependency) to 100 (least dependency). It takes about one minute to assess a patient.

The original BI uses a crude scoring system, since changes in points do not appear to correspond to equivalent changes in all the scales. Also, patients can be at the highest (0) point on the scale and still become more dependent and can similarly exceed the lowest (100) value. Modified versions of the BI largely overcome these deficiencies. For example, Shah et al. (1989) expand the number of categories and propose changes to the scoring procedures (Appendix E15). The BI and its modified versions continue to be used widely as a simple method of assessing the effectiveness of rehabilitation outcome.

Many ADL scales exist, and the Katz et al. (1963) index is another widely used example. The concept here is that loss of skills occurs in a particular sequence, with complex functions suffering before others. Therefore six items were chosen so as to represent a hierarchical ordering of difficulty. A simplified scoring system is provided, in which the number of activities that require assistance are summed to provide a single score. Thus while ‘0’ indicates that no help is required, ‘6’ means that there is dependency for all the listed activities. The Katz index has been used with both children and adults, and for a wide range of conditions. In comparison with the BI, which measures ability, the Katz index measures independence.

Instrumental activities of daily living (IADL) scales include items that reflect ability to live and adapt to the environment. This includes activities such as shopping and travelling, and thus these scales evaluate one’s ability to live independently within the community, as opposed to needing help with basic functions such as dressing and washing oneself. One example is the Functional Activity Questionnaire (FAQ), which was designed for use in community studies of normal ageing and mild senile dementia (Pfeffer et al., 1982).

1.8 Conclusions

Definitions of QoL are controversial. Different instruments use different definitions, and frequently no specific model for QoL is stated formally. There is a wide range of QoL instruments available, although this range is likely to be reduced once the purpose of evaluating QoL is considered. In a clinical trial setting, the disease area and therapies being evaluated will usually limit the choice. Common features of the instruments are that the patients themselves are asked, there are frequently several subscales, the scales are often based upon multiple items and the scales represent constructs that cannot be measured directly. In Chapters 3–7, we shall explain methods for constructing such scales. Most importantly, we describe the desirable measurement properties of scales. We show how to ‘validate’ scales, and how to confirm whether an instrument appears to be consistent with the hypothetical model that the designers intended.