

47. Richards MA, Hopwood P, Ramirez, *et al.* Doxorubicin in advanced breast cancer: influence of schedule on response, survival and quality of life. *Eur J Cancer* 1992, 28A, 1023–1028.
48. Recht A, Hayes DF. Local recurrence following mastectomy. In Harris JR, Hellman S, Henderson IC, Kinne DW, eds. *Breast Disease*, 2nd edition. Philadelphia, Lippincott, 1990, 527–541.
49. Recht A, Eberlein TJ, Sadowsky NL. Local recurrence following breast conservation. In Harris JR, Hellman S, Henderson IC, Kinne DW, eds. *Breast Diseases*, 2nd edition. Philadelphia, Lippincott, 1990, 541–547.
50. Toma S, Leonessa F, Paridaens R. The effects of therapy on oestrogen receptors in breast cancer. *J Steroid Biochem* 1985, 23, 1105–1109.
51. Toma S, Leclercq G, Legros N, *et al.* Estrogen receptor variations in neoplastic tissue during the course of disease in patients with recurrent breast cancer. *Recent Results Cancer Res* 1984, 46, 4233–4236.
52. Leclercq G, Bojar H, Goussard J, *et al.* Abbott monoclonal enzyme immunoassay measurement of oestrogen receptors in human breast cancer: a European multicentre study. *Cancer Res* 1986, 71, 1266–1272.
53. Noguchi S, Motomura K, Imaoka S, Koyama H. Up-regulation of estrogen receptor by tamoxifen in human cancer. *Cancer* 1993, 71, 1266–1272.
54. Klijn JGM, Beras EMJJ, Foekens J. Prognostic factors and response to therapy in breast cancer. *Cancer Surveys* 1993, in press.
55. Cavalli F, Beer M, Martz G. Concurrent or sequential use of cytotoxic chemotherapy and hormone treatment in advanced breast cancer: report of the Swiss group for clinical cancer research. *Br Med J* 1983, 286, 5–8.
56. Mouridsen MT, Rose C, Engelsman E. Combined cytotoxic and endocrine therapy in postmenopausal patients with advanced breast cancer. A randomised study of CMF vs CMF plus tamoxifen. *Eur J Cancer Clin Oncol* 1985, 12, 291–299.
57. Toueini EA, Paridaens R, Heuson JC. Utilisation optimale des combinaisons-hormonales pour le traitement du cancer du sein au stade advance. Nouvelles Perspectives therapeutiques? *Louvain Med* 1986, 105, 111–120.
58. Paridaens R. Altering cell kinetics with endocrine therapy. In Henderson IC, ed. *Adjuvant Therapy of Breast Cancer*. Boston, Kluwer Academic Publishers, 1992, 292–313.
59. Perez DJ, Harvey VJ, Robinson BA, *et al.* A randomised comparison of single-agent doxorubicin and epirubicin as first-line cytotoxic therapy in advanced breast cancer. *J Clin Oncol* 1991, 9, 2148–2152.
60. Wilson KS, Paterson AHG. First-line mitoxantrone chemotherapy for advanced breast cancer. *Cancer Treat Rep* 1986, 70, 1021–1022.
61. Sledge GW, Loehrer PJ, Roth BJ, *et al.* Cisplatin as first-line therapy for metastatic breast cancer. *J Clin Oncol* 1988, 6, 1811–1814.



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## Measurement and Valuation of Quality of Life in Economic Appraisal of Cancer Treatment

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In the economic evaluation (EE) of technologies in cancer treatment at least three endpoints are relevant: costs, survival and quality of life (QoL). This article is focused on QoL. EE requires the use of generic and valuation QoL instruments at a disease non-specific level, but the inclusion of cancer-specific instruments may be advisable, particularly for reasons of explanation if changes in dimensions are small or conflicting. Given the pros and cons of the available questionnaires, we advocate the use of the Nottingham Health Profile, the EuroQol and the Rotterdam Symptom Checklist. In our experience the QoL issue in EE linked with cancer trials is associated with practical problems like questionnaire composition, follow-up time, interviewing schedule, patients' compliance and doctors' acceptance. These problems are discussed and some practical guidelines for the design of QoL measurement in cancer trials are given.

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### INTRODUCTION

CANCER is a major cause of illness and death, responsible for almost a quarter of total mortality in Western countries. During the last few decades cancer treatment has shown a rapid evolution. It is now a multidisciplinary treatment strategy incorporating surgery, radiotherapy, chemotherapy and/or immunotherapy. Treatment usually has important side-effects, especially radiotherapy and chemotherapy. For example, radiotherapy causes tiredness, skin injury and emotional discomfort. Chemo-

therapy, often considered even more burdensome, is given over longer periods and its toxicity causes hair loss, nausea and vomiting, fatigue and emotional problems. Consequently, those involved in the care and treatment of cancer patients have wondered whether improvements in survival probabilities outweigh the burden of these severe side-effects in all cases [1]. Not only life years gained, but also the quality of years alive is at issue.

The high incidence and prevalence of cancer make it a major

economic issue. The direct medical costs are considerable, especially during primary treatment and metastatic periods and amount to 5% of health care expenditure in the Netherlands [2]. Future expenditure may be even higher due to the increased use of expensive drugs and radiotherapy equipment, the growing emphasis on various kinds of palliative interventions and survival success. The prevalence of morbidity, mortality and the consequent loss in labour and household production also cause substantial indirect costs. These phenomena and trends imply a growing role of economic evaluation (EE) in the cancer field and justify consideration of the specific problems of applying EE in this area. In the EE of technologies in cancer treatment at least three endpoints are relevant: costs, survival and quality of life (QoL). QoL will be the focus of our discussion. The discussion is based on a literature survey and our own experience with EE linked with cancer trials in the Netherlands, concerning patients with haematological malignancies and solid tumours.

### OBJECTIVES OF QoL RESEARCH

When two treatment modalities differ with respect to QoL the main clinical endpoint, mortality, should be considered in relation to outcome indicators for QoL, such as clinical outcome data, disease-specific QoL measures and general scales, although the choice between these is not clear cut. Drummond and Davies point out that the different types of measures complement each other by adding important information about the consequences of various health care interventions [3]. The usual objective of carrying out QoL research is to gain insight into the reactions of patients to cancer and on cancer treatment and the interrelations of these different reactions with the overall QoL. Furthermore, data concerning the impact of a certain therapy on QoL may increase the knowledge about the effectiveness of such therapy [1].

QoL studies generally give a description of health status. Depending on the type of study, they deal with more or less objective features of health. Most studies use dimensions of the concept such as the physical, psychological and social dimensions [4]. More extended concepts even incorporate material and religious dimensions. To evaluate a specific therapy in clinical studies, the endpoints most commonly used are survival rates, disease- and/or symptom-free survival, response rates and response duration. When QoL is taken into account, there is more emphasis on the physical and psychological aspects of life, sometimes complemented with aspects of social functioning.

EE is intended to support health policy at different levels of decision making. In cancer treatment, decisions are generally made in a public sector context, implying that one tries to maximise health outcome given a social budget. This requires the summary measure used in EE to be applicable to health care interventions in general, and also to be uniform in the sense that all interventions are to be judged in an equal manner. If the treatment is to be seen more as a private good, and subject to an individual decision, economic methods exist to derive a numeric value for the utility of outcome; thus a cost-benefit analysis

becomes feasible, allowing an absolute judgement on the efficiency of a treatment strategy.

From the economic perspective, the objective of studying QoL is to determine the contribution of changes in QoL to a summary measure for the outcome of an intervention. Such summary measures may be in natural units (as "life-years" commonly used in cost-effectiveness analysis), in terms of utility (as in cost-utility analysis) or in monetary terms (as in cost-benefit analysis). When there is more than one effect parameter (e.g. survival and health status improvement) or when effects are measured in more dimensions of QoL, a value judgement (utility weight) should be given to each of these parameters or QoL dimensions in order to arrive at such summary measures. As in cancer treatment, both survival and QoL (in several dimensions) are important aspects of outcome, and only cost-utility and cost-benefit analysis are appropriate instruments to measure the efficiency of cancer treatment.

### DESCRIPTION AND VALUATION OF QoL IN EE

Descriptive instruments can be divided into two main categories: the generic instruments and disease-specific questionnaires [5]. Generic instruments are developed to measure all health dimensions. They can be used over a wide range of disease categories and are, therefore, suited to function as generally applicable descriptive instruments for measuring QoL improvement in EE. In this respect they provide a reference for quantitative assessment of QoL changes in EE and have been used in many economic appraisals.

Generic instruments most frequently used are: the Nottingham Health Profile (NHP) [6], the Sickness Impact Profile (SIP) [7] and the abbreviated RAND-Medical Outcome Study questionnaire [8]. The newly developed Short Form-36 may be regarded as an extension of the abbreviated RAND-Medical Outcome Study questionnaire / RAND-MOS 20, or indeed as a reduction of the original longer RAND-MOS questionnaire [9].

Disease-specific instruments measure health problems specific for an illness or disease category. These instruments are measuring specific QoL aspects which are typical for a particular disease, and are, therefore, more sensitive for changes in health of patients having that disease. Concerning cancer, these instruments can be divided into:

- a. Cancer-specific questionnaires (for all cancers) and
- b. Specific cancer questionnaires (for one type of cancer).

The following cancer-specific instruments are often used: the Functional Living Index for Cancer [10], Spitzer QL index [11], European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC Core QoL) [12], Cancer Rehabilitation Evaluation System—Short Form (CARES-SF) [13] and the Rotterdam Symptom Checklist (RSCL) [14]. Examples of specific cancer instruments are: the Breast Cancer Chemotherapy Questionnaire [15], the Performance Parameters for Head and Neck Cancer [16] and the Linear Analog Self-Assessment (LASA) of Voice Quality for laryngeal cancer [17].

For the description of QoL in EE, generic instruments suffice for overall comparison and testing, but the inclusion of specific instruments may be advisable, particularly for reasons of explanation if changes in dimensions are small or conflicting. By using generic instruments it is not always possible to gain insight into how changes in health have taken place. For some generic questionnaires, an algorithm is available to calculate a summary measure, but this may not reflect the weights of the various

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dimensions in the health questionnaire as may be derived from value judgements of the relevant patient group or other relevant representative groups.

When strategies score differently on different dimensions and when one needs a summary measure of outcome comparable across a range of interventions, it is necessary to get valuation of health states in one single dimension representing an overall judgement of QoL of a health state. This would then allow the calculation of “quality adjusted life years”, where a life year gained is “adjusted” using this value judgement for QoL. To acquire valuations, respondents are requested to value health states. These states are derived from a set of health state descriptors. The values usually range from 0 to 1 (0 = “worst imaginable health state”, 1 = “best imaginable health state”). By means of modelling techniques a multi-attribute utility function may be derived to predict values of any composition of health states. There are three methods of acquiring valuations:

- direct rating (e.g. determining a point on a line with clearly defined endpoints),
- standard gamble (choosing between options under uncertainty) and
- time trade-off (choosing between options with different durations of a particular health status) [18, 19].

Furthermore, there are two basic approaches used to measure the utility of health status. In one approach, actual patients who are in a particular health state are used as subjects to determine their utility for such a state. Using subjective utility assessments is most in line with conventional welfare theory. In the other approach, the health states are assessed by subjects who may or may not have personal experience with the health state being measured, but are thought to represent public opinion. Which approach is preferable depends on the viewpoint of the study. When a study is conducted from the societal viewpoint and is pertinent to public policy decision making, the appropriate utilities are those of the general public [18]. If a fixed set of utility values generated from a representative sample from the general public can be related to all possible outcomes from a generic health questionnaire, and if such a generic instrument would then be used to measure health outcomes in an EE, this would add to the comparability of results from EEs and be in line with the public sector context of decision making to be supported with results from an EE. The problem with soliciting value judgements from persons without relevant disease experience is that the person should truly understand what the described health state is like. For some of the generic health measurement instruments (e.g. the NHP) such a set of utility values is known allowing the calculation of QALYs gained when such a generic instrument is used to assess health outcomes. The descriptive part of the EuroQoL instrument [20] is especially developed to be used in EEs and a validated set of utility values is available for this instrument [20, 21]. Other available valuation instruments are the Quality of Well-being Scale (QWB) [11], the McMaster Utility Measurement Questionnaire (MUMQ) [22], the Torrance's Health State Classification System [23] and the Rosser & Kind Index [24].

#### CHOICE OF MEASUREMENT INSTRUMENTS

In clinical trials the choice of measurement instruments depends on criteria such as psychometric features (internal consistency, reliability, validity, etc.), specific patient features, feasibility and on the possibility of gaining insight into the QoL

aspects of the disease itself, and into the side-effects of treatment. QoL measurements in EE should foremost allow comparison across different technologies and diseases. This requires the inclusion of a generic health measurement instrument with the opportunity to derive utility values (or indeed an instrument soliciting value judgements directly from the patients) and, if deemed necessary for reasons explained above, the inclusion of a cancer-specific instrument. The precise combination of instruments depends on the required psychometric and specific patient features and feasibility aspects. An important aspect of the latter is the duration of the whole interview. Table 1 describes the psychometric features and the duration of the instruments.

Concerning the generic instruments, there are hardly any differences between the psychometric features of the instruments mentioned. The test-retest reliability is slightly in favour of the NHP and the SIP. Concerning the internal consistency per dimension the NHP is preferable to the SIP. All instruments mentioned have content and construct validity. Considering the psychometric features, we prefer the NHP to the SIP and the RAND-MOS 20.

The RSCL and the CARES-SF seem to be suitable cancer-specific instruments to be used in EE. Both instruments have good test-retest reliabilities. When comparing the internal consistency and validity of the tests, there is some preference for the RSCL. In addition, this instrument has the potential to add items (illness or treatment-related variables). By adding items concerning possible side-effects associated with a particular treatment, it is possible to gain more insight into these side-effects. For example, in a study comparing the cost effectiveness of a treatment with a colony stimulating factor and a conventional treatment, we added some items concerning possible side-effects associated with the colony stimulating factor (see \* in Appendix). As there is little information on the psychometric features of the EORTC Core QoL questionnaire, this questionnaire has not been taken into account. However, this questionnaire is still used in several EORTC trials. Thus, in the near future more information about the psychometric features of this questionnaire may be expected.

As stated, in EE valuation of health states in terms of one value judgement is necessary. The valuation instruments mentioned are divided into two parts, a descriptive and a valuation part. By using the descriptive part it is possible to construct health states which can be evaluated by the general public. The evaluation part mostly consists of a thermometer which enables the patient to evaluate his or her own health state. When a study is conducted from a social viewpoint the valuations of the health states by the general public have to be taken into account, but by acquiring valuations of own health states by patients the opportunity arises to compare these with the values from the general public. However, when a validated set of utility values is available, the use of the descriptive part may be sufficient. Concerning valuation instruments, the Torrance's Health State Classification System, and the Rosser & Kind Index have good reliability features, but the internal consistency of these questionnaires is unknown. The Torrance's Health State Classification System is used less often and is, therefore, not appropriate. The MUMQ lasts about 45 min and the Rosser & Kind Index lasts at least 1.5 h, so these instruments are also not appropriate for EE of technologies in cancer treatment. The valuation instrument developed by the EuroQoL group (rating scale using a thermometer) has good psychometric features. The descriptive part of the EuroQoL lasts about 1 min, the valuation part about 20 min.

Table 1. Description and valuation of quality of life

	Reliability (test-retest)	Internal consistency	Validity	Interview duration
Generic measurement instruments				
Nottingham Health Profile (NHP)				
Physical Mobility	0.77–0.88	0.81	Content	10 min
Pain		0.77	Construct	
Sleep		0.69		
Social isolation		0.42		
Emotional reaction		0.75		
Energy		0.68		
Sickness Impact Profile (SIP)				
Physical		Overall:		
Psychological	0.90–0.91	0.81–0.94	Content	20–30 min
Overall	0.79–0.84	Per dimension:	Construct	
	0.75–0.92	0.23–0.80 (NL)		
Rand Medical Outcome Study (RAND- MOS 20)				
Physical functioning	0.78	0.85	Content	3–4 min
Role functioning	0.69	0.80	Construct	
Bodily pain	0.58	—		
Social functioning	0.75	—		
Mental health	0.83	0.89		
General health perception	0.85	0.91		
Cancer-specific measurement instruments				
Rotterdam Symptom Checklist	0.82–0.88	0.81–0.93	Content	8 min
			Construct	
Cancer Rehabilitation Evaluation System-Short Form (CARES-SF)	0.86	0.61–0.85	Concurrent	Unknown
Valuation instruments				
Quality of Well-being Scale (QWB)	0.90	Unknown	Content	18 min (descr)
			Construct	Unknown (val)
EuroQol	0.69–0.94	Not relevant	Content	1 min (descr)
				20 min (val)
McMaster Utility Measurement Questionnaire (MUMQ)	0.66–0.94	Not relevant	Content	45 min
				(descr and val)
Torrance's Health State Classification System	0.86–0.94	Unknown	Unknown	Unknown
Rosser & Kind Index	0.79–1.00	Unknown	Content	10 min (descr)
				> 1.5 h (val)

References: [14, 25, 26]. descr, descriptive point; val, valuation point.

The QWB scale also has good psychometric features, but the descriptive part lasts about 18 min. While combining this instrument with a generic and a cancer-specific instrument, the duration of the whole interview would become too long. For that reason we prefer the use of the EuroQol to the QWB.

When using the NHP, the RSCL and the descriptive part of the EuroQol the whole interview would last about 20 min. We know from experience, based on 200 patient questionnaires administered at several states in the cancer treatment, that this is acceptable to patients.

## DESIGN AND PRACTICAL ISSUES

For the design of QoL measurement in EE of technologies in cancer treatment at least the following issues have to be taken into account: the choice of respondent, the method of data collection, the time and frequency of administering questionnaires and the analysis of data.

QoL questions are usually addressed to the patient. When the patient is not in a position to answer the questions, for example, due to serious health problems, the respondent could be a relative, nurse or doctor [27]. There are several methods of

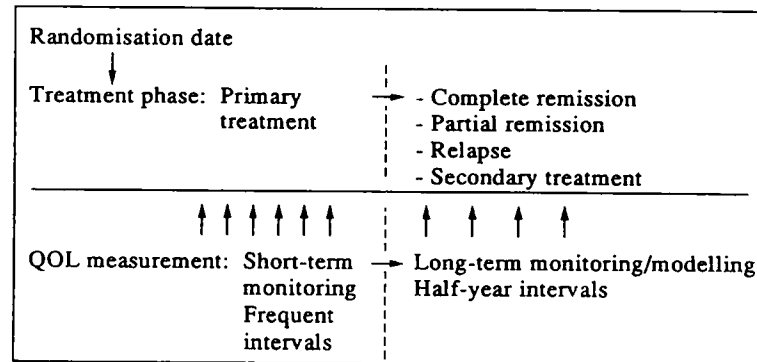


Fig. 1.

data collection available, namely verbal (interview), written (questionnaires) and the personal computer. The written questionnaires are most often used and require less infrastructural arrangements.

Ideally, the data collected should describe QoL of patients before, during and after treatment. The choice of time scale depends on the natural history of the disease and on the timing and pattern of treatment. During intensive treatment periods it may be important to have frequent measurement of QoL, sometimes intervals of 1 or 2 days may be desirable [28]. If there is a survival benefit it is important to take into account QoL during life years gained. In this respect, it is necessary to make a distinction between curative and palliative treatment modalities. In both modalities QoL measurement is very important, but the outcome indicators differ. In palliative treatment modalities, QoL is the single most important outcome indicator. For curative treatment modalities, the most important indicator is the assessment of QoL of life years gained, which is estimated by a separate observation of survival and QoL.

There are several constraints on the choices regarding frequency and timing of QoL assessments. If these are infrequent, then transient effects most likely during and after each treatment, may be missed. On the other hand, enquiries which are too frequent may well be too imposing on the patient, especially as this may be a time of particular stress because of the disease and its treatment. Patients' compliance is likely to depend on the way in which the assessment forms are explained to patients if self-assessment is required, the degree of encouragement given and the frequency with which the completed forms are collected and inspected; hence in a multicentre trial, patients' compliance may vary considerably from centre to centre [28]. Good coordination may enhance response rates and this may require one person being responsible for all aspects of processing of the interviews.

As EE generally requires life-long follow-up, a modelling approach may be necessary to predict life-long consequences. By specifying a simulation model or a MARKOV model defining various states characterised by health status and/or specific treatment (associated with a cost profile), the follow-up period of the actual clinical trial may be reduced (Fig. 1). It will be assumed that each state can be characterised by a unique quality of life. The following disease states are possible: disease-free, partial remission, relapse (symptom-free), relapse (symptoms) and terminal state. The measurement and valuation of QoL of patients in the terminal phase of cancer may be difficult, because these patients may be "off protocol" and difficult to approach. Acceptable compliance rates require motivation of the patient,

sophistication of the procedure and a permissive attitude towards the ideal interview schedule.

To analyse the data several statistical methods and computer programmes are available. The choice depends on the design and the type of data. The study protocol should include a brief description of how the data are to be analysed, including the tests which are to be used.

## DISCUSSION

QoL measurement and valuation is an essential part of economic appraisal of programs in cancer treatment. To improve the comparability of the results of such studies and to increase the opportunities to generalise from the resulting findings it is necessary to achieve standardisation in design of QoL research and the choice of instruments. Given that in most prospective studies a 'piggyback' economic analysis is performed, meaning that the economic evaluation is added on to a clinical trial (sometimes after major decisions on design and data collection have been taken), the economic analyst finds himself in a stronger position when there is already consensus among researchers about the requirements for QoL measurement from the economic perspective. This paper aims at contributing to consensus building in this area.

A practical problem in the selection of instruments is their availability for use in studies. There seems to be a tendency toward commercialisation and consequent restriction of usage which may hamper a free scientific discourse on psychometric properties and pros and cons of the available instruments. In our opinion there is not yet enough empirical data to decisively assess the comparative advantages of existing measurement and valuation instruments and no thresholds should be formed for producing such evidence.

A final problem is the measurement and valuation of QoL in the terminal phase of cancer. In prospective trials it is often difficult to organise data collection on QoL of patients in the final stages of the disease as they may be "off protocol" or otherwise difficult to approach. It seems practical to launch a specific research program to measure QoL in these stages and to analyse differences across disease categories in order to produce a set of generally applicable values to be used in other studies.

1. Haes JCJM de, Knippenberg FCE van. The quality of life of cancer patients: a review of the literature. *Soc Sci Med* 1985, 20, 809-817.
2. Koopmanschap MA, Roijen L van, Bonneux L. *Kosten van ziekten in Nederland*. Instituut Maatschappelijke Gezondheidszorg, Instituut voor Medische Technology Assessment, Erasmus Universiteit, 1991.

3. Drummond MF, Davies L. Economic analysis alongside clinical trials. *Int J Technol Assess Health Care* 1991, 7, 561–573.
4. Hörnquist JO. The concept of quality of life. *Scand J Soc Med* 1982, 10, 57–61.
5. Patrick DL, Deyo RA. Generic and disease-specific measures in assessing health status and quality of life. *Med Care* 1989, 27, S217–S232.
6. Hunt SM, McEwen J, McKenna SP. *Measuring Health Status*. London, Croom Helm, 1986.
7. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The sickness impact profile: development and final revision of a health status measure. *Med Care* 1981, 19, 787–805.
8. Stewart AL, Hays RD, Ware JE. The MOS Short-form General Health Study—reliability and validity in a patient population. *Med Care* 1988, 26, 724–735.
9. McHorney CA, Ware JE, Rogers W, Raczek AE, Rachel JF. The validity and relative precision of MOS Short- and Long-form health status scales and Dartmouth COOP charts. *Med Care* 1992, 30, MS253–MS265.
10. Schipper H, Clinch J, McMurray A, Levitt M. Measuring the quality of life of cancer patients. The functional living index-cancer: development and validation. *J Clin Oncol* 1984, 2, 472.
11. McDowell I and Newell C. *Measuring Health—a Guide to Rating Scales and Questionnaires*. Oxford, Oxford University Press, 1987.
12. Aaronson NK, Bullinger M, Ahmedzai S. *A Modular Approach to Quality-of-life Assessment in Cancer Clinical Trials. Recent Results in Cancer Research*. Berlin, Springer-Verlag, 1988.
13. Ganz PA, Schag CAC, Lee JJ, Sim MS. The CARES: a generic measure of health-related quality of life for patients with cancer. *Quality-of-Life Res* 1992, 1, 19–29.
14. Haes JCJM de, Knippenberg FCE van, Neijt JP. Measuring psychological and physical distress in cancer patients: structure and application of the Rotterdam Symptom Checklist. *Br J Cancer* 1990, 62, 1034–1038.
15. Levine MN, Guyatt GH, Gent M, *et al.* Quality of life in stage II breast cancer: an instrument for clinical trials. *J Clin Oncol* 1988, 6, 1798–1810.
16. Lansky SB, List MA, Ritter-Sterr C, *et al.* Performance parameters in head and neck patients. *Proc Am Soc Clin Oncol* 1988, 7, 156 (abstract 603).
17. Llewellyn-Thomas HA, Sutherland HJ, Hogg SA, *et al.* Linear analogue self-assessment of voice quality in laryngeal cancer. *J Chron Dis* 1984, 37, 917–924.
18. Drummond MF, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. Oxford, Oxford University Press, 1989.
19. Torrance GW. Utility approach to measuring health-related quality of life. *J Chron Dis* 1987, 40, 593–600.
20. The EUROQOL Study Group. EuroQoL, a new facility for the measurement of health-related quality of life. *Health Policy* 1990, 16, 147–161.
21. Essink-Bot ML, Bonsel GL, Maas PJ van der. Valuation of health states by the general public: feasibility of a standardized measurement procedure. *Soc Sci Med* 1990, 31, 1201–1206.
22. Bennett K, Torrance GW. *McMaster Rheumatoid Arthritis Utility Measurement Questionnaires*. Hamilton, Canada, McMaster University, Dept. of Clinical Epidemiology and Biostatistics, 1990.
23. Torrance GW, Boyle MH, Horwood SP. Application of multi-attribute utility theory to measure social preferences for health states. *Oper Res* 1982, 1043–1069.
24. Rosser R, Kind P. A scale of valuations of states of illness: is there a social consensus? *Int J Epidemiol* 1978, 7, 347–358.
25. Essink-Bot ML, Rutten-van Molken MPMH. *Het Meten van de Gezondheidstoestand: Inventarisatie van Meetinstrumenten voor Medical Technology Assessment*. Instituut Maatschappelijke Gezondheidszorg, Instituut voor Medische Technology Assessment, Erasmus Universiteit Rotterdam, 1991.
26. Schag CAC, Ganz PA, Heinrich RLH. Cancer Rehabilitation Evaluation System—Short Form (CARES-SF). *Cancer* 1991, 68, 1406–1414.
27. Sprangers MA, Aaronson NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease: a review. *J Clin Epidemiol* 1992, 45, 743–760.
28. Fayers PM, Jones DR. Measuring and analysing quality of life in cancer clinical trials: a review. *Stat Med* 1983, 2, 429–446.

## APPENDIX

### Example of a QoL questionnaire

#### Nottingham Health Profile

Listed below are some problems which people may have in their daily life.

Look down the list and put a tick in the box under **yes** for any problem you experienced **during the last week**. Tick the box under **no** for any problem you didn't experience. The problems may resemble each other but they are different nonetheless. Will you please answer every question. If you are not sure whether to say yes or no, tick whichever answer you think is more true at the moment.

	Yes	No
1 I'm tired all the time	<input type="checkbox"/>	<input type="checkbox"/>
2 I have pain at night	<input type="checkbox"/>	<input type="checkbox"/>
3 Things are getting me down	<input type="checkbox"/>	<input type="checkbox"/>
4 I have unbearable pain	<input type="checkbox"/>	<input type="checkbox"/>
5 I take tablets to help me sleep	<input type="checkbox"/>	<input type="checkbox"/>
6 I've forgotten what it's like to enjoy myself	<input type="checkbox"/>	<input type="checkbox"/>
7 I'm feeling on edge	<input type="checkbox"/>	<input type="checkbox"/>
8 I find it painful to change position	<input type="checkbox"/>	<input type="checkbox"/>
9 I feel lonely	<input type="checkbox"/>	<input type="checkbox"/>
10 I can only walk about indoors	<input type="checkbox"/>	<input type="checkbox"/>
11 I find it hard to bend	<input type="checkbox"/>	<input type="checkbox"/>
12 Everything is an effort	<input type="checkbox"/>	<input type="checkbox"/>
13 I'm waking up in the early hours of the morning	<input type="checkbox"/>	<input type="checkbox"/>
14 I'm unable to walk at all	<input type="checkbox"/>	<input type="checkbox"/>
15 I'm finding it hard to make contact with people	<input type="checkbox"/>	<input type="checkbox"/>

16 The days seem to drag	<input type="checkbox"/>	<input type="checkbox"/>
17 I have trouble getting up and down stairs and steps	<input type="checkbox"/>	<input type="checkbox"/>
18 I find it hard to reach for things	<input type="checkbox"/>	<input type="checkbox"/>
19 I'm in pain when I walk	<input type="checkbox"/>	<input type="checkbox"/>
20 I lose my temper easily these days	<input type="checkbox"/>	<input type="checkbox"/>
21 I feel there is nobody I am close to	<input type="checkbox"/>	<input type="checkbox"/>
22 I lie awake for most of the night	<input type="checkbox"/>	<input type="checkbox"/>
23 I feel as if I'm losing control	<input type="checkbox"/>	<input type="checkbox"/>
24 I'm in pain when I'm standing	<input type="checkbox"/>	<input type="checkbox"/>
25 I find it hard to dress myself	<input type="checkbox"/>	<input type="checkbox"/>
26 I soon run out of energy	<input type="checkbox"/>	<input type="checkbox"/>
27 I find it hard to stand for long (e.g. at the kitchen sink, waiting for a bus)	<input type="checkbox"/>	<input type="checkbox"/>
28 I'm in constant pain	<input type="checkbox"/>	<input type="checkbox"/>
29 I feel I am a burden to people	<input type="checkbox"/>	<input type="checkbox"/>
30 It takes me a long time to get to sleep	<input type="checkbox"/>	<input type="checkbox"/>
31 Worry is keeping me awake at night	<input type="checkbox"/>	<input type="checkbox"/>
32 I feel that life is not worth living	<input type="checkbox"/>	<input type="checkbox"/>
33 I sleep badly at night	<input type="checkbox"/>	<input type="checkbox"/>
34 I'm finding it hard to get on with people	<input type="checkbox"/>	<input type="checkbox"/>
35 I need help to walk about outside (e.g. a walking aid or someone to support me)	<input type="checkbox"/>	<input type="checkbox"/>
36 I'm in pain when going up and down stairs or steps	<input type="checkbox"/>	<input type="checkbox"/>
37 I wake up feeling depressed	<input type="checkbox"/>	<input type="checkbox"/>
38 I'm in pain when I'm sitting	<input type="checkbox"/>	<input type="checkbox"/>

Now we would like you to think about the activities in your life which may be affected by health problems.

In the list below, tick **yes** for each activity in your life which is being affected by your state of health. Tick **no** for each activity which is not being affected.

When you are not sure or when you do not want to answer the question...please tick the box under the question remark...("“?”")

Is your present state of health causing problems with your...

	Yes	?	No
39 Job or work (that is, paid employment)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
40 Looking after the home (examples: cleaning and cooking, repairs, odd jobs around the home)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
41 Social life	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
42 Home life (that is, relationships with other people in your home)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
43 Sex life	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
44 Interests and hobbies (sports etc.)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
45 Holidays	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

#### EuroQol—descriptive part

By placing a tick in one box in each group below, please indicate which statements best describe your own health state **during the last week**.

46 <b>Mobility</b>	
I have no problems in walking about	<input type="checkbox"/>
I have some problems in walking about	<input type="checkbox"/>
I am confined to bed	<input type="checkbox"/>
47 <b>Self-care</b>	
I have no problems washing or dressing myself	<input type="checkbox"/>
I have some problems washing or dressing myself	<input type="checkbox"/>
I am unable to wash or dress myself	<input type="checkbox"/>
48 <b>Usual activities</b> (e.g. work, study, housework, family or leisure activities)	
I have no problems with performing my usual activities	<input type="checkbox"/>
I have some problems with performing my usual activities	<input type="checkbox"/>
I am unable to perform my usual activities	<input type="checkbox"/>
49 <b>Pain/Discomfort</b>	
I have no pain or discomfort	<input type="checkbox"/>
I have moderate pain or discomfort	<input type="checkbox"/>
I have extreme pain or discomfort	<input type="checkbox"/>
50 <b>Anxiety/Depression</b>	
I am not anxious or depressed	<input type="checkbox"/>
I am moderately anxious or depressed	<input type="checkbox"/>
I am extremely anxious or depressed	<input type="checkbox"/>

#### Rotterdam Symptom Checklist

In the list below you will be asked about your symptoms. Would you please, for all symptoms mentioned, indicate to what extent

you have been bothered by it, by circling the answer most applicable to you. The questions are related to the past week.

Have you, during the past, week been bothered by

	Not at all	A little	Quite a bit	Very much
51 Lack of appetite	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
52 Irritability	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
53 Tiredness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
54 Worrying	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
55 Sore muscles	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
56 Depressed mood	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
57 Lack of energy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
58 Low back pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
59 Nervousness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
60 Nausea	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
61 Desperate feelings about the future	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
62 Difficulty sleeping	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
63 Headaches	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
64 Vomiting	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
65 Dizziness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
66 Decreased sexual interest	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
67 Tension	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
68 Abdominal aches	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
69 Anxiety	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
70 Heartburn/belching	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
71 Diarrhoea	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
72 Shivering	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
73 Tingling hands or feet	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
74 Difficulty concentrating	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
75 Sore mouth/ pain when swallowing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
76 Loss of hair	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
77 Burning/sore eyes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
78 Shortness of breath	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
79 Dry mouth	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
80* Constipation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
81* Painful joints	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
82* Palpitation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
83* Rash, eczema	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
84* Sweating, perspiring	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Finally, a number of activities is listed below. We do not want to know whether you actually do these, but only whether you are able to perform them presently. Would you please mark the answer that applies most to your condition of the past week.

	Unable	Only with help	Without help, with difficulty	Without help
85 Care for myself (wash etc.)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
86 Walk about the house	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
87 Housekeeping	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
88 Climb stairs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
89 Odd jobs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
90 Walk out of doors	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
91 Shopping	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
92 Go to work	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Would you please check whether you answered all questions?  
Thank you for your help.