

Patient-Reported

**PATIENT-
REPORTED
OUTCOME
MEASUREMENT
GROUP, OXFORD**

**A STRUCTURED REVIEW
OF
PATIENT-REPORTED
OUTCOME MEASURES
(PROMs)
FOR LUNG CANCER**

**Report to the Department of
Health, 2010**



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**A STRUCTURED REVIEW OF PATIENT-REPORTED
OUTCOME MEASURES FOR PATIENTS WITH LUNG CANCER,
2010**

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EXECUTIVE SUMMARY

Aims of the report

The aims of this report are to review the evidence of using PROMs for people with lung cancer; and to produce a short-list of the most promising generic and cancer-specific instruments.

The methods of the review are described and the results of the search, including sources and search terms used to identify specific published research. Details of this evidence are presented firstly for generic PROMs evaluated with people with lung cancer, followed by cancer-specific PROM results. The report concludes with discussion and recommendations.

Results

One generic instrument evaluated with people with lung cancer was identified in this review:

1. SF-36

This review identified one preference-based measure used with people with lung cancer:

1. EQ-5D

Two cancer-specific instruments were identified in this review:

1. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)
2. Functional Assessment of Cancer Therapy - General (FACT-G)

Finally, four lung cancer-specific PROMs were identified:

1. European Organization for Research and Treatment of Cancer Quality of Life Lung-specific Questionnaire (EORTC QLQ-LC13)
2. Functional Assessment of Cancer Therapy - Lung (FACT-L)
3. Lung Cancer Symptom Scale (LCSS)
4. Lung Cancer Symptom Scale – Mesothelioma (LCSS-Meso)

Recommendations

The SF-36 should be considered as a generic quality of life instrument. The EQ-5D has specific advantages if a short preference-based measure is needed. However both these instruments are general in scope and it is therefore recommended that they are used together with a lung-cancer-specific instrument.

Based on the volume of evaluations and good measurement and operational characteristics, the following are highlighted as promising PROMs for potential piloting in the NHS in people with lung cancer.

- EORTC QLQ-C30
- EORTC QLQ-LC13
- FACT-L

INTRODUCTION

Background

Patient-reported outcome measures (PROMs) offer enormous potential to improve the quality and results of health services. They provide validated evidence of health from the point of view of the user or patient. They may be used to assess levels of health and need in populations, and in users of services, and over time they can provide evidence of the outcomes of services for the purposes of audit, quality assurance and comparative performance evaluation. They may also improve the quality of interactions between health professionals and individual service users.

Lord Darzi's Interim Report on the future of the NHS recommends that patient-reported outcome measures (PROMs) should have a greater role in the NHS (Darzi 2007). The new Standard NHS Contract for Acute Services, introduced in April 2008, included a requirement to report from April 2009 on patient-reported outcome measures (PROMs) for patients undergoing Primary Unilateral Hip or Knee replacements, Groin Hernia surgery or Varicose Vein. Furthermore, Lord Darzi's report 'High Quality Care for All' (2008) outlines policy regarding payments to hospitals based on quality measures as well as volume. These measures include PROMs as a reflection of patients' experiences and views. Guidance has now been issued regarding the routine collection of PROMs for the selected elective procedures (DH, 2008) and, since April 2009, the collection of PROMs for the selective elective procedures has been implemented and is ongoing.

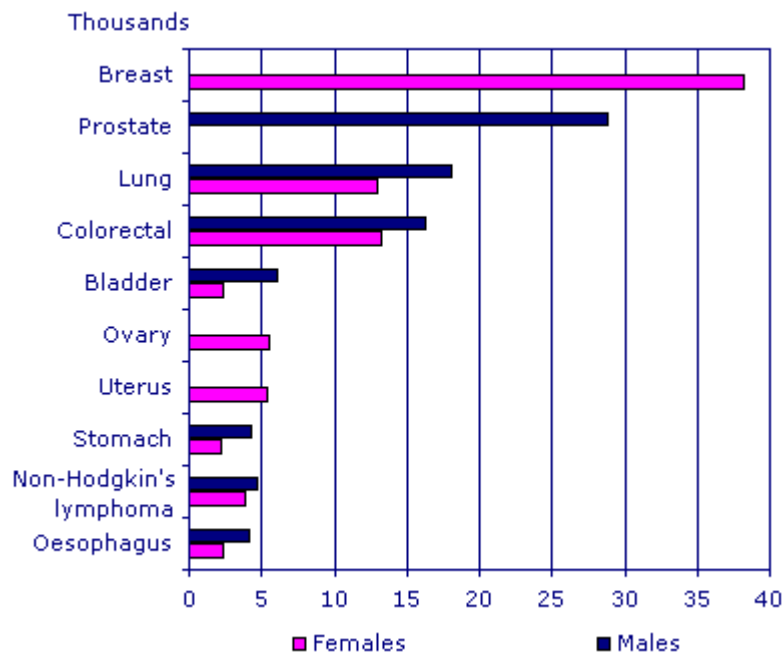
In light of recent policy to include PROMs as an important quality indicator, the Department of Health now seek guidance on PROMs which can be applied in patients with cancer and have commissioned the Patient-reported Outcome Measurement Group, Oxford to review the evidence of PROMs for selected cancers. It is proposed that the most common cancers, as identified via the Office for National Statistics, should be the subject of review in terms of most promising PROMS. Lung, breast, colorectal and prostate cancer are highlighted as being the four most common cancers, accounting for half of the 239,000 new cases of malignant cancer (excluding non-melanoma skin cancer) registered in England in 2005 (Figure 1). On scrutinising cumulative incidence data from the cancer registry of the Oxford region, findings support that these four cancers are the most common. According to the Department of Health's Cancer Reform Strategy (2007), which aims to place the patient at the centre of cancer services, a 'vision 2012' has been created for each of these four cancer types, highlighting the progress that it is hoped will be made by 2012 in terms of the cancer pathway. Underlying these visions are the aims to achieve full implementation of improving outcomes guidance. In this context, PROMs are an important resource to monitor cancer outcomes.

Lung cancer

Lung cancer is one of the four most common cancers in England (Table 1), with 39,027 new patients diagnosed in the UK in 2006 (Cancer Research UK). In England and Wales, nearly 29,000 deaths were attributed to lung cancer in 2002. Lung cancer is the most common cause of cancer death for men, who account for 60% of lung cancer

cases. In women, lung cancer is the second most common cause of cancer death after breast cancer (Office for National Statistics, 2003).

Figure 1: Incidence of the major cancers, 2005, England (ONS, 2007)



Lung cancers are classified into two main categories:

- Small-cell lung cancers (SCLC)
- Non-small-cell lung cancers (NSCLC)

Small-cell lung cancers are about 20% of cases, whereas non-small-cell lung cancers account for the other 80% approximately. This later type of lung cancer includes squamous cell carcinomas, adenocarcinomas and large cell carcinomas (NICE guidance on lung cancer¹). Malignant pleural mesothelioma is a type of lung cancer, highly symptomatic and with a median survival of 6 to 9 months (Vogelznag et al., 2003), and with a highly causative relationship to asbestos (Hollen et al., 2006).

Survival rates for lung cancer are very poor: less than 21.4% patients were alive one year after diagnosis, and less than 6% were alive 5 years after diagnosis. Sir Richard Doll linked tobacco smoking to lung cancer in the early fifties (Doll & Hill, 1950), and trends of lung cancer incidence reflect the changes in smoking habits over the XXth century (Quinn et al., 2001). Although 1-year survival has improved by about 5% since the early 1970's, there has been little improvement in 5-year survival.

¹ The reader should note that the document 'The Diagnosis and Treatment of Lung Cancer' is currently being updated by NICE. This update will be published in March 2011.

METHODS

Aim of the report

The aim of this report is to identify Patient-reported Outcome Measures (PROMs) which have been evaluated with patients with lung cancer.

Structure of the report

The methods of the review are described and the results of the search, including sources and search terms used to identify specific published research. Details of this evidence are presented firstly for generic PROMs evaluated with people with lung cancer, followed by cancer-specific PROM results including those focusing specifically on lung cancer symptoms. The report concludes with discussion and recommendations.

Methods for the review

a) Search terms and results: identification of articles

The searches were conducted using three main sources.

Records in the University of Oxford PROM bibliography database were searched up to December 2005 using specific keywords. This database was compiled by the PROM group with funding from the Department of Health and the Information Centre, and hosted by the University of Oxford².

The Ovid search engine was used to explore a number of relevant databases³ from January 2006 until February 2010, using a comprehensive search strategy (see Appendix A).

Hand searching of titles of key journals from October 2009 was conducted. The following journals were selected:

- Health and Quality of Life Outcomes
- Quality of Life Research.
- Journal of Clinical Oncology
- British Journal of Cancer
- Cancer
- Lung Cancer

The following supplementary sources were searched:

- The National Institute for Health Research: Health Technology Assessment Programme
- The Cochrane library (<http://www.thecochranelibrary.com/>)

² The PROMs bibliography can be accessed free of charge at <http://phi.uhce.ox.ac.uk/home>.

- The EQ-5D website: reference search facility (<http://www.euroqol.org/>)
- ‘instrument name’ searches were conducted for the commonly cited PROMs identified in the initial phase and websites of the developers were identified
- NHS Database of Economic Evaluations (<http://www.crd.york.ac.uk/crdweb>) was used to identify the utility measures used in cost-effectiveness studies

The number of relevant articles identified through each source is shown in Table 1 and Appendix A.

b) Inclusion criteria

Titles and abstracts of all articles were assessed for inclusion/exclusion by one reviewer and a selection agreement was checked by another reviewer. Included articles were retrieved in full. Published articles were included if they provided evidence of measurement and/or practical properties (Fitzpatrick et al., 1998).

Articles were retrieved, assessed for relevance and catalogued according to the PROM for which they provided evidence (note that a single paper frequently provided information on more than one measure). Papers were included if the patients were diagnosed with any type lung cancer and the questionnaires administered were in English language. Papers were excluded if the questionnaires were administered in languages other than English, or if the questionnaires were administered to the general public or carers rather than to lung cancer patients or lung cancer survivors.

Sample:

- Patient with lung cancer (any type)
- English-speaking populations
- Sample ≥ 50 lung patients

Study design selection:

- studies where a principal PROM is being evaluated
- studies evaluating several PROMs concurrently
- applications of PROMs with sufficient reporting of methodological issues

Specific inclusion criteria for generic and disease-specific instruments:

- the instrument is patient-reported
- there is published evidence of measurement reliability, validity or responsiveness following completion in the specified patient population
- the instrument will ideally be multi-dimensional (it is at the reviewer’s discretion to include PROMs which are specific to a health condition but have a narrow focus, for example, a specific dimension of health, such as symptoms)
- evidence is available from English language publications, and instrument evaluations conducted in populations within UK, North America, Australasia

c) Exclusion criteria

- Clinician-assessed instruments
- Studies evaluating the performance of non-patient reported measures of functioning or health status where a PROM is used as a comparator indicator
- Studies with a sample $n \leq 50$

e) Data extraction

Data were extracted on the psychometric performance and operational characteristics of each PROM. Assessment and evaluation of the methodological quality of PROMs was performed independently by two reviewers adapting the London School of Hygiene appraisal criteria outlined in their review (Smith et al., 2005). These criteria were modified for our review (Appendix C). The final short-listing of promising PROMs to formulate recommendations is based on these assessments and discussion between reviewers.

For all PROMs included in the review, evidence is reported for the following measurement criteria:

- reliability
- validity
- responsiveness
- precision

Operational characteristics, such as patient acceptability and feasibility of administration for staff, are also reported.

RESULTS

Searches identified nearly 1600 potentially relevant records. When assessed against the inclusion and exclusion criteria of this review, 57 articles were included (see Table 1 and Appendix A).

Table 1: Number of articles identified by the literature review (after deduplicating)

Source	Results of search	Number of articles included in review
PROM database	22	10
Ovid	1566	45
Hand searching	3	3
TOTAL	--	58

RESULTS: GENERIC PROMs

One generic PROM was identified that had been used with patients with lung cancer in English language populations, and for which adequate evidence of psychometric properties was available to enable appraisal.

1. Medical Outcomes Study Health Survey instruments (SF-36).

This instrument is summarised in Appendix C.

a) Medical Outcomes Study Health Survey instruments (SF-36)

The Medical Outcomes Study (MOS) Short Form 36-item Health Survey (SF-36) is intended for application in a wide range of conditions and with the general population. The instrument assess health across eight domains (Ware., 1997), namely Bodily pain (BP), General Health Perceptions (GH), Mental health (MH), Physical functioning (PF), Role limitations due to emotional health problems (RE), Role limitations due to physical health problems (RP), Social functioning (SF), and Vitality (VT). An additional health transition item, not included in the final score, assesses change in health.

Three papers (none of them from the UK) provided data for the use of SF-36 in English-speaking lung cancer populations.

The SF-36 PCS and MCS discriminated patients with different cancers with significantly different scores between patients with lung, prostate and colorectal cancer. Lung patients scores were significantly lower than the comparators and below population norms (Grünfield et al., 2009). Further support for discriminative validity is reported in Sarna et al. (2006) with statistically significantly poorer scores on all domains and component summary scores for women with lung cancer and their family members.

The PCS and PF, RP, BP and GHP domain scores detected change in a large prospective study of people pre-cancer diagnosis and post diagnosis of various cancers including lung (112). Scores were significantly poorer once cancer was diagnosed and lower than those without cancer. The MCS and RE, MH, VT and SF also detected change between and within groups (Reeve et al., 2009).

RESULTS: PREFERENCE-BASED PROMs

One preference-based PROM was identified that had been used with patients with lung cancer in English language populations, and for which adequate evidence of psychometric properties was available to enable appraisal.

1. European Quality of Life Questionnaire (EuroQol EQ-5D)

This instrument is summarised in Appendix C.

1) European Quality of Life Questionnaire (EuroQol EQ-5D)

The EQ-5D (EuroQol Group, 1990; Brazier et al., 1993) is a generic preference-based measure. There are five single item dimensions: mobility, self-care, usual function status, pain and/or discomfort, and anxiety and/or depression.

Three papers, all of them from the UK, provided data for this review.

Some evidence of convergent validity is reported with higher concordance of EQ-5D scores with patient-reported symptoms than for physician reported symptoms (Basch et al., 2009).

Distribution-based and anchor-based methods of evaluating minimally important differences for the EQ-5D in patients with various cancers including lung (50) are reported in Pickard et al. (2007, UK). Both methods of estimation converged with MID_s for the EQ-5D UK index-based utility scores ranging from 0.08 to 0.16 and for VAS 0.07.

Ring et al. (2008, UK) explored the applicability of an electronic version of EQ-5D and FACT-L versus the traditional pen and paper approach in a cohort of 50 NSCLC. They found a strong degree of association by both methods (e-PRO and paper) for each individual question and the questionnaire as a whole (all $p < 0.0001$). Mean completion time for the electronic administration was longer than the pen and paper time. Most patients (60% vs. 12%) stated that they preferred the e-PRO method (Ring et al., 2008, UK).

Another multi-attribute utility instrument (MAU) was developed in 2000 by Hawthorne et al. in Australia: the Assessment of Quality of Life (AQoL). This review identified only one study using this questionnaire with lung cancer patients. Manser et al. (2006) assessed quality of life of 92 lung cancer patients in a prospective, non-experimental cohort study, supporting good validity and reliability (Cronbach's $\alpha = 0.76$) of the instrument. However the authors warn about some uncertainty about the AQoL's sensitivity to different health states in this specific population.

RESULTS: CANCER & LUNG CANCER SPECIFIC PROMs

A total of six cancer and lung cancer-specific PROMs were identified that had been used with patients in English language populations, and for which adequate evidence of psychometric properties was available to enable appraisal.

Two *cancer*-specific instruments were identified in this review:

1. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)
2. Functional Assessment of Cancer Therapy - General (FACT-G)

Four *lung cancer*-specific specific PROMs were identified in this review:

1. European Organization for Research and Treatment of Cancer Quality of Life Lung-specific Questionnaire (EORTC QLQ-L13)
2. Functional Assessment of Cancer Therapy - Lung (FACT-L)
3. Lung Cancer Symptom Scale (LCSS)
4. Lung Cancer Symptom Scale - Mesothelioma(LCSS-Meso)

These instruments are summarised in Appendix D.

Some of the lung cancer-specific instruments are extended modules of general cancer instruments for example the EORTC and the FACT, we therefore present them in the following order. However, the reader should note they should be used as independent questionnaires.

1) European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core Module (EORTC QLQ-C30)

The EORTC QLQ-C30 (Aaronson et al., 1993) is a 30-item cancer-specific instrument. Multi-trait scaling was used to create five functional domain scales: Physical, Role, Emotional, Social and Cognitive; two items evaluate global QoL; in addition three Symptom scales assess: Fatigue, Pain and Emesis; and six single items assess further symptoms.

Five papers provided data of EORTC QLQ-C30 for this review; one of them was from the UK.

Validity for EORTC QLQ-C30 was illustrated in a study evaluating quality of life in a sample of NSCLC patients, where the QLQ-C30 discriminated between participants in the intervention arm (186 patients undergoing adjuvant chemotherapy) and in the observation arm (173 patients), with significant differences in the domains of Global quality of life, Physical functioning, Role functioning and Social functioning showing better scores for the observation arm at 3 months, returning to baseline score at 9 months (Bezjak et al., 2008).

The QLQ-C30 discriminated between different types of cancers (lung, colorectal and prostate) in a study exploring peri-diagnostic and survival wait times (Grunfeld, 2009, UK).

Predictive validity of QLQ-C30 was illustrated in a study with 538 cancer patients (101 lung cancer) where Function and Symptom scales were predictive of overall patient satisfaction upon univariate analysis (Lis et al., 2009).

Regarding responsiveness, the QLQ-C30 detected statistically significant improvement in the areas of Global quality of life, Physical functioning, Role functioning, Emotional functioning and Social functioning when assessed at 3 months after chemotherapy (Bezjak et al., 2008). In a randomised open trial exploring the effects of SRL172 (killed *Mycobacterium vaccae*) with 419 NSCLC patients, QLQ-C30 detected a statistically significant change in scores between and within groups at the end of the 15-week treatment, showing a significantly improved patient quality of life in the intervention group (O'Brien et al., 2004, UK).

For the Physical function domain of QLQ-C30, mean change in scores of 9.2 was significantly related, on average, to change in “very much worse” to “moderately worse”, or from “no change” to “a little change” as anchors in a study aiming at determining the significance of changes (MID) in HRQoL scores to patients with lung cancer (n=111), together with breast cancer patients (n=246) (Osoba et al., 1998).

In a study interpreting the significance of quality of life scores in 111 SCLC patients receiving chemotherapy, Osoba et al. (1998) reported a reasonable response rate of 72% at baseline and at week 4.

2) European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Lung Cancer 13 (EORTC QLQ-LC13)

The EORTC QLQ-C30 core questionnaire can be supplemented by the additional lung module QLQ-LC13, resulting in a 43-item disease and cancer site-specific quality of life questionnaire. The QLQ-LC13 module items evaluate symptoms such as cough, haemoptysis, shortness of breath, sore mouth or tongue, dysphagia, tingling hands or feet, hair loss and pain. The response options and scoring system are the same as for the EORTC QLQ-C30, and the administration is similar.

The reader should note that the developers of EORTC QLQ-LC13 indicate it is not possible to use the LC13 alone (without the core module QLQ-C30), since the module has been designed to be used together with the core questionnaire, and the content validity is based upon this combination. All papers included in this review use the QLQ-LC13 in this manner.

Seventeen papers are referenced in this review, of which 11 are UK studies.

The subscales of Physical function, Fatigue and Dyspnea of QLQ-LC13 discriminated between young and older patients after major lung resection (Ferguson et al., 2009). In a trial of different types of chemotherapy with 433 NSCLC patients, the questionnaire discriminated between study arms, and detected significant change of overall quality of life scores within intervention groups (Booton et al., 2006, UK). Further evidence is reported in a chemoradiation trial with 138 NSCLC participants. The QLQ-LC13 discriminated between patients in different treatment arms at baseline, and

responsiveness was also demonstrated with significant changes between and within groups in swallowing difficulty and pain reduction (Sarna et al., 2008).

In a trial by Wheatley-Price et al. (2008), the QLQ-LC13 discriminated between known groups (young and older patients) in a study with 731 NSCLC patients in terms of delay of presentation of symptoms.

Predictive validity of QLQ-LC13 was illustrated in a trial with locally advanced NSCLC, where baseline global quality of life scores was a predictor of long-term overall survival (Movsas et al., 2009). Predictive validity was also illustrated in a study with elderly people with lung cancer undergoing palliative radiotherapy, where poor Physical and Social function scores at baseline, were associated with premature death (Turner et al., 2005, UK). However these results should be interpreted with caution as these calculations are based in a small sample (29 participants died out of a sample of 132), and none of the symptoms of lung cancer discriminated between age groups.

Responsiveness was illustrated in a study with 107 advanced NSCLC patients, where EORTC QLQ-LC17 scores detected significant change in quality of life between baseline and week 12 (Brown et al., 2007, UK)⁴.

A shortened version of QLQ-LC13 was used in a trial exploring quality of life before and after lung lobectomy in 422 elderly patients (Burfeind et al., 2008), where only the subscales of chest pain, arm/shoulder pain and dyspnea were administered, together with the main body of QLQ-C30. The questionnaire scores showed significant change at 3 months, and again at 6 and 12 months where scores in all domains except Physical functioning had returned to baseline.

The QLQ-LC13 showed responsiveness and could discriminate between intervention arms in several symptom subscales in a trial assessing the effects of thalidomide combined with chemotherapy versus placebo in 724 small cell lung cancer (SCLC) (Lee et al., 2009a, UK). The QLQ-LC13 also detected significant change between and within groups in a multicentre randomised trial comparing two arms of treatment with either erlotinib or paclitaxel + carboplatin (Lilenbaum et al., 2008). The QLQ-LC13 showed significant change in the subscales of fatigue, alopecia, physical worsening and dyspnea in a small UK based trial with 43 mesothelioma patients (O'Brien et al., 2006, UK).

In a study with NSCLC (Lee et al., 2009b, UK), QLQ-LC14 discriminated between intervention arms and detected change within those groups, on the subscales of insomnia, constipation and peripheral neuropathy.

In a trial comparing gemcitabine and carboplatin versus cisplatin and etoposide for 241 patients with SCLC, QLQ-LC17 detected significant change within groups over time for two of the toxicity subscales (hair loss and impaired cognitive functioning), and discriminated between intervention arms (Lee et al., 2007, UK).

⁴ The EORTC QLQ-LC13 is the latest version of this questionnaire (Salvo et al., 2009). This review has included papers that used older versions such as the LC14 and the LC17.

All the studies reporting response / completion rates in this review have observed a generally high at baseline but soon decline (Lee et al., 2009a, UK; Lee et al., 2007, UK; Mills et al., 2008, UK; Muers et al., UK; Sarna et al., 2008; Lilenbaum et al., 2008). This could be due to the toxicity of the treatments or the advance of the disease.

The EORTC QLQ-LC13 was used in an A5 weekly format diary with 115 inoperable lung cancer patients, showing poorer quality of life when scored using both the FACT-L and the Palliative Care Quality of Life Index. The authors argue that this could be due to the lack of training and support for patients and staff (Mills et al., 2008, UK).

The EORTC QLQ-C30 & LC13 questionnaires have been used in a number of UK studies on lung cancer patients (Cox et al., 2006; Muers et al., 2008; Win et al., 2008). No significant differences were reported in these studies and therefore little psychometric evidence is available.

3) Functional Assessment of Cancer Therapy - General Version (FACT-G)

The FACT-G (Cella et al., 1993) is a 27-item cancer-specific instrument with four domains: Physical, Social, Emotional, and Functional wellbeing, and a total score. Each question is rated on a 5-point Likert scale.

This review identified only two papers using the FACT-G in an English-speaking population; none of which were from the UK.

The FACT-G showed good discriminative validity when patients allocated to different treatment arms obtained different quality of life scores at baseline, as well as responsiveness when it detected significant change within groups, in a trial of 161 NSCLC patients (Socinski et al., 2006).

Floor effects were observed in a randomised controlled trial evaluating the effects of HRQoL assessment: patients rated items relating to the level of impairment or toxicity on the extremely negative end (Rosenbloom et al., 2007).

4) Functional Assessment of Cancer Therapy - Lung Version (FACT-L)

The FACT-L is a 36-item lung cancer-specific scale that supplements the general version (FACT-G). The FACT-L has five domains; the four domains already covered by the FACT-G: physical well-being (PWB), functional well-being (FWB), social well-being (SWB), emotional well-being (EWB), and an additional 7-item lung cancer specific subscale (LCS), making a total of 37 items. Each question is rated on a 5-point Likert scale, giving a total score for each category as well as a total overall score from 0 (worst quality of life) to 135 (best quality of life). The LCS subscale can be used independently of FACT-G. In addition, an additional measure of quality of life, a summary score of physical and function domains can be obtained using the 21-item Trial Outcome Index (TOI) by combining scores on the PWB, FWB and LCS subscales. As a result, the FACT-L can be scored in three different ways (FACT-L, LCS and TOI).

Eleven papers provided data for this review, of which two were UK studies.

Internal consistency of the TOI was demonstrated in a study with 116 lung cancer patients, where the coefficient alpha was 0.89 (Cella et al., 1995).

In a trial exploring quality of life in 51 lung cancer patients who smoke (Browning et al., 2009), the FACT-L (version 3) showed good reliability with Cronbach's alpha coefficients of 0.81 or higher, as well as convergent validity when compared against the Lung Cancer Symptom Scale (LCSS), especially for the LCS which showed the strongest correlation.

Discriminative validity was illustrated in a study with 216 advanced NSCLC patients by Cella et al. (2005), where they reported lower LCS, FACT-L and TOI baseline scores compared normative data.

The FACT-L Total score, PWB, FWB and EWB subscales discriminated between groups of patients in a study evaluating the glutathione metabolic genes on outcomes (including quality of life) with 186 NSCLC patients (Yang et al., 2009).

A study analysing self-efficacy in 152 patients with lung cancer and their informal caregivers, the PWB and FWB subscales of FACT-L were able to discriminate between types of patient-carer dyads (Porter et al., 2006). Furthermore, the FACT-L discriminated between intervention groups in a study assessing the effect on quality of life of the completion a weekly-diary format of the EORTC QLQ-C30 in 115 inoperable lung cancer patients (Mills et al., 2008, UK).

One trial used scored the FACT-L, the LCS and the TOI separately with 216 symptomatic advanced NSCLC patients (Cella et al., 2005), and the three instruments were able to show clinically meaningful improvement. A best overall response of improved was defined as an increase in TOI or FACT-L score of ≥ 6 points sustained for ≥ 4 weeks.

The FACT-L also detected significant change in different trials with NSCLC patients (Cella et al., 2002 [using FACT-L version 2]; Goss et al., 2009; Johnson et al., 2008).

Ring et al. (2008, UK) analysed the results of an electronic version of FACT-L versus a traditional pen and paper, results of both methods showed a high degree of correlation. In the same study, mean scores of LCS were significantly higher when determined using the e-PRO method than when using the paper method.

Response rates for the FACT-L was over 84% in a study with 216 NSCLC patients (Cella et al., 2005); in the same study, completion rate the LCS was over 82%.

Several trials have reported a high baseline completion rate of FACT-L followed by a reduced one (Goss et al., 2009; Socinsky et al., 2006). Similarly to the results reported for other questionnaires, this could be due to toxicity or poorer health status.

One study explored the applicability of an electronic version of FACT-L (together with EQ-5D) versus the traditional pen and paper approach in a cohort of 50 NSCLC. Mean completion time for the electronic administration was longer than the pen and paper time. The difference in time taken to complete the e-PRO may reflect the average age (60 years) and the familiarity of patients with filling out questionnaires compared with

the unfamiliar technology of electronic hand-held devices. Most patients (60% vs. 12%) stated that they preferred the e-PRO method (Ring et al., 2008, UK).

In addition, a version of the Functional Assessment Cancer Therapy questionnaire called the Functional Assessment of Cancer Therapy – Lung Symptom Index-12 (FLSI-12) was developed and validated in 2007 by Eton et al. This review found one study using the FLSI-12 with NSCLC patients to assess performance status (Cella et al., 2008).

The anemia, neutropenia and fatigue versions of the Functional Assessment Cancer Therapy questionnaire have also been used in studies with lung cancer patients (Glaspay et al., 2006; Wagner et al., 2007; Wright et al., 2007).

5) Lung Cancer Symptom Scale (LCSS)

The Lung Cancer Symptom Scale (LCSS) was developed in the USA by Hollen et al. in 1993, aiming to provide a disease and site-specific measure of quality of life, particularly for use in clinical trials. It is a 9-item questionnaire which evaluates five domains associated with lung malignancies and their effect on overall symptomatic distress, functional activities, and global QL. The LCSS provides both a patient and an observer (health care professional) 6-item scale. Each item is scored using a VAS. The 9-item patient scale takes 3 to 8 minutes to complete and it can be interview or telephone-administered.

Seven papers provided evidence of LCSS for this review; none of them was from the UK.

In the development study (Hollen et al., 1993), LCSS was administered to 121 lung cancer patients, showing good content validity, high internal consistency, good reproducibility and feasibility.

The LCSS is scored by the patient using a VAS for each item does present some limitations regarding compatibility with data management and software programs. A version of the LCSS using an 11-point response numerical rating scale (NRS) has been developed to address this issue. Hollen et al. (2005) evaluated the equivalence of this NRS version and the initial VAS-scoring system of this questionnaire with a sample of 68 NSCLC patients. This study reported good feasibility, good reliability (internal consistency) and convergent validity.

In a study with 207 NSCLC patients, the LCSS showed good construct and criterion validity, good correlation with gold standard instruments, and good internal consistency (alpha coefficient=0.82) (Hollen et al., 1994).

In a trial exploring quality of life in 50 lung cancer patients who smoke (Browning et al., 2009), the LCSS showed convergent validity when compared against the FACT-L (version 3), as well as good internal consistency with a coefficient alpha of 0.84.

The LCSS discriminated between patients according to intervention groups (chemotherapy with or without celecoxib) at baseline in a phase II trial with 133

NSCLC patients (Lilenbaum et al., 2006). However, overall toxicity rates and LCSS scores were similar between patients treated or not treated.

Responsiveness of LCSS was illustrated in a study evaluating symptom severity 1 to 4 months after thoracotomy for lung cancer in 94 patients (Sarna et al., 2010). There was a clinically meaningful improvement in symptom severity (>10mm as a cut point) in appetite, dyspnea and pain. However, only a minority had meaningful reductions in fatigue and cough.

Compliance rate for the completion of LCSS was over 71.9% in a randomised trial with 250 patients with NSCLC (Fidias et al., 2009).

More than 80% of 133 NSCLC patients completed the LCSS survey throughout all treatment cycles, with a 93.9% completion rate at end of treatment in a study by Lilenbaum et al. (2006).

An instrument specific for mesothelioma patients, the LCSS-Meso, was developed by Hollen et al. (2004, 2006). It is based on the LCSS but consists of an 8-item patient scale (the item evaluating haemoptysis was excluded from the original LCSS) and a 6-item observer scale. This review did not identify any articles using this questionnaire.

Other PROMs used with lung cancer patients

Cancer symptoms

Patients with cancer often experience high symptom burden. This is reflected in the number of symptom measures available. Twenty-one cancer symptom instruments were identified in a systematic review (Kirkova et al., 2006). Of these, 18 were self-reported and most contained less than 20 items. None were specific to lung cancer nor was there any substantive evidence reported for any of these measures in relation to people with lung cancer.

This review identified one measure specific to patients with lung cancer: the Patient Symptom Assessment in Lung Cancer. It assesses nine lung cancer-specific symptoms: shortness of breath, cough, chest pain, coughing up blood, loss of appetite, interference with sleep, hoarseness, fatigue and interference with activities. The latter item is an indicator of the impact and burden of the presence of symptoms on functioning. Six of the symptoms are from the LCSS. A Total score is obtained. Supportive evidence of reliability, one factor structure, and construct validity is reported. The Total score is reported responsive to clinical change and tumour progression with high responsiveness indices (Chen et al., 2007, 2008).

Several other measures are available to assess the prevalence and related distress of symptoms. These tend to be either general symptom measures which have been developed with a population of people with chronic or advanced illness including cancer and others specific to cancer and cancer sites. Examples include the following:

- Edmonton Symptom Assessment Scale (general, palliative care symptoms) (Bruera et al., 1991).

- Symptom Distress Scale (cancer related symptoms) (McCorkle. 1987 ; Brecht et al., 1997).
- M.D. Anderson Symptom Distress Inventory (cancer-related symptoms) (Cleeland et al., 2000; Wang et al., 2010).

Other PROMs used with lung cancer patients

Two other measures were identified with limited evidence.

The Ferran's Quality of Life Index questionnaire measures overall QoL and QoI in four domains: Health and physical, Social and economic, Psychological and spiritual, and Family. Responses are obtained on a 6 point Likert scale in 2 parts: satisfaction with aspects of life and the importance of these aspects. Scores range from 0 to 30 with higher scores indicating a better QoL. Scores are also determined by weighted satisfaction responses with importance responses. Statistically significant differences in survival have been reported for people with different cancers including lung using score cut-off values. For example, the Health and function scores ≤ 17.4 and ≥ 17.4 were predictive of survival with the median survival being 9.5 and 23 months respectively ($p < 0.001$) (Lis et al., 2007). This included various cancer groups as well as lung cancer patients

The Cancer Therapy Satisfaction Questionnaire has been developed for use in a wide range of cancer types and stages but specifically for patients receiving both oral and intravenous chemotherapy, focusing on compliance, feelings about side effects and satisfaction with therapy. There are 18 items but not all are relevant to every patient. Some questions are about oral medication and others for intravenous therapy. Lung cancer patients have been involved in the development and subsequent psychometric evaluation; including a UK population. Some supportive evidence of a three domain structure is reported of Side effects, Satisfaction with therapy and Expectations of therapy. Internal consistency is reported as high. Substantial ceiling effects are reported for Expectations of therapy and satisfaction. Moderate correlation of scores is reported between CTSQ domains with corresponding domains of other instruments (Treatment Satisfaction Questionnaire for Medication; EORTC). MID is calculated as 0.5 SD of baseline scores and 1 SEM. To note: all psychometric criteria are in relation to all cancers (Trask et al., 2008).

CONCLUSIONS AND RECOMMENDATIONS

The full-text articles for 178 papers were retrieved and reviewed. Those papers describing studies not used in English language populations or using dimension-specific instruments, symptom checklists or clinician ratings were discarded. There were 58 papers identified that provided useful data for the review.

Two generic, two cancer-specific and four lung cancer-specific PROMs were identified that have been evaluated with patients with lung cancer in English language populations, and for which adequate evidence of psychometric properties was available to enable appraisal (Tables 3 and 4).

The SF-36 was identified as the only generic instrument used to evaluate quality of life in lung cancer patients. The EQ-5D was the preference-based measure identified in this review. Compared to the cancer and lung cancer specific instruments, the SF-36 and EQ-5D have relatively small amounts of evidence.

There are three main contenders amongst the cancer and lung cancer specific instruments. The EORTC QLQ-LC13 has a more robust body of evidence in the literature, followed by the FACT-L and the LCSS.

The evidence relating the scoring of the FACT-L presents some limitations in relation to different methods of scoring and subsequent feasibility. This is disappointing because essentially it is an attractive questionnaire based on content and patient acceptability.

The LCSS was designed as a lung cancer-specific instrument. However promising the content validity of this instrument is, the evidence found suggests some limitations regarding feasibility (Hollen et al., 2005).

As pointed out in the introduction, lung cancer has a very poor survival rate: less than 6% of patients are still alive 5 years after diagnosis. This means that a good part of the evidence available for this disease is focused on palliative and supportive care. In particular, this review has included 22 papers (out of a total of 70) that evaluate quality of life in lung cancer from a palliative/supportive care perspective.

This review identified a number of instruments that focus on symptoms specific to patients with lung cancer. These instruments have little evidence and are too narrow in focus to be considered further in evaluating quality of life in lung cancer patients.

The literature identified in this review concerning the use of the EORTC QLQ-LC13 in lung cancer English-speaking populations has showed good psychometric properties. Of all the instruments evaluated in this review, the EORTC QLQ-LC13 stands out as the one having more favourable evidence supporting its use.

Cancer survivorship

The instruments included in this review have been used with patients with recent diagnosis or undergoing treatment, principally to evaluate the effectiveness of interventions. However, as more patients are living longer following treatment, there is

increasing interest in measuring quality of life amongst the long-term survivors of cancer. In this context, our recommendations regarding generic instruments will likely remain appropriate, but the content of condition-specific instruments may lose face validity as the predicament of survivorship is different to undergoing treatment. However, lung cancer has a very poor survivorship rate. This makes quality of life survivorship measurement particularly challenging. Since the survival rates are much higher in other types of cancer (for instance an 86% for breast cancer) at the present time of writing, evidence about survivorship tends to focus on these other types of cancer and papers exploring lung cancer survivorship are a minority (Pearce et al., 2008; National Cancer Survivorship Initiative Vision, 2010).

Recommendations

The SF-36 should be considered as a generic measure for patients with lung cancer.

The EQ-5D should be considered as a preference-based measure.

However it is recommended that they are used together with a lung-cancer specific instrument.

Three condition-specific instruments have supportive evidence used in relation to lung cancer:

- EORTC QLQ-C30
- EORTC QLQ-LC13
- FACT-L

Table 3: Appraisal of psychometric and operational performance of generic PROMs used with lung cancer

PROM	Reproducibility	Internal consistency	Validity: Content	Validity: Construct	Responsiveness	Interpretability	Floor/ceiling/precision	Acceptability	Feasibility
Generic									
SF-36	0	0	0	+	+	0	0	0	0
Preference-based									
EQ-5D	0	n/a	0	+	0	0	0	+	+

0 not reported — no evidence in favour + some limited evidence in favour ++ some good evidence in favour +++ good evidence in favour.

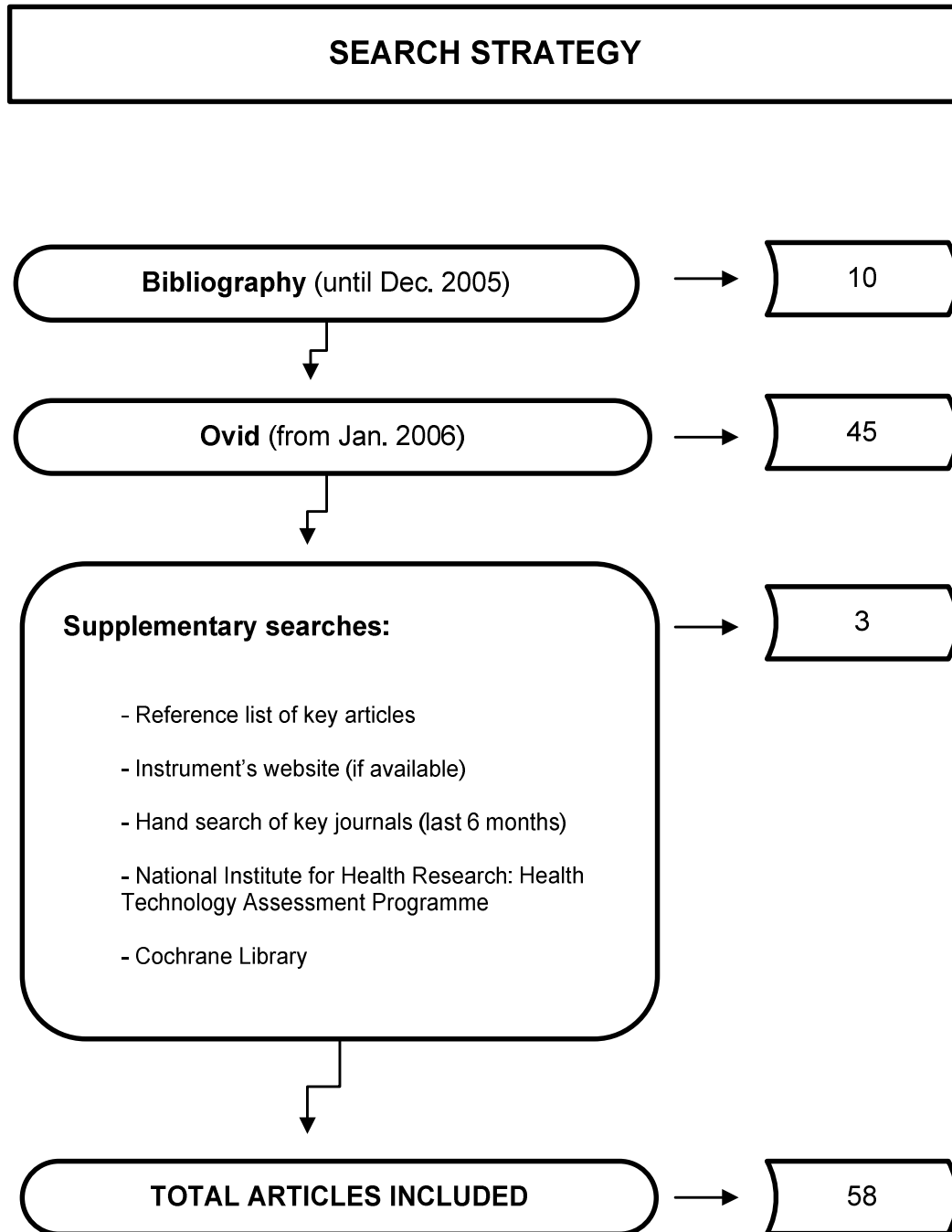
Table 4: Appraisal of psychometric and operational performance of cancer & lung cancer-specific PROMs

Instrument (n of studies)	Reproducibility	Internal consistency	Validity: Content	Validity: Construct	Responsiveness	Interpretability	Floor/ceiling/precision	Acceptability	Feasibility
EORTC QLQ-C30 (5)	0	0	++	+	+	0	0	+	+
EORTC QLQ-LC13 (17)	0	0	++	+++	+++	0	0	+	+++
FACT-G (2)	0	0	++	+	0	0	0	0	0
FACT-L (11)	0	++	++	++	++	0	0	++	++
LCSS (7)	0	+	+	++	+	0	0	+	0

0 not reported — no evidence in favour + some limited evidence in favour ++ some good evidence in favour +++ good evidence in favour.

APPENDIX A:

SEARCH STRATEGY



SEARCH SOURCES & SEARCH TERMS

Four databases were searched using the search engine Ovid (from January 2006 until February 2010):

- AMED (Allied and Complementary Medicine)
- EMBASE
- PsycInfo
- Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE (R)

The following is the complete search strategy used to search in the databases using the search engine Ovid:

1. hr-pro.ab,ti.
2. hrpro.ab,ti.
3. hrql.ab,ti.
4. hrqol.ab,ti.
5. ql.ab,ti.
6. qol.ab,ti.
7. quality of life.mp.
8. "health index*".ab,ti.
9. health indices.ab,ti.
10. "health profile*".ab,ti.
11. health status.mp.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. patient.ab,ti.
14. self.ab,ti.
15. child.ab,ti.
16. parent.ab,ti.
17. carer.ab,ti.
18. proxy.ab,ti.
19. 13 or 14 or 15 or 16 or 17 or 18
20. report.ab,ti.
21. reported.ab,ti.
22. reporting.ab,ti.
23. appraisal*.ab,ti.
24. appraised.ab,ti.
25. rated.ab,ti.
26. rating*.ab,ti.
27. based.ab,ti.
28. assessed.ab,ti.
29. assessment*.ab,ti.
30. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. 19 adj 30
32. disability.ab,ti.
33. function.ab,ti.
34. functional.ab,ti.
35. functions.ab,ti.

36. subjective.ab,ti.
37. utility.ab,ti.
38. utilities.ab,ti.
39. wellbeing.ab,ti.
40. well being.ab,ti.
41. 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
42. index.ab,ti.
43. indices.ab,ti.
44. instrument.ab,ti.
45. instruments.ab,ti.
46. measure.ab,ti.
47. measures.ab,ti.
48. questionnaire*.ab,ti.
49. profile.ab,ti.
50. profiles.ab,ti.
51. scale.ab,ti.
52. scales.ab,ti.
53. score.ab,ti.
54. scores.ab,ti.
55. status.ab,ti.
56. survey.ab,ti.
57. surveys.ab,ti.
58. 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57
59. 41 adj2 58
60. 31 or 59
61. 12 or 60
62. "cancer*".ab,ti.
63. "carcinoma*".ab,ti.
64. "adenocarcinoma*".ab,ti.
65. "malignan*".ab,ti.
66. "tumor*".ab,ti.
67. "tumour*".ab,ti.
68. "neoplasm*".ab,ti.
69. "metasta*".ab,ti.
70. 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69
71. lung.ab,ti.
72. pulmonary.ab,ti.
73. bronchus.ab,ti.
74. bronchial.ab,ti.
75. bronchoalveolar.ab,ti.
76. alveolar.ab,ti.
77. non small cell.ab,ti.
78. nonsmall cell.ab,ti.
79. non oat cell.ab,ti.
80. squamous.ab,ti.
81. adenosquamous.ab,ti.
82. large cell.ab,ti.
83. small cell.ab,ti.
84. 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83

- 85. 70 adj5 84
- 86. mesothelioma.ab,ti.
- 87. thymoma.ab,ti.
- 88. 85 or 86 or 87
- 89. 61 and 88

APPENDIX B:

APPRAISAL CRITERIA

The methods that will be used for assessing the performance of PROMs were developed and tested against multi-disciplinary consensus and peer review. They focus on explicit criteria to assess reliability, validity, responsiveness, precision, acceptability and feasibility. A pragmatic combination of the criteria developed and used in previous reports to DH by the Oxford and LSHTM groups will be used.

The appraisal framework focuses on psychometric criteria and PROMs must fulfil some or all to be considered as a short-listed instrument. Practical or operational characteristics are also assessed (acceptability and feasibility) (Appendix B: Appraisal framework).

Once evidence has been assessed for eligibility, records considered as inclusions will be assembled for each PROM identified. Measurement performance and operational characteristics will be appraised using the following rating scale independently by two reviewers and inter-rater reliability calculated.

Psychometric and operational criteria	
0	<i>not reported</i>
-	<i>no evidence in favour</i>
+	<i>some limited evidence in favour</i>
++	<i>some good evidence in favour</i>
+++	<i>good evidence in favour</i>

Appraisal criteria (adapted from Smith et al., 2005 and Fitzpatrick et al., 1998; 2006)

PROM	Reproducibility	Internal consistency	Validity: Content	Construct	Responsiveness	Interpretability	Floor/ceiling/precision	Acceptability	Feasibility

Appraisal component	Definition/test	Criteria for acceptability
Reliability		
Reproducibility/Test-retest reliability	The stability of a measuring instrument over time; assessed by administering the instrument to respondents on two different occasions and examining the correlation between test and re-test scores	Test re-test reliability correlations for summary scores 0.70 for group comparisons
Internal consistency	The extent to which items comprising a scale measure the same construct (e.g. homogeneity of items in a scale); assessed by Cronbach's alpha's and item-total correlations	Cronbach's alphas for summary scores ≥ 0.70 for group comparisons Item-total correlations ≥ 0.20
Validity		
Content validity	The extent to which the content of a scale is representative of the conceptual domain it is intended to cover; assessed qualitatively during the questionnaire development phase through pre-testing with patients. Expert opinion and literature review	Qualitative evidence from pre-testing with patients, expert opinion and literature review that items in the scale represent the construct being measured Patients involved in the development stage and item generation
Construct validity	Evidence that the scale is correlated with other measures of the same or similar constructs in the hypothesised direction; assessed on the basis of correlations between the measure and other similar measures	High correlations between the scale and relevant constructs preferably based on a priori hypothesis with predicted strength of correlation

Construct validity (continued)	The ability of the scale to differentiate known-groups; assessed by comparing scores for sub-groups who are expected to differ on the construct being measured (e.g a clinical group and control group)	Statistically significant differences between known groups and/or a difference of expected magnitude
Responsiveness	The ability of a scale to detect significant change over time; assessed by comparing scores before and after an intervention of known efficacy (on the basis of various methods including t-tests, effect sizes (ES), standardised response means (SRM) or responsiveness statistics	Statistically significant changes on scores from pre to post-treatment and/or difference of expected magnitude. The recommended index of responsiveness is the effect size, calculated by subtracting the baseline score from the follow up score and dividing by the baseline SD. Effect sizes can be graded as small (<0.3), medium (~0.5), or large (>0.8).
Floor/ceiling effects	The ability of an instrument to measure accurately across full spectrum of a construct	Floor/ceiling effects for summary scores <15%
Practical properties		
Acceptability	Acceptability of an instrument reflects' respondents' willingness to complete it and impacts on quality of data	Low levels of incomplete data or non-response
Feasibility/burden	The time, energy, financial resources, personnel or other resources required of respondents or those administering the instrument	Reasonable time and resources to collect, process and analyse the data.

APPENDIX C:

GENERIC INSTRUMENTS

This Appendix provides a brief description of the generic PROMs included in this review.

a) SF-36: Medical Outcomes Study 36-item Short Form Health Survey (Ware and Sherbourne, 1992; Ware et al., 1994; Ware, 1997)

The Medical Outcomes Study (MOS) Short Form 36-item Health Survey (SF-36) is derived from the work of the Rand Corporation during the 1970s (Ware and Sherbourne, 1992; Ware et al., 1994; Ware, 1997). It was published in 1990 after criticism that the SF-20 was too brief and insensitive. The SF-36 is intended for application in a wide range of conditions and with the general population. Ware et al., (1994; 1997) proposed that the instrument should capture both mental and physical aspects of health. International interest in this instrument is increasing, and it is by far the most widely evaluated measure of health status (Garratt et al., 2002a).

Items were derived from several sources, including extensive literature reviews and existing instruments (Ware and Sherbourne, 1992; Ware and Gandek, 1998; Jenkinson and McGee, 1998). The original Rand MOS Questionnaire (245 items) was the primary source, and several items were retained from the SF-20. The 36 items assess health across eight domains (Ware, 1997), namely bodily pain (BP: 2 items), general health perceptions (GH: 5 items), mental health (MH: 5 items), physical functioning (PF: 10 items), role limitations due to emotional health problems (RE: 3 items), role limitations due to physical health problems (RP: 4 items), social functioning (SF: 2 items), and vitality (V: 4 items), as shown in Table 3.1. An additional health transition item, not included in the final score, assesses change in health. All items use categorical response options (range: 2-6 options). Scoring uses a weighted scoring algorithm and a computer-based programme is recommended. Eight domain scores give a health profile; scores are transformed into a scale from 0 to 100 scale, where 100 denotes the best health. Scores can be calculated when up to half of the items are omitted. Two component summary scores for physical and mental health (MPS and MCS, respectively) can also be calculated. A version of the SF-36 plus three depression questions has been developed and is variously called the Health Status Questionnaire (HSQ) or SF-36-D.

The SF-36 can be self-, interview-, or telephone-administered.

b) EuroQol-EQ-5D (The EuroQol Group, 1990; revised 1993)

The European Quality of Life instrument (EuroQol) was developed by researchers in five European countries to provide an instrument with a core set of generic health status items (The EuroQol Group, 1990; Brazier et al., 1993). Although providing a limited and standardized reflection of HRQL, it was intended that use of the EuroQol would be supplemented by disease-specific instruments. The developers recommend the EuroQol

for use in evaluative studies and policy research; given that health states incorporate preferences, it can also be used for economic evaluation. It can be self or interview-administered.

Existing instruments, including the Nottingham Health Profile, Quality of Well-Being Scale, Rosser Index, and Sickness Impact Profile were reviewed to inform item content (The EuroQol Group, 1990). There are two sections to the EuroQol: the EQ-5D and the EQ thermometer. The EQ-5D assesses health across five domains: anxiety/depression (AD), mobility (M), pain/discomfort (PD), self-care (SC), and usual activities (UA). Each domain has one item and a three-point categorical response scale; health 'today' is assessed. Weights based upon societal valuations of health states are used to calculate an index score of -0.59 to 1.00 , where -0.59 is a state worse than death and 1.00 is maximum well-being. A score profile can be reported. The EQ thermometer is a single 20 cm vertical visual analogue scale with a range of 0 to 100, where 0 is the worst and 100 the best imaginable health.

Summary of generic instruments:

<i>Instrument</i>	<i>Domains (no. items)</i>	<i>Response options</i>	<i>Score</i>	<i>Completion (time in minutes)</i>
SF-36: MOS 36-item Short Form Health Survey (36)	Bodily pain (BP) (2) General health (GH) (5) Mental health (MH) (5) Physical functioning (PF) (10) Role limitation-emotional (RE) (3) Role limitation-physical (RP) (4) Social functioning (SF) (2) Vitality (V) (4)	Categorical: 2-6 options Recall: standard 4 weeks, acute 1 week	Algorithm Domain profile (0-100, 100 best health) Summary: Physical (PCS), Mental (MCS) (mean 50, sd 10)	Interview (mean values 14-15) Self (mean 12.6)
European Quality of Life Questionnaire (EuroQol-EQ5D) (5+1)	Anxiety/depression (1) Mobility (1) Pain/discomfort (1) Self-care (1) Usual activities (1) EQ-thermometer Global health (1)	Categorical: 3 options <i>EQ-thermometer</i> VAS Current health	Summation: domain profile Utility index (-0.59 to 1.00) <i>Thermometer</i> VAS (0-100)	Interview or self

Summary of generic instruments: health status domains (after Fitzpatrick et al., 1998)

<i>Instrument</i>	<i>Instrument domains</i>							
	Physical function	Symptoms	Global judgement	Psychol. well-being	Social well-being	Cognitive functioning	Role activities	Personal construct
SF-36	x	x	x	x	x		x	
EQ-5D	x	x	x	x	x		x	

APPENDIX D:

CANCER & LUNG CANCER-SPECIFIC PROMs

This Appendix provides a brief description of the cancer and lung cancer-specific PROMs included in this review.

a) European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Aaronson et al., 1993

The EORTC QLQ-C30 (Aaronson et al., 1993) is a 30-item cancer-specific measure of health status and HRQoL. There are five functional domain scales: physical, role, emotional, social and cognitive; two items evaluate global QoL; three symptom scales assess: fatigue, pain and emesis; and six single items to assess symptoms such as dyspnoea, sleep disturbance, appetite, diarrhoea and constipation, and financial impact. The scales for global health and HRQoL comprise seven-point Likert scales; the other 28 items use four-point Likert scales ranging from 'not at all' to 'very much'. Each domain scale is transformed to a scale of 0-100. For the functional and global rating scales higher scores represent a better level of functioning; conversely, for the symptom-oriented scales, higher scores represent more severe symptoms.

Extensive patient input during an international field study contributed to the development of the QLQ-C30, initially with lung cancer patients (Aaronson et al., 1993) and subsequently with patients with heterogeneous diagnoses (Osoba et al., 1994). Content validity of the QLQ-C30 has been maintained via modifications to improve the content, specifically in terms of the Role Functioning scale and a conceptual difficulty (undue emphasis on physical functioning) in the global QoL scale (Osoba et al., 1997).

b) European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-LC13)

The EORTC QLQ-C30 core questionnaire (30 items) can be supplemented by the additional lung module QLQ-LC13 (13 items), resulting in a 43-item condition and site specific quality of life questionnaire. The QLQ-LC13 module items evaluate symptoms such as cough, haemoptysis, shortness of breath, sore mouth or tongue, dysphagia, tingling hands or feet, hair loss and pain. The response options and scoring system are the same as for the EORTC QLQ-C30, and the administration and completion time are similar.

The reader should note that the developers of EORTC QLQ-LC13 indicate it is not possible to use the LC13 alone (without the core module QLQ-C30), since the module has been designed to be used together with the core questionnaire, and the content validity is based upon this combination.

The reader should also note that, regarding the scoring, that item 13 of QLQ-LC13 is not included in any scale of the scoring system. This is due to the fact that this question refers to the use of concomitant medication, and such medication is not always allowed/available. Hence, the use of this item is trial specific.

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

The 27-item FACT-G (Cella et al., 1993) measures global health-related QoL and four different dimensions thereof (i.e. physical, social, emotional, and functional well-being). The instrument is considered appropriate for use with any form of cancer and there are a number of scales that can be added to the FACT-G in order to measure disease- and treatment-specific components of the cancer experience. Answers are provided on a scale of Not at all; A little; Somewhat; Quite a bit; Very Much, in the context of ‘during the past seven days’. Items are scored from 0-4, with negatively-phrased items requiring reverse response scores. Higher scores represent better well-being on each of the dimensions or better global QoL when combined. Content validity is supported via item generation methodology. Items were generated using semi-structured interview input from cancer patients and oncology specialists. Patients first completed other QoL questionnaires in order to provide them with insight into potential QoL issues of relevance to them whilst the specialists reviewed these instruments and endorsed any items they felt were important as well as highlighting any QoL issues they felt were not covered in these instruments. Pilot testing and data reduction proceeded (Cella et al., 1993).

d) Functional Assessment of Cancer Therapy – Lung (FACT-L)

The FACT-L is a 10-item lung cancer specific module that supplements the Functional Assessment of Cancer Therapy – General (FACT-G). The 10 items are added to the 27 core items of the FACT-G, hence becoming a 37-item questionnaire.

The FACT-L consists of 5 subscales: physical wellbeing (PW, 7 items), social and family wellbeing (SW, 7 items), emotional wellbeing (EW, 6 items), functional wellbeing (FW, 7 items) and the Lung Cancer Subscale (LCS, 10 items). Scores can be produced through three different calculations; a combined total of all domains (FACT-L total), the Lung Cancer Score (LCS) and a Treatment Outcome Index (TOI) can be calculated by summing the FACT-G physical and functional domains and the LCS. Answers are provided on a scale of Not at all; A little; Somewhat; Quite a bit; Very Much, in the context of ‘during the past seven days’. Items are scored from 0-4, with negatively-phrased items requiring reverse response scores. Higher scores represent better well-being on each of the dimensions or better global QoL when combined.

e) Lung Cancer Symptom Scale (LCSS)

The Lung Cancer Symptom Scale (LCSS) was developed in the USA by Hollen et al. in 1993, aiming to provide a disease and site-specific measure of quality of life, particularly for use in clinical trials with lung cancer patients. It is a 9-item questionnaire which evaluates seven symptoms (one item for each: appetite, fatigue, cough, shortness of breath, blood sputum, pain and general symptom burden), functional activity (1 item) and global quality of life (1 item) associated with lung malignancies. The LCSS provides also an observer (health care professional) 6-item scale. Each item is scored using a 0-100 mm VAS (where 0=worst, 100=best), and the score is the length of the line marked by the patient. The average of the aggregate score

of all nine items is used to obtain a total score, and the mean of the six symptom items can be used to calculate 'average symptom burden index'.

The 9-item patient scale takes 3 to 8 minutes to complete and it can be interview or telephone-administered (previous explanation of VAS required).

f) Lung Cancer Symptom Scale - Mesothelioma (LCSS-Meso)

Malignant pleural mesothelioma is a specific type of lung cancer that presents distinctive characteristics that may not be covered by the previous questionnaires. Recently, Hollen et al. (2004, 2006) developed an adapted version of LCSS for patients with mesothelioma: the LCSS-Meso, with an 8-item patient scale (the item evaluating hemoptysis was dropped from the original LCSS; the rest of the items remain the same) and a 6-item observer scale. Feasibility was good, with a high completion rate; there was good internal consistency (alpha coefficient=0.66), and good stability using test-retest ($r=0.87$). Content, construct and criterion validity, as well as specificity, were also good.

Scoring, administration and completion time are similar to those from LCSS.

Summary of cancer and lung cancer-specific instruments

<i>Instrument name (total items)</i>	<i>Domains (No. Items)</i>	<i>Response options</i>	<i>Scoring</i>	<i>Administration Completion time</i>	<i>Licensing information</i>
European Organization for Research and Treatment of Cancer Quality of Life core Questionnaire, EORTC QLQ-C30 (30)	Physical function (5) Role activities (2) Symptoms (12) Cognitive functioning (2) Emotional well-being (4) Social well-being (2) Financial difficulties (1) <i>2 global questions:</i> Overall health Overall QoL	4-point Likert scales where 1 (best), 4 (worst). 7-point Likert scales for global health and QoL questions Recall: past week (except for PF)	Subscale scores transformed into 0-100 scores using an algorithm. Aggregation of subscale scores not recommended by developers.	Under 10 minutes.	No charge for use in academic settings, but written consent required for each study. Royalty fee, based on no. of patients, payable for commercial studies.
European Organization for Research and Treatment of Cancer Lung Cancer module, EORTC QLQ-LC13 (43)	<i>As above, plus:</i> Cough Haemoptysis Shortness of breath (3) Sore mouth/tongue Dysphagia Tingling hands/feet Hair loss Pain (4)	<i>As above</i>	<i>As above</i>	10-15 minutes	<i>As above</i>
Functional Assessment of Cancer Therapy - General version, FACT-G (27)	Physical well-being (7) Social/family well-being (7) Emotional well-being (6) Functional well-being (7)	5-point Likert scales Recall: past seven days	Items are scored from 0-4, with negatively-phrased items requiring reverse response scores. Higher scores represent better well-being on each of the dimensions or better global QoL when combined.	Interview, telephone, or self-administration. 5-10 minutes	Use of English versions of FACT/FACIT measures is free of charge, on condition of sharing data. Users must complete an agreement and submit project information for each study.

Functional Assessment of Cancer Therapy - Lung cancer, FACT-L (36)	<i>As above, plus:</i> Shortness of breath Weight loss Cognitive functioning Cough Hair loss Appetite Thoracic tightness Breathing Smoking - regret	<i>As above</i>	Three scoring options: - FACT-L total - Lung Cancer Subscale (LCS) - Trial Outcome Index (TOI)	<i>As above</i>	<i>As above</i>
Lung Cancer Symptom Scale, LCSS (9)	Symptoms (7) Functional (1) Overall QoL (1)	0-100 mm VAS for each item (where 0=worst, 100=best) Recall: past day	Score = length of line marked by patient; average of the aggregate score of all nine items used for a total score. Mean of the six symptom items can be used to calculate 'average symptom burden index'.	Telephone interview (face-to-face interview for initial administration) 3-5mins (8mins for initial demonstration)	License fee payable for sponsored clinical trials with 50+ patients. Fee waiver may be negotiated for smaller trials, trials without a sponsor, and 'special uses'. Protocol summary must be submitted and user agreement completed. Data sharing expected.

Summary of cancer and lung cancer-specific instruments: health status domains:

<i>Instrument</i>	Physical function	Symptoms	Global judgment	Psychological well-being	Social well-being	Cognitive functioning	Role activities	Personal constructs	Treatment satisfaction
EORTC QLQ-C30	X	X	X	X	X	X	X	X	
EORTC QLQ-L13	X	X	X	X	X	X	X	X	
FACT-G	X		X	X	X		X		
FACT-L	X		X	X	X			X	
LCSS	X	X	X						

APPENDIX E:

LICENSING & CONTACT DETAILS

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) & Lung Module (EORTC QLQ-L13):

EORTC Headquarters
Quality of Life Department
Ave. E. Mounier 83, B.11
1200 Brussels
Belgium
Fax: +32 (0)2 779 45 68
Tel: +32 (0)2 774 1678
E mail: ken.cornelissen@eortc.be
http://groups.eortc.be/qol/questionnaires_qlqc30.htm
http://groups.eortc.be/qol/questionnaires_modules.htm

Functional Assessment of Cancer Therapy – General Version (FACT-G) & Lung Version (FACT-L):

FACIT.org
381 South Cottage Hill Ave
Elmhurst, IL 60126
USA
Tel: (+1) 877 828 3228
Fax: (+1) 630 279 9465
E mail: information@facit.org
<http://www.facit.org/qview/qlist.aspx>

Lung Cancer Symptom Scale (LCSS) & Mesothelioma Version (LCSS-Meso):

Patricia Hollen, PhD, RN
Quality of Life Research Associates, LLC
3445 Seminole Trail
Suite 214
Charlottesville, VA 22911
USA
Fax : 1.434.975.1101
E-mail: p.hollen@virginia.edu
<http://www.lcss-ql.com/index.htm>

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