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Velikova, Galina; Coens, Corneel; Efficace, Fabio; Greimel, Eva; Grønvold, Mogens; Johnson, Colin

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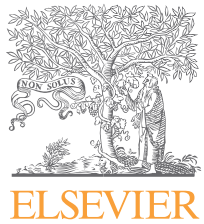

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Health-Related Quality of Life in EORTC clinical trials – 30 years of progress from methodological developments to making a real impact on oncology practice

G. Velikova[a,], C. Coens[b], F. Efficace[c], E. Greimel[d], M. Groenvold[e,f], C. Johnson[g], S. Singer[h,i], L van de Poll-Franse[j,k], T. Young[l], A. Bottomley[b], on behalf of EORTC Quality of Life Group and EORTC Quality of Life Department*

[a] *Chair of EORTC Quality of Life group, University of Leeds, Leeds Institute for Molecular Medicine, St James's University Hospital, Bexley Wing, Beckett street, Leeds, LS9 7TF, UK*
[b] *EORTC Quality of Life Department, EORTC Headquarters, Ave. E. Mounier 83, B.11, 1200 Brussels, Belgium*
[c] *Italian Group for Adult Hematologic Diseases (GIMEMA). Head, Health Outcomes Research Unit. Rome, Italy*
[d] *Medical University Graz, Auenbruggerplatz 14, 8036 Graz, Austria*
[e] *Department of Palliative Medicine, Bispebjerg Hospital, Copenhagen, Denmark*
[f] *Institute of Public Health, University of Copenhagen, Copenhagen, Denmark*
[g] *University of Southampton and Southampton University Hospitals NHS Trust, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK*
[h] *Department of Health Psychology and Applied Psychodiagnostics, University of Wuppertal, Germany*
[i] *Department of Medical Psychology and Medical Sociology, University of Leipzig, Germany*
[j] *Comprehensive Cancer Centre South/Eindhoven Cancer Registry, Eindhoven, The Netherlands*
[k] *CoRPS – Center of Research on Psychology in Somatic diseases, Department of Medical Psychology, Tilburg University, The Netherlands*
[k] *Lynda Jackson Macmillan Centre for cancer support & information, Mount Vernon Cancer Centre, Northwood, Middlesex HA6 2RN, UK*

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ABSTRACT

The impact of cancer on patients' lives can be measured using self-reported questionnaires, known as Health-Related Quality of Life (HRQOL) measures. HRQOL is defined as a multi-dimensional construct covering disease and treatment-related symptoms, physical, psychological, and social functioning.

The EORTC Quality of Life Group (QLG) was created in 1984 with the mission to develop measures of HRQOL and to promote and coordinate clinical studies concerning the quality of life of cancer patients. The EORTC Quality of Life Department (QL Department) was founded in 1993 with the support of an EU grant to provide administrative, practical and scientific support to co-operative groups conducting clinical trials with HRQOL outcomes.

We are proud to report significant scientific achievements that have made us international leaders in HRQOL research and have led to real changes to cancer patient treatments.

We developed a modular system for HRQOL measurement consisting of the EORTC QLQ-C30, a core cancer quality of life questionnaire and supplementary questionnaire modules. The EORTC-QLQ-C30 has been one of the most widely used cancer

* Corresponding author. Prof Galina Velikova, St James's University Hospital, Bexley Wing, Beckett Street, Leeds LS9 7TF, UK. Tel: +44 113 2067917. *E-mail address:*g.velikova@leeds.ac.uk (G. Velikova).

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questionnaires in randomized trials in oncology as demonstrated by systematic reviews. To date, the EORTC QLQ-C30 has been translated and linguistically validated into more than 60 languages.

HRQOL outcome measures have been an integral part of EORTC clinical trials for the last 30 years. We present examples of significant, practice-changing clinical trials evaluating HRQOL in several cancer sites, such as brain tumors, breast and ovarian cancers, and malignant melanoma. In a series of systematic reviews, we examined the quality of reporting HRQOL in international cancer clinical trials, and the impact of the results on oncology practice that led to a recommendation to improve CONSORT (Consolidated Standards of Reporting Trials) with regard to reporting of HRQOL.

The QLG is an international leader in methodological research in the measurement of HRQOL in oncology and pursues research in several key areas, such as cross-cultural differences between populations in HRQOL assessment, Computer-Adaptive Testing, electronic administration of EORTC QLQ-C30, and summary scores for EORTC QLQ-C30.

In summary, the QLG and QL Department have been international leaders in the field. Our questionnaires have brought HRQOL assessment to the fore in many international trials that have changed oncology practice and brought the patient's perspective into cancer research.

1. Introduction

Cancer and its treatment have a profound impact on patients' lives that can lead to difficulties in fulfilling family roles, the ability to work, or the participation in usual social activities. Even when successfully treated, cancer may lead to longer-term physical and psychological morbidity. The importance of measuring not only the objective effects of cancer treatment, but also its subjective impact on patients, has long been recognized in clinical cancer research and oncology practice.[1] Patient symptoms, functioning, and overall well-being can be measured using carefully developed and validated self-reported questionnaires, known as HRQOL or Patient-Reported Outcome measures. HRQOL is defined as a multi-dimensional construct covering at least several key dimensions, such as disease- and treatment-related symptoms, physical, psychological and social functioning.[2]

HRQOL outcome measures have been an integral part of EORTC (European Organisation for Research and Treatment of Cancer) clinical trials for the last 30 years. The EORTC created the QLG in 1984 with the mission to develop measures of patient-reported outcomes in cancer, including HRQOL, and to promote and coordinate clinical studies concerning the quality of life of cancer patients. The QL Department based at EORTC Headquarters was established in 1993 with the support of an EU grant to provide administrative, practical, and scientific support to all co-operative groups conducting clinical trials that implement HRQOL measures.

The QLG has a multi-disciplinary membership with representatives from the medical and nursing professions as well as psychologists, statisticians, and social scientists. Members come from seventeen European countries, including Eastern Europe. Beyond Europe the QLG has members from Taiwan, Australia, Canada, Japan, Israel, Egypt, Brazil, Hong Kong, Nepal, India, Central and South America. The QLG thrives as an enthusiastic dynamic group with a successful and active research program that can make a significant international impact.

Over the years the HRQOL program has focused on three major areas:

(1) **Methodological research:** aimed at developiong and refining questionnaires for assessing the HRQOL of patients in oncology clinical trials, in other well-designed research studies, and in clinical practice.
(2) **Implementation in clinical trials:** collaborating with EORTC Research Groups in implementing HRQOL studies within their clinical trial programs.
(3) **Scientific research in patient-reported outcomes:** conducting research to better understand the effects of cancer and its treatment on the HRQOL of diverse populations of patients with cancer and to investigate possible cross-cultural differences in these effects.

In each of those areas we are proud to report significant scientific achievements that have made us international leaders in HRQOL research and, more importantly, have led to real changes in the treatment of cancer patients.

2. Development and validation of a modular system for HRQOL measurement: EORTC QLQ-C30, a core cancer quality of life questionnaire and supplementary questionnaire modules

In the 1990s the QLG introduced the concept of *modular HRQOL measurement* in oncology based on a core cancer questionnaire and cancer site-specific modules covering specific symptoms, treatment side-effects, and functional problems.[3] The QLG was the first to publish detailed guidelines on development of questionnaire modules that have set the standard internationally and have been widely used by researchers and clinicians worldwide.[4] These have been regularly updated and are now in their fourth edition (available online).

The most notable achievement of QLG is the development and validation of the core EORTC HRQOL questionnaire, known as EORTC QLQ-C30. The EORTC QLQ-C30 was validated in multiple European countries and published in 1993.[5] Evidence-based information on clinically meaningful differences in the scores of EORTC QLQ-C30 and recommendations for sample size calculations using the EORTC QLQ-C30 sub-scales are available.[6–9] The EORTC-QLQ-C30 has been one of the most widely used cancer questionnaires in randomized trials in oncology as demonstrated by systematic reviews.[10–12] User agreements for the EORTC QLQ-C30 have been signed in more than 9,000 clinical trials or academic studies worldwide. The EORTC QLQ-C30 represents probably the most widely known example of the influence of the EORTC on international cancer research (QLG Scientific Advisory Committee review report 2010).

In addition to the EORTC QLQ-C30, there is a portfolio of supplementary questionnaire modules that are cancer site-specific or symptom/quality of life domain-specific, many of which are used in clinical trials (see Table 1). This continues to be an active area of research with ongoing development of questionnaires for hematological malignancies, malignant melanoma, doctor–patient communication, as well as updates to existing modules to capture the effects of new treatment modalities.

A truly unique feature of the EORTC questionnaires is that attention is paid to cultural and linguistic issues from the beginning of the developmental process. As the globalization of clinical trials continues to increase, the issues of the translation quality and cultural equivalence of subjective measures are of paramount importance. The QLG is an international leader in developing guidelines for translations.[13] All of our questionnaires are developed simultaneously in at least three European languages, and all validated questionnaires are made available in at least eight key European languages.

To date, the EORTC QLQ-C30 has been translated and linguistically validated into more than 60 languages, with more than 20 additional local adaptations and further translations in progress. Translations include all major Western languages, and many African and Asian languages. The translation work is a dynamic and growing endeavor. The current list of existing translations can be viewed in Table 2.

The QLG created the EORTC *Item Bank*, a searchable database that contains all items (i.e., questions) from validated modules and all their translations. It is a rich resource for developing questionnaires, as it ensures compatibility between different EORTC questionnaires and their translations, avoids duplicating work, and

Table 1 – Available EORTC questionnaire modules

Module	Code
Validated EORTC Modules	
Bone metastases	BM22
Brain	BN20
Breast	BR23
Cervical	CX24
Colorectal	CR29
Colorectal liver metastases	LMC21
Endometrial	EN24
Gastric	STO22
Head & neck	H&N35
Information	INFO25
Lung	LC13
Multiple myeloma	MY20
Oesophageal	OES18
Oesophago-gastric	OG25
Ovarian	OV28
Palliative care	PAL15
Prostate	PR25
EORTC Modules in process of validation[a]	
Carcinoid/neuroendocrine	NET21
Cholangiocarcinoma and gallbladder	BIL21
Chronic lymphocytic leukaemia	CLL16
Elderly	ELD15
Fatigue	FA13
Hepatocellular carcinoma (primary liver cancer)	HCC18
High dose chemotherapy	HDC29
Muscle invasive bladder cancer	BLM30
Ophthalmic	OOPT30
Pancreatic	PAN26
Chemotherapy-induced peripheral neuropathy	CIPN20
Radiation proctitis	PRT23
Spiritual wellbeing	SWB36
Superficial bladder cancer	BLS24
Testicular	TC26

[a] Developmental phase is completed, and large scale validation in an international study is at various stages. Can be used in clinical trials, but final psychometric data is not available yet.

Table 2 – Existing translations and adaptations of the EORTC QLQ-C30 questionnaire

Language	Local adaptations	Language	Local adaptations
Afrikaans		Lithuanian	
Arabic	Middle East, North Africa	Malay	Malaysia, Singapore
Bengali		Malayalam	
Bosnian		Maltese	
Bulgarian		Marathi	
Burmese		Norwegian	
Catalan		Persian	
Cebuano		Polish	
Chinese	China, Hong Kong, Malaysia, Singapore, Taiwan	Portuguese	Portugal, Brazil
Croatian		Punjabi	
Czech		Romanian	
Danish		Russian	Russia, Belarus, Georgia
Dutch		Serbian	
Estonian		Sinhala	
Finnish		Slovak	
French	Europe, Canada	Slovenian	
German		Sotho	
Greek		Spanish	Spain, Argentina, Chile, Colombia, Costa Rica, Guatemala, Mexico, Peru, Puerto Rico, USA
Gujarati		Swedish	Sweden, Finland
Hebrew		Tagalog	India, Malaysia
Hindi		Tamil	
Hungarian		Telugu	
Icelandic		Thai	
Ilocano		Turkish	
Indonesian		Ukrainian	
Italian		Urdu	India, Pakistan
Japanese		Vietnamese	
Kannada		Xhosa	
Kiswahili		Yoruba	
Korean		Zulu	
Latvian			

makes possible creation of *ad hoc* trial/research-specific questionnaires using well-developed and validated items. [14]

The Group has developed five key publications supporting the application of its measurement system in clinical trials and other research projects. These are regularly updated and provided free of charge to all academic users and can be downloaded from http://groups.eortc.be/qol:

(1) the EORTC QLQ-C30 scoring manual;
(2) guidelines for questionnaire module development;
(3) translation guidelines;
(4) guidelines for conducting clinical trial-based HRQOL investigations;
(5) reference values for the EORTC QLQ-C30 for a wide range of cancer diagnoses and for the general population.

A platform for electronic administration of EORTC QLQ-C30 is currently under development.

3. Examples of practice-changing EORTC trials that included HRQOL

HRQOL is an integral part of most EORTC clinical trials and has been systematically implemented over the last 15 years. Over 130 EORTC clinical trials have a HRQOL element, typically as a secondary endpoint. However, given that most regulatory bodies such as EMEA and FDA now fully accept HRQOL as a valid endpoint and issue label claims based on the impact of treatment on patients, we believe the use of HRQOL in future EORTC studies will only continue to grow.

In Table 3 we present examples of significant practice-changing clinical trials with HRQOL sub-studies, all designed and conducted by the QL Department and run in collaboration with most of the EORTC Research Groups. Just a couple of examples from Table 3 can demonstrate how HRQOL studies contributed to changing clinical oncology practice.

In patients with glioblastoma, we studied the addition of concomitant and adjuvant temozolomide to the standard treatment with radiotherapy and demonstrated that temozolomide significantly improved survival without a negative effect on HRQOL.[17] This treatment is now the standard of care in newly diagnosed patients with glioblastoma.

Dose-intensive chemotherapy had generated much interest in the treatment of patients with locally advanced breast cancer as it might offer a survival benefit. We compared the effects of such an approach with those of standard chemotherapy on HRQOL.[20] Patients assigned the intensified treatment had a significantly lower overall HRQOL score during the first three months, but scores returned to near baseline with no difference between groups at 12 months and up to 2 years. This was the first randomized trial to show that dose-intensive treatment may lead to a temporary reduction of HRQOL, followed by recovery, thus enabling clinicians to give accurate information to their patients and informing further research on intensive treatment for patients with breast cancer.

These collaborative efforts have proved to be highly successful and demonstrate the importance of multi-disciplinary international collaboration. The EORTC, with its strong network of clinical and methodological groups and a keen interest in HRQOL, can provide important clinical and patient-reported outcomes results that are far reaching and have an impact on patient care on an international scale.

The QL Department, on behalf of the EORTC Research Groups, undertook the largest meta-analysis of HRQOL data using the EORTC QLQ-C30.[24] The results provide the most robust and compelling evidence amassed to date that HRQOL scores can provide additional prognostic information that can be used to assist in the prediction of survival in cancer patients. The meta-analysis was based on information provided at baseline by 7417 patients who had completed the EORTC QLQ-C30 questionnaire. The patients participated in 30 randomized controlled trials conducted by the EORTC between 1986 and 2004, representing 11 different cancer sites. Variables assessed in the meta-analysis included age, sex, WHO performance status, distant metastases, cancer site, and the 15 EORTC QLQ-C30 scales. The HRQOL parameters physical functioning, pain, and appetite loss, provided significant prognostic information as did age, sex, and distant metastases. These results strongly indicate that in some cancer populations selected EORTC QLQ-C30 HRQOL scales provide valuable prognostic information when combined with socio-demographic and clinical information.

In a series of systematic reviews across many disease sites, we examined the quality of reporting HRQOL in international cancer clinical trials and the impact of the results on oncology practice. This research undertaken over a five-year period identified several hundred cancer clinical trials in major disease areas (lung, breast, prostate, brain, etc.) and made recommendations for the need to improve CONSORT with regard to reporting of HRQOL in clinical trials.[10–12,25–29]

4. The QLG is an international leader in methodological research in the measurement of HRQOL in oncology

The QLG undertakes successful methodological research in a number of key areas:

Cross-cultural differences between populations in HRQOL assessment.[30–32] A large project database incorporating 125 datasets representing EORTC QLQ-C30 data from over 30,000 individuals from 50 countries was used in a specific statistical analysis based on Item Response Theory (known as Differential Item Functioning). This identified a number of item translations (pain, social function) with evidence of differential performance when compared with the original English version. Results for the UK, North America, and Australia were fairly similar but variations occurred for Eastern European and Asian countries. Our results suggested that the reasons for Asian countries were primarily cultural rather than linguistic, in contrast with Europe where response patterns followed linguistic lines. Some of these effects were large enough to impact on the results of clinical trials. The project demonstrated that these statistical methods are useful for detection of differences between translations that can be due to either translation or cultural factors and thus can be taken into consideration when interpreting international studies. We used computer simulations to provide recommendations about the sample size requirements for future trials using differential item functioning analyses of HRQOL instruments.[33]

Computer-Adaptive Testing (CAT) Version of QLQ-C30. This research aims to generate a dynamic, computer-adaptive version of the EORTC QLQ-C30, based on modern psychometric theory and techniques. The basic idea of CAT is to tailor the questionnaire to the individual respondent. Based on the responses to the preceding items it is estimated which item should be asked next to obtain maximal information on that individual's HRQOL (symptom level, functional status, etc.). Basing the CAT on item response theory methods allows one to directly compare scores between individuals even though they may have answered different sets of

Table 3 – Selected examples of EORTC trials with HRQOL sub-studies which informed clinical practice

Clinical trials	Clinical findings	Key HRQOL findings
HRQOL in brain tumors and brain radiotherapy		
Prophylactic cranial irradiation (PCI) in patients with extensive-disease small-cell lung cancer (ED SCLC) [15]	PCI leads to fewer symptomatic brain metastases and improved survival	Short-term results up to three months showed a negative impact of PCI on fatigue and hair loss. The impact of PCI on global health status as well as on functioning scores was more limited. For global health status, the observed mean difference was 8 points on a scale 0 to 100 at six weeks ($P = 0.018$) and three months ($P = 0.055$). PCI should be offered to all responding ED SCLC patients. Patients should be informed of the potential adverse effects from PCI.
Treatment with combined procarbazine, CCNU (lomustine), and vincristine (PCV) chemotherapy after radiotherapy (RT) compared with RT alone in anaplastic oligodendrogliomas EORTC 26951 trial [16]	Adjuvant PCV improves progression-free survival	PVC had a major impact on nausea/vomiting, loss of appetite, and drowsiness during and shortly after treatment. There were no long-term effects of PCV chemotherapy.
Radiotherapy alone versus radiotherapy with concomitant and adjuvant temozolomide for patients with glioblastoma [17]	Survival was higher for patients assigned combination treatment compared with those assigned standard radiotherapy	At first follow-up, groups differed only in social functioning, favoring the radiotherapy-only group. Over subsequent assessments, HRQOL was much the same between treatment groups. The results indicate that temozolomide during and after radiotherapy for patients with newly diagnosed glioblastoma significantly improved survival without a negative effect on HRQOL and this treatment is now the standard of care.
Malignant melanoma		
Adjuvant therapy with pegylated interferon alfa-2b versus observation in resected stage III melanoma [18]	Treatment with PEG-IFN-α-2b had a significant and sustained effect on recurrence free survival in this patient population	A negative effect was observed on global HRQOL, two functioning scales (social and role functioning) and three symptom scales (appetite loss, fatigue, and dyspnea) at each post-baseline assessment with the PEG-IFN-α-2b arm being the more impaired. Adjuvant PEG-IFN-α-2b might not be the most appropriate therapy for patients with high-risk melanoma, and appropriate dose reduction and symptom management approaches can be used to reduce the unwanted side effects of treatment.
Malignant mesothelioma		
A phase III trial of first-line treatment with raltitrexed, a thymidine synthase inhibitor, and cisplatin compared to cisplatin alone in patients with malignant pleural mesothelioma (MPM). [19]	The combination of raltitrexed and cisplatin improved overall survival compared with cisplatin alone	An extensive analysis of the HRQOL data did not show any difference in on any of the scales, thus confirming that a combination chemotherapy of cisplatin and an antifolate is superior to cisplatin alone in patients with MPM, without harmful effect on HRQOL.
Breast cancer		
Dose-intensive chemotherapy as neo-adjuvant treatment of patients with locally advanced breast cancer [20]	No differences were found in primary end point of progression-free survival	Patients assigned the intensified treatment had a significantly lower overall HRQOL score during the first three months than did those assigned standard treatment ($p = 0.0015$). However, scores returned to near baseline, with no difference between groups, at 12 months and up to two years. We concluded that dose-intensive treatment only has a temporary effect on HRQOL, thus enabling more research on intensive treatment for patients with breast cancer.
Patients with metastatic breast cancer receiving the combination of doxorubicin and paclitaxel (AT) or doxorubicin and cyclophosphamide (AC) as first-line chemotherapy treatment [21]	No differences in the efficacy study end points were observed between the two treatment arms. Treatment-related toxicity compromised doxorubicin-delivered dose-intensity in the paclitaxel-based regimen	There were no statistically significant differences in HRQOL between the two treatment groups. In both groups, selected aspects of HRQOL were impaired over time, with increased fatigue, although some clinically significant improvements in emotional functioning were seen, as well as a reduction in pain over time. Overall, global quality of life was maintained in both treatment groups. This information is important when advising women patients of the expected HRQOL consequences of treatment regimens.

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Table 3 – *(continued)*

Clinical trials	Clinical findings	Key HRQOL findings
Head and neck cancer		
Induction chemotherapy in unresectable locoregionally advanced head and neck cancer patients (docetaxel, cisplatin, 5-fluorouracil [TPF] vs cisplatin 5-fluorouracil [PF]) [22]	An improved progression-free and overall survival with less toxicity was found when docetaxel (T) was added to cisplatin and 5-fluorouracil (PF) for induction before radiotherapy	There was a trend towards improved global HRQOL during the treatment period. At six months after the end of radiotherapy, global HRQOL was higher in the TPF arm than in the PF arm, with bigger improvement in swallowing and coughing problems. Induction chemotherapy with TPF before radiotherapy not only improves survival and reduces toxicity compared with PF but also seems to improve global HRQOL in a more sustainable manner.
Ovarian cancer		
Phase III ovarian cancer trial of neoadjuvant chemotherapy followed by surgery compared with upfront debulking surgery followed by chemotherapy, EORTC 55971 trial [23]	Survival was similar in the upfront debulking surgery arm compared to the neoadjuvant chemotherapy arm	No HRQOL differences were observed either. These results will enable clinicians to provide evidence-based information to patients to support decision making.

items. CAT has several advantages over traditional fixed-length questionnaires such as increased measurement precision (smaller samples required), the questionnaire can be adapted to the individual study (or even to the respondent), avoidance of asking uninformative questions, and immediate calculation and presentation of results. [34–36] The development of CAT requires more work than traditional questionnaires. For each of the 14 HRQQL domains in the EORTC QLQ-C30, an 'item pool' has to be developed. For physical function (PF), for example, an analysis of 975 previously used PF items identified in the literature led to the development of 51 new items that were tested with 1,176 patients from six countries. Statistical evaluations reduced this to an item pool of 31 items which will be further tested. [34,35] Similar work is being done for the other domains involving researchers from 12 countries, and it is expected to collect data from over 10,000 patients. [36] Scores obtained with the EORTC CAT system are comparable with EORTC QLQ-C30 scores thus maintaining the benefits of using a questionnaire already implemented and reported in many published studies.

Electronic administration of EORTC QLQ-C30. Increasingly many patient-reported outcomes measures are administered in electronic formats including touch-screen computers, web-based administration, mobile telephones using screen data entry, and over the phone using Interactive Voice Response (IVR). Electronic administration reduces the burden of data management, improves data quality, and allows real-time scoring and immediate use of results in clinical practice. Many of our Group members and other researchers worldwide use EORTC QLQ-C30 in electronic formats, but until recently the QLG has not formally supported a particular electronic platform. A new project aims to provide a web-based platform for electronic administration of EORTC QLQ-C30 and the modules based on a software solution called Computer-based Health Evaluation System (CHES). [37] CHES is a PC-program for the computerized assessment, calculation, and presentation of psychosocial and medical data. Data is entered by patients themselves *via* touch-screen or over the Internet. The software application has a number of features: graphical presentation of results, flag system for abnormal scores, clinical report generator, data export/import module, interface to clinical information systems, and study monitoring module. This electronic platform will be explored in EORTC clinical trials.

Summary scores for EORTC QLQ-C30. Further research is being undertaken to explore the possibility of generating summary scores (so-called higher order factors) from the EORTC QLQ-C30. In clinical trials, summary scores could simplify certain analyses and minimize the chance of Type I errors through multiple comparisons. In a large existing sample of cancer patients (n = 9000), we empirically examined and compared the statistical fit of a number of alternative measurement models by means of confirmatory factor analysis. A model comprising of Physical Health and Mental Health was best fitting the data. These results will lead to an algorithm for the computation of summary scores for Physical Health and Mental Health for the EORTC QLQ-C30.

5. Conclusion

The QLG and QL Department have been international leaders in the development of patient-reported outcome measures in oncology and their implementation in oncology trials. Our most notable achievement is the development and dissemination of the EORTC QLQ-C30 which, based on evidence from several systematic reviews, is now arguably the most widely used cancer HRQOL instrument. We established internationally accepted guidelines for questionnaire development.

Our translation procedures set the highest standards for questionnaire translation and are used worldwide. These world-leading achievements have contributed to bringing HRQOL assessment to the fore in many international trials conducted by the EORTC and other groups, have changed oncology practice, and enhanced the patient perspective in clinical cancer research. The Group now looks to the future with CAT and CHES projects and developing ways to use information technology to improve precision of HRQOL assessment and accessibility to web-based interfaces that will maximize the value of the data collected with EORTC questionnaires.

6. Acknowledgements

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7. Conflict of interest statement

The EORTC Quality of Life Group business model involves charges for pharmaceutical companies using the EORTC instruments in commercial clinical trials. The generated income is invested in supporting the administration of the instruments and in scientific research in the field of HRQOL in cancer. Academic use of EORTC instruments is free of charge.

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