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Position Paper

The challenges and achievements involved in implementing Quality of Life research in cancer clinical trials

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Abstract

Over the last decade, Quality of Life (QOL) research has become an important aspect of cancer clinical trials. A dramatically increasing number of published studies, both randomised and non-randomised, report QOL outcomes. There is increasing evidence that QOL results impact on both future research and treatment decisions for clinicians. The rising number of studies with QOL components is mirrored within the European Organization for Research and Treatment of Cancer (EORTC), one of the largest cancer clinical trial organisations in Europe. Clinical trial groups have frequently reported on the difficulties and challenges of implementing QOL research. In the following paper, we therefore examine past experience in EORTC QOL studies, with a focus on the challenges presented and the improved approaches that are being implemented to obtain more meaningful outcomes.

Keywords: Cancer; QOL; Clinical trials; EORTC; Methodology

1. Introduction

Extensive research in the field of cancer care is beyond the means of individual European laboratories and hospitals. Therefore, it is more effectively accomplished through multidisciplinary, multinational research efforts such as those provided by the European Organization for Research and Treatment of Cancer (EORTC). Its aims are to conduct, develop, coordinate and stimulate laboratory and clinical research to improve European management of cancer by increasing patients' survival expectation and Quality of Life (QOL).

QOL research holds a critical position in the understanding of not simply how much additional time a patient can gain, but, more importantly, just how *valuable* that time can be made. Without knowing the *quality* of the time remaining, a large piece of the therapy puzzle is missing. For example, is it worth patients undergoing gruelling chemotherapy regimes that induce nausea and vomiting, impact on acute and long-term fatigue and social function, yet only provide a very short-term survival advantage?

Clinical trials organisations such as the EORTC, Medical Research Council (MRC) and National Cancer Institute-Canada (NCI-C), are all well placed to undertake such QOL research. Yet conducting research within such a large setting is fraught with difficulties that are well documented [1,2]. In the following paper, we aim to highlight the progress and achievements within the EORTC QOL research programme over the last decade, noting the challenges faced and the approaches employed to overcome them.

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2. The key challenges facing the EORTC in implementing QOL research

2.1. Measurement challenges

A major challenge faced in clinical trials, particularly during the early 1990s, centred on the lack of any agreed standardised measures to assess QOL in cancer patients [3,4]. However, by 1993 the EORTC QOL Group (QLG) had successfully developed the EORTC QLQ-C30 instrument. This allowed researchers to routinely use a validated measure [5] specifically designed for use in the majority of international cancer clinical trials. According to Gotay and Wilson [6], it is now one of the most widely used measures in clinical trials worldwide. With a vibrant module development programme [7,8] and with the new QLG item bank of over 500 questionnaire items [9], the EORTC is rarely unable to find a suitable trial item or measure.

2.2. Translations and cultural validity

The EORTC faces a considerable challenge in working with over 32 different countries presenting a multitude of cultures and languages. Therefore, it is critical that QOL instruments are developed with cultural validity and are translated accurately into other languages [10,11]. Translated measures are extremely expensive resources, intensive in terms of time and finance, especially when following the stringent procedures of *good practice* [10]. In the mid-1990s, the EORTC QLG had only a limited number of translations available in core European languages. This may have impacted on recruitment in some early trials. For example, in the EORTC trials reported by Fossa and colleagues [12] and Curran and colleagues [13] a less than optimal recruitment was achieved, due partly to a lack of available translations. However, with the development in 2000 of an EORTC QLG translation programme, all EORTC measures were quickly and accurately translated into the majority of languages required [10].

2.3. Trials including QOL research within the EORTC—practices for implementing QOL in EORTC clinical trials

Since the EORTC began to implement QOL research into its clinical trials, the number of trials including QOL has increased steadily (Fig. 1). These are typically randomised phase III clinical trials, all with international patient accrual. Different parties are involved in the implementation of QOL research into EORTC clinical trials. These include the EORTC Clinical Group conducting the trial, the EORTC QOL Unit and a liaison member from the Joint Scientific Committee of the EORTC QLG [14]. Within the QLG a Joint Scientific Committee was formed, consisting of members with expertise in the field of QOL and a specific disease site or treatment modality [15].

These *liaison members* and/or QOL Unit members interact with EORTC Clinical Groups dedicated to a specific disease site or treatment modality, providing advice on the opportunities for implementation of QOL research in new trials. If QOL research is deemed relevant in a certain trial, the liaison member is involved in the design of the QOL study and participates in the analysis and publication. The QOL Unit provides centralised support for the development of the QOL protocol section, reviews the content and oversees the entire developmental process [15].

We report here a brief review that has been completed on data from EORTC clinical trials with a QOL com-

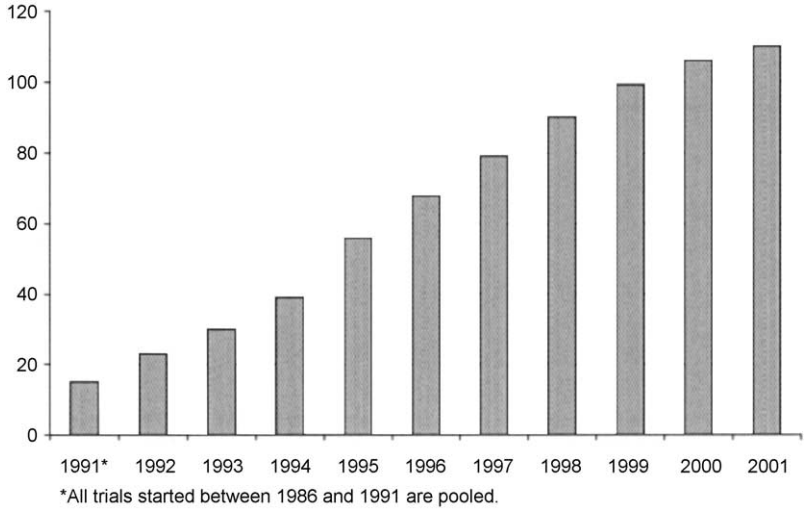

Fig. 1. Number of closed and ongoing EORTC clinical trials including QOL research by year. EORTC, European Organization for Research and Treatment of Cancer; QOL, Quality of Life.

Table 1
Current and closed EORTC cancer clinical trials containing a QOL component

Study[a]	Title
05962	Infusional 5-fluorouracil with or without cisplatin and with or without chronomodulation against locally-advanced or metastatic pancreatic cancer. A multicentre randomised phase III trial.
05963	First-line infusional 5-fluorouracil, folinic acid and oxaliplatin for metastatic colo-rectal cancer or loco-regional recurrency. Role of chronomodulated delivery upon survival. A multicentre randomised phase III trial.
06863	A randomised phase III study of autologous bone marrow transplantation versus intensive consolidation during first complete remission in acute myelogenous leukaemia (AML-8A).
06903	A randomised phase III multicentre trial comparing LD-ARA-C alone versus LD-ARA-C + granulocyte macrophage-colony stimulating factor (GM-CSF) versus LD-ARA-C + recombinant interleukin-3 for patients with myelodysplastic syndromes and at high risk of developing acute leukaemia.
06931	Randomised phase III study of induction (ICE versus MICE versus DCE) and intensive consolidation (IDIA versus NOVIA versus DDIA) followed by allogeneic bone marrow transplantation or a randomised autologous BMT versus autologous peripheral stem cell transplantation in acute myelogenous leukaemia.
06942	A randomised phase III trial of 2-chloro-deoxyadenosine versus fludarabine in patients with pretreated B-chronic lymphocytic leukaemia.
06952	Induction with all-*trans* retinoic acid in combination with idarubicin followed by intensive consolidation followed by bone marrow transplantation or a randomised maintenance treatment depending upon the amount of minimal residual disease.
06954	Randomised phase III study to evaluate the value of recombinant human (rHu)G-CSF in induction and of an oral schedule as consolidation treatment in elderly patients with acute myelogenous leukaemia (AML-13 protocol) (Jointly with the GIMEMA).
08925	A randomised trial of two cisplatin-based combination chemotherapies in advanced non-small cell lung cancer. A phase II study leading to a phase III.
08941	Randomised trial of surgery versus radiotherapy in patients with stage IIIa non-small cell lung cancer after a response to induction-chemotherapy.
08962	A phase III study of marimastat in patients with small-cell lung cancer following a response to first line chemotherapy.
08971	Survival in an international phase III prospective randomised LD small-cell lung cancer vaccination study with adjuvant BEC2 and Bacillus Camille Guerin (BCG).
08972	Randomised phase III study comparing induction chemotherapy to daily low dose cisplatin both combined with high-dose radiotherapy using concomitant boost technique in patients with inoperable non-small cell lung cancer stage I, II and low-volume stage III.
08975	Randomised study with new combination chemotherapies in advanced non-small cell lung cancer.
08976	Phase II study: temozolomide in malignant mesothelioma.
08983	Phase III study of raltitrexed (tomudex) and cisplatin versus cisplatin in malignant pleural mesothelioma.
10001	A randomised phase II-III trial evaluating the efficacy of capecitabine and vinorelbine in anthracycline and taxane pretreated metastatic breast cancer.
10801	A randomised phase III clinical trial to assess the value of breast conserving therapy in stage I and II breast cancer.
10850	Phase III trial on operable breast cancer in the elderly. Tumour excision plus tamoxifen compared with modified radical mastectomy.
10902	Randomised phase III study comparing short, intensive preoperative combination chemotherapy with similar therapy given postoperatively.
10921	A multicentre randomised phase III study of dose-intensive chemotherapy as primary treatment in a multimodality approach for locally advanced inflammatory breast cancer.
10923	Paclitaxel (Taxol) versus doxorubicin as first-line chemotherapy in advanced breast cancer: a randomised phase II study with crossover.
10924	Double-blind randomised phase III multicentre trial comparing the effect of oral pamidronate (CGP 23339A—Aredia) with placebo in patients with newly diagnosed bone metastases from breast cancer.
10952	Adjuvant tamoxifen versus tamoxifen plus fenretinide in postmenopausal women with node-positive T1/T2/T3 tumours or node-negative T2/T3 tumours. A randomised phase III study.
10961	Doxorubicin/taxol as first-line chemotherapy in advanced breast cancer: a randomised study versus standard doxoruicin/cyclophosphamide combination regimen. A phase II study leading to a phase III.
10974	Conservative local treatment versus mastectomy after induction chemotherapy in locally advanced breast cancer: a randomised phase III study.
10981	After mapping of the axilla: radiotherapy or surgery?
10992	Hormonal replacement therapy after breast cancer diagnosis—is it safe? Protocol for randomised clinical study concerning hormonal replacement therapy after previous radical breast cancer treatment.
15001	An international field study of the reliability and validity of the EORTC QLQ-C30 and a disease-specific questionnaire module (the QLQ-STO22) in assessing the quality of life of patients with gastric cancer.
15011	An international field study of the reliability and validity of the EORTC QLQ-C30 version 3 and a disease-specific questionnaire module (QLQ-PR25) for assessing quality of life of patients with prostate cancer.
15012	An international field-testing study of the reliability and validity of a patient satisfaction module (QLQ-SAT32) assessing cancer patients' perception of the quality of care received within the hospital.

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Table 1 (*continued*)

Study[a]	Title
15861	EORTC study group on quality of life protocol 15861. Development of a core quality of life questionnaire for use in cancer clinical trials.
15931	An international field study of the reliability and validity of the EORTC QLQ-C30 (v. 3.0) and a disease-specific questionnaire module (the QLQ-BR23) in assessing the quality of life of patients with breast cancer.
15941	An international field study of the reliability and validity of the EORTC QLQ-C30 (v. 3.0) and a diagnosis-specific module (the EORTC QLQ-H&N35) in assessing the quality of life of patients with head and neck cancer.
15961	An international field study of the reliability and validity of the EORTC QLQ-C30 and a disease specific questionnaire module (the EORTC QLQ-OES24) in assessing quality of life of patients with oesophageal cancer.
15982	An international field study of the reliability and validity of a disease specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer.
18871	Adjuvant phase III trial in malignant melanoma comparing interferon r alpha-2 to r gamma with a control group after surgical removal of either high risk primary (>3 mm) or curative resection of lymph node metastasis (stage IIB).
18951	Randomised phase III trial. Treatment of metastatic melanoma with DTIC, CDDP and interferon (IFN)-alpha with or without interleukin-2 (IL-2).
18952	Phase III trial. Postoperative adjuvant interferon-alpha 2b (Intron-A) treatment after resection of thick primary melanoma and/or regional lymph node metastases 'intermediate-high dose' versus 'intermediate-low dose' IFN alpha versus observation.
18981	Temozolomide versus temozolomide + whole brain radiation in stage IV melanoma patients with asymptomatic brain metastases.
18991	Adjuvant PEG-intron treatment in stage III melanoma versus observation after regional lymph node dissection. A multicentre randomised phase III trial.
20931	Protocol H8 for a prospective controlled trial in stage I-II supradiaphragmatic Hodgkin's disease. Evaluation of treatment efficacy and (long-term) toxicity in three different prognostic subgroups. H8 Trial.
20962	Evaluating the MBVP chemotherapy schedule followed by consolidating radiotherapy in non-AIDS-related primary central nervous system (CNS) lymphoma (NAPCL).
20963	Marrow ablative chemo-radiotherapy and autologous stem cell transplantation followed by interferon-alpha maintenance treatment versus interferon-alpha maintenance alone after a chemotherapy-induced remission in patients with stages III or IV follicular HNL. A prospective, randomised phase III clinical trial.
20971	A phase III randomised study on low-dose total body irradiation and involved field radiotherapy in patients with localised, stages I and II, low grade non-Hodgkin's lymphoma (20971/22997).
20982	Prospective controlled trial in clinical stages I-II supradiaphragmatic Hodgkin's disease. Evaluation of treatment efficacy, (long-term) toxicity and quality of life in two different prognostic subgroups.
20991	Diffuse large B cell and peripheral T cell non-Hodgkin's lymphomas (NHL) in the elderly. Influence of prolonged oral etoposide added to CHOP combination chemotherapy in patients with good physiological status. An EORTC randomised phase II-III trial including geriatric assessment and quality of life.
20992	Diffuse large B cell and peripheral T-cell non-Hodgkin's lymphoma in the frail elderly. Progressive and cautious treatment strategy in poor status patients. A phase II trial with emphasis on geriatric assessment and quality of life.
22003	A multicentre randomised trial of high versus standard doses of prophylactic cranial irradiation in limited small cell lung cancer complete responders.
22844	Radiation therapy of low-grade astrocytoma and oligodendroglioma of the adult.
22845	Phase III trial of radiation therapy versus no radiation therapy for cerebral gliomas (low-grade astrocytoma and oligodendroglioma) of the adult.
22925	Phase III study to evaluate a cisplatin–cyclophosphamide combination and an abdomino-pelvic irradiation followed by a pelvic boost in completely resected high risk stage Ia/Ib and Ic/IIa/IIb epithelial ovarian carcinomas.
22931	Phase III randomised study on postoperative radio- and chemotherapy in patients with locally advanced head and neck carcinomas.
22932	Phase III randomised study on the role of the booster dose of postoperative radiotherapy in patients with early stage carcinomas of head and neck.
22952	No radiotherapy versus whole brain radiotherapy for 1–3 brain metastases from solid tumour after surgical resection or radiosurgery. A randomised phase III trial.
22954	Phase III study on larynx preservation comparing radiotherapy versus concomitant chemo-radiotherapy in resectable hypopharynx and larynx cancers.
22961	Long-term adjuvant hormonal treatment with luteinising hormone-releasing hormone (LHRH) analogue versus no further treatment in locally advanced prostatic carcinoma treated by external irradiation and a 6 months combined androgen blockade—a phase III study.
22962	A phase III study comparing conventional versus hyperfractionated radiotherapy, with or without concomitant chemotherapy, in patients with head and neck squamous cell carcinoma.
22972	Focal fractionated conformal stereotactic boost following conventional radiotherapy of high-grade gliomas: a randomised phase III study.
22991	Three dimensional conformal radiotherapy alone versus three dimensional conformal therapy plus adjuvant hormonal therapy in localised T1b-c,N0,M0 prostatic carcinoma. A phase III randomised study.
22993	Prophylactic cranial irradiation in extensive disease small-cell lung cancer.

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Table 1 (*continued*)

Study[a]	Title
24001	Randomised phase III study on the selection on the target volume in postoperative radiotherapy for cervical lymph node metastases of squamous cell carcinoma from an unknown primary (CUP).
24941	A randomised phase III study of supportive care plus methotrexate versus supportive care only in patients with metastatic or recurrent squamous cell carcinoma of the head and neck.
24954	Phase III study on larynx preservation comparing induction chemotherapy and radiotherapy versus alternating chemo-radiotherapy in resectable hypopharynx and larynx cancers (jointly with the EORTC Radiotherapy Cooperative Group).
24971	A randomised phase III multicentre trial of neoadjuvant docetaxel (Taxotere) plus cisplatin plus 5-fluorouracil versus neoadjuvant cisplatin plus 5-fluorouracil in patients with locally advanced inoperable squamous cell carcinoma of the head and neck.
26951	Phase III study of adjuvant procarbazine, CCNU and vincristine chemotherapy in patients with highly anaplastic oligodendroglioma (randomised).
26952	Treatment of primary CNS lymphoma in immunocompetent patients aged over 60 years with chemotherapy alone: a phase II trial.
26981	Concomitant and adjuvant temozolomide and radiotherapy for newly diagnosed glioblastoma multiforme. A randomised phase III study.
30004	Chemoresection with 4 weekly intravesical instillations of mitomycin C versus transurethral resection followed by one single immediate instillation of mitomycin C in single small papillary stageTa, T1 bladder tumours.
30012	A randomised controlled trial of interferon-alpha, interleukin-2 and 5-fluorouracil versus interferon-alpha alone in patients with advanced renal cell carcinoma.
30853	A randomised prospective phase III study of the treatment of patients with metastatic prostatic cancer to compare the therapeutic effect of orchidectomy versus LHRH-analogue depot (zoladex) preparation supplemented by an anti-androgen (flutamide).
30865	Phase III estracyt versus mitomycin-C in hormone escaped advanced prostate cancer.
30891	Phase III study comparing early versus delayed orchidectomy, or early versus delayed treatment with a depot LHRH analogue (Buserelin) respectively, in patients with asymptomatic non-metastatic prostate cancer T0-4 N0-2 M0.
30892	Phase III study comparing endocrine treatment with flutamide or cyproterone acetate in patients with painless metastatic prostate cancer with favourable prognostic factors.
30893	Phase III study comparing orchidectomy and orchidectomy + mitomycin C in patients with metastatic prostate cancer with poor prognostic factors.
30903	Phase III trial of flutamide versus prednisone in hormone-resistant metastatic prostate cancer.
30921	A prospective multicentre randomised study comparing strontium89 chloride and palliative local field radiotherapy in patients with hormonal escaped advanced prostatic cancer.
30941	A randomised phase III study of 3 BEP versus 3 BEP-1 EP, and the 5-day schedule versus 3 days per cycle in good prognosis germ cell cancer.
30943	Randomised phase III trial of immediate versus deferred hormonal therapy in patients with elevated prostate-specific antigen (PSA) after definitive treatment for localized prostate cancer.
30944	Randomised phase II trial assessing estramustine and vinblastine combination chemotherapy versus. Estramustine alone in patients with hormone escaped progressive metastatic prostate cancer.
30954	Intermittent maximal androgen blockade in patients with metastatic prostate cancer: feasibility study.
30955	Phase III adjuvant trial: Interleukin-2, interferon-alpha and 5-fluorouracil for patients with high risk of relapse after surgical treatment for renal cell carcinoma (RCC).
30972	Randomised phase III study of JM-216 oral platinum plus prednisone or prednisone alone in patients with hormone-refractory prostate cancer.
30974	A randomised phase III study of sequential high-dose cisplatinum/etoposide/ifosfamide plus stem cell support versus BEP in patients with poor prognosis germ cell cancer.
30982	A randomised comparison of single agent carboplatin with radiotherapy in the adjuvant treatment of stage I seminoma testis following orchidectomy.
30983	A randomised phase II/III study of taxol-BEP versus BEP in patients with intermediate prognosis germ cell cancer.
30986	Randomised phase II/III study assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in previously untreated patients with advanced urothelial cancer ineligible for Cisplatin-based chemotherapy.
30991	Randomised phase III step-up study on initial antiandrogen monotherapy in comparison with watchful waiting in asymptomatic T1-3 any G (any Gleason) N0 or NxM0 prostate cancer patients without local treatment with curative intent.
40004	CLOCC trial (chemotherapy + local ablation versus chemotherapy): randomised phase III study of local treatment of liver metastases by radiofrequency combined with chemotherapy versus chemotherapy alone in patients with unresectable colorectal liver metastases.
40923	Phase III clinical trial of chemotherapy with 5-fluorouracil and L-leucovorin following potentially curative resection of liver or lung metastases from colorectal cancer (jointly with the National Cancer Institute of Canada (NCIC) Clinical Trials Group and the Gruppo Interdisciplinare Valutazione Interventi in Oncologia (GIVIO)).
40924	Randomised phase II-III clinical trial of cisplatin + 5-fluorouracil versus cisplatin + 5-fluorouracil with alpha-interferon in metastatic pancreatic cancer.
40941	Phase II study of i.v. vinorelbine and cisplatinum in the treatment of patients with metastatic epidermoid carcinoma of oesophagus previously untreated by chemotherapy.
40952	Randomised phase III study of weekly 24 h infusion of high-dose 5-fluorouracil with or without folinic acid versus bolus 5-fluorouracil plus folinic acid in advanced colorectal cancer.
40953	Randomised phase II study of weekly 24 h infusion of high dose 5-fluorouracil plus or minus folinic acid (HD-FU/FA) versus HD-FU/FA plus biweekly cisplatin in advanced gastric cancer.
40954	Randomised phase III study of preoperative chemotherapy followed by surgery versus surgery alone in locally advanced gastric cancer (cT3 and cT4NxM0).

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Table 1 (*continued*)

Study[a]	Title
40961	Phase II trial. Weekly high dose 5-fluorouracil and folinic acid in metastatic pancreatic carcinoma.
40986	CPT-11 in combination with weekly 24-h infusion 5-fluorouracil plus FA relative to weekly 24-h infusion plus FA alone in patients with advanced colorectal cancer.
55005	A randomised phase III study comparing gemcitabine plus carboplatin monotherapy in patients with advanced epithelial ovarian carcinoma who failed first-line platinum-based therapy.
55012	A phase III study of cisplatin plus topotecan followed by paclitaxel plus carboplatin versus paclitaxel plus carboplatin as first-line chemotherapy in women with newly diagnosed advanced epithelial ovarian cancer.
55931	Intergroup phase III comparison of a combination of Taxol–platinum and a combination of cyclophosphamide–platinum chemotherapy in the treatment of advanced epithelial ovarian cancer.
55951	Taxol or oxaliplatin in platinum-pretreated advanced ovarian cancer patients.
55955	A randomised trial in relapsed ovarian cancer: Early treatment based on CA 125 levels alone versus delayed treatment based on conventional clinical indicators—MRC OV05 and EORTC/GCCG 55955.
55963	A randomised phase III study for the treatment of recurrent epithelial ovarian cancer: Chemotherapy alone versus chemotherapy followed by secondary cytoreductive surgery in patients with a treatment-free interval of more than 12 months.
55971	Randomised phase III study comparing upfront debulking surgery versus neo-adjuvant chemotherapy in patients with Stage IIIc or IV epithelial ovarian cancer.
55981	A randomised trial of paclitaxel/epirubicin/carboplatin combination (TEC) versus paclitaxel/carboplatin (TC) in the treatment of women with advanced ovarian cancer.
55984	A randomised trial of Adryamicin (A) Cisplatin (P) chemotherapy versus Paclitaxel (T) Adryamicin (A) and Cisplatin (P) in patients with metastatic/relapsed or locally advanced inoperable endometrial cancer.
55994	Randomised phase III study of neoadjuvant chemotherapy followed by surgery versus concomitant radiotherapy and chemotherapy in International Federation of Gynecology and Obstetrics (FIGO) stage IIB cervical cancer.
62941	Randomised multicentre phase III trial comparing docetaxel to doxorubicin in previously untreated patients with advanced and/or metastatic soft-tissue sarcoma.
70931	Influence of dose intensity on survival in the G-CSF supported treatment of human immunodeficiency virus (HIV)-associated non-Hodgkin's lymphomas of high malignancy: a randomised and risk-adjusted phase III multicentre trial.

[a] EORTC study numbers are constructed as follows: XXYYZ, with XX being the number of the EORTC Clinical Group conducting the trial, YY being the year the trial was first proposed, and Z the rank of the trial; e.g. 08962 is the second trial proposed by the EORTC Lung Cancer Group in 1996. EORTC Clinical Group numbers are listed in Table 3. Table 1 also includes intergroup trials, either joint or coordinated by the EORTC. They are also referred to by means of the EORTC trial number.

ponent [16]. These data are stored in a newly developed database to monitor all EORTC studies having a QOL component. These studies are listed in Table 1. New studies are continuously added to this database, and information related to compliance, study status and number of patients are updated on a 6-monthly basis. Most of these studies (Table 2) are phase III studies ($n=83$) and phase II/III studies ($n=10$). A minority of the studies are phase II ($n=8$) or feasibility studies ($n=1$). The EORTC has also conducted a number of field studies ($n=8$), intended to test the psychometric properties of the questionnaires developed by the EORTC QLG.

A steady increase has occurred over the years in the number of phase III studies initiated, along with an increase in the number of phase II/III studies. This becomes apparent when comparing recent data with the data presented in 1998 by Kiebert and colleagues ([17], Table 2). The accelerated rise in the number of phase II/III studies, as opposed to the limited number of new phase II studies implementing QOL research, is due to the policy adopted by the EORTC to not include QOL systematically in phase II studies. Typically, phase II studies are designed to identify possible biological antitumour activity and to further identify drug toxicity.

An exception is made when a phase II study continues as a phase III study. Here, phase II is used to collect QOL data in addition to significant clinical data. This QOL data may then be used as a source of information for the QOL research design of the phase III trial. Data from phase II patients may also be used in final analysis, if all conditions remain equal. This strategy has been used increasingly during the last decade (Table 2).

In almost all EORTC studies, QOL serves as a secondary endpoint when included in a trial. QOL is a primary endpoint only in field studies initiated by the EORTC QLG, intended to test the psychometric properties of the EORTC QLQ-C30 and disease-specific modules. The EORTC Head and Neck Cancer Group conducted a trial with QOL as a primary endpoint, examining methotrexate versus supportive care in metastatic squamous cell carcinoma patients (EORTC trial 24941). This well designed trial was nevertheless abandoned after a year because of poor patient recruitment. However, it is not unusual to see QOL as a secondary endpoint in most studies, as other groups such as the NCI-C also have limited numbers of studies where QOL is a primary endpoint [18].

One obvious challenge for the EORTC is the very different national systems used to recruit and collect QOL data from patients. Presently, there are over 32 countries involved in QOL research throughout Europe and beyond. We have noted that those EORTC groups who undertake most QOL studies within their clinical trials seem to have good levels of QOL data compliance. This may relate to the familiarity with using QOL tools in a research setting, and may reflect the importance of QOL assessment in a given disease site. Groups less active in terms of QOL tend to have lower compliance. For example, the most active EORTC group undertaking QOL studies is the EORTC Genito-Urinary (GU) Group. Because many of their early studies suffered problems of low compliance, it was suggested that investigators' unfamiliarity with QOL instruments created such a poor compliance [12]. However, subsequent studies have provided high levels of compliance and useful outcomes in terms of significant publications.

In comparison, many other Groups, while successful and motivated in clinical trials, may have relatively few QOL studies, or none, involved in their trials. Some groups' studies with QOL data have been aborted while other QOL data cannot be analysed due to problems of low compliance. In part this may reflect the difficulties of collecting data in selected population groups; or possibly it could reflect the lack of investigators' experience in working with QOL data (Table 3). In part this may be a reflection that QOL issues are not key issues for these research protocols, or simply that these groups are undertaking fewer phase III trials and more

Table 2
Evolution of the number of EORTC clinical trials including QOL by phase

	1998 [17]	2002[a]
Phase II	6	8
Feasibility	1	1
Phase II/III	2	10
Phase III	32	83
Field study	3	8

[a] Cut-off date 15 July 2002.

Table 3
Open, closed or aborted QOL trials by group

EORTC Group	EORTC Group number	Open	Closed	Aborted
Aids-Related Tumors Study Group	70	0	0	1
Boron Neutron Capture Therapy Group	11	0	0	0
Brain Tumor Group	26	2	5	1
Breast Cancer Group	10	3	7	2
Chronotherapy Group	05	1	1	0
Early Clinical Studies Group	16	1	0	0
Gastrointestinal Tract Cancer Group	40	3	8	0
Genito-Urinary Tract Cancer Group	30	7	11	3
Gynaecological Cancer Group	55	5	4	1
Head and Neck Cancer Group	24	2	1	4
Leukemia Group	06	0	4	2
Lung Cancer Group	08	3	5	1
Lymphoma Group	20	4	2	1
Melanoma Group	18	2	3	0
Quality of Life Group	15	3	5	0
Radiotherapy Group	22	7	3	6
Soft Tissue and Bone Sarcoma Group	62	0	0	1

phase I or phase II studies where QOL is not a key issue.

We examined studies including a QOL component which were aborted and have listed the reasons for the failure of these trials in Table 4. It is evident that, in all but two trials, the trials' clinical endpoint was not achieved and trials were closed for reasons other than QOL complications alone. In only two trials, QOL was aborted due to a low compliance rate.

We examined published EORTC trials in Table 5. Here it can be seen that 19 trials have already been successfully published, and we are presently awaiting a further 20 trials to mature for analysis and publication. Given recent publications which questioned the value of QOL studies in cancer clinical trials (e.g. [19]); we examined these in terms of recommendations and impact as reported by authors in the original papers. Some 17 trials (89%) provided data that was either used for future clinical treatment recommendations or additional research, with recommendations being limited in six of these trials. Typically such limitations were due to low compliance and subsequent lower power of the QOL data, thereby making the results less representative of a larger population. The majority of these 19 trials (63%, $n=12$) resulted in separate publications from the clinical data. This often can occur in cases where QOL data is significant, given the difficulties of combining QOL reporting with reporting of clinical outcomes [20]. Only two trials provided non-informative data, typically due to extremely low compliance and being trials that began in the early years of QOL implementation in the EORTC.

Table 4
Reasons for aborted studies

Aborted	Reason	*N*
Study aborted as a whole	Low accrual	10
	Negative outcome	4
	Reason unknown	1
QOL part of study aborted	Low QOL compliance	2
	Total	17

Table 5
Published QOL data in EORTC trials to date[a]

Publication of QOL data	Category[b]	Number of studies published
Published in separate QOL paper	A	9
	B	3
	C	0
Published in main article[c]	A	2
	B	3
	C	2
Awaiting further analysis/data maturation		20

[a] Publications from the EORTC QLG were not mentioned here, since their studies are field studies, and not clinical trials.

[b] Publications of QOL data were categorised independently by two authors according to the usefulness of the data, defined here as the possibility to generate recommendations for treatment and further research from the QOL data. The categories were defined as follows, using data and authors reports:

A: 'full use': recommendations could be made for future treatment and research.

B: 'limited use': no clear recommendations could be made based on the data, but some information could be gathered to support future research (typically studies with low compliance).

C: 'non informative': no conclusions could be drawn from the QOL data, e.g. due to extremely low QOL compliance.

Even if data is categorised as 'non informative', it may at least be used for retrospective analysis, validity tests, prognostic factor tests or cross-cultural analysis.

[c] No separate QOL paper written, QOL data is published jointly with clinical data.

3. Approaches to improving EORTC QOL implementation

While it is evident that many EORTC trials are adding to our knowledge, the challenges of poor compliance are clearly seen. Detailed below are a number of recent initiatives that should increase the quality of QOL studies undertaken within the EORTC.

3.1. Guidelines on designing and implementing QOL data collection

In early clinical trials, the EORTC noted that a fundamental issue was standardisation of the way trials were designed and QOL data was collected. Working with liaison experts, a manual was produced [15], reflecting a standard approach to collecting QOL data.

3.2. Education

A survey conducted by Young and Maher [21] analysed results from 63 data managers and EORTC investigators with regard to their view of QOL within the EORTC and their perceived barriers to undertaking QOL data collection. These indicated a lack of understanding regarding many aspects of QOL, suggesting the need for education and training.

Over the last 5 years, the EORTC has provided courses and training for EORTC groups and EORTC Data Center staff. Education sessions may help to increase compliance, for example, by instructing clinicians on the importance of their involvement in making trials with QOL data successful by encouraging data to be completed and sent to the centre [22]. Training for research nurses and on-site cancer clinical trial data managers can help them to understand the *soft concept of QOL*,

thus giving them a clearer understanding of how the data can be interpreted and used [1,23]. Additionally, where centralised data management occurs, training in instrument development, coding and other aspects can motivate and facilitate better QOL understanding.

3.3. Guidelines for standardised data collection

Missing data has been identified as a major issue in QOL measurement in cancer clinical trials [24], especially in an international setting. This is a large scale problem: institutions may differ substantially, not only with regard to cultural issues, but also in terms of the logistics of patient care, and financial and personnel resources [2]. In order to harmonise the mode of QOL data collection across all institutions, the EORTC QOL Unit has developed standardised guidelines for QOL data collection in clinical trials, which are included in each protocol containing QOL components. These guidelines advise on questionnaire administration and data collection (Fig. 2).

Collecting information on the reason for missing data is important since there is strong evidence that often QOL data is not missing *at random*; therefore it cannot be ignored without introducing bias [25]. In order to investigate the reasons for missing QOL trial data, a *QOL questionnaire completion module* is added to each case report form (CRF), documenting if the patient has completed the QOL form at the specific visit linked to the CRF (Fig. 3).

3.4. Standardisation of QOL research protocol chapters

To ensure high quality QOL studies are designed, a minimum set of standard requirements that must be addressed in any QOL study protocol has been devised. All protocol chapters are reviewed extensively by the protocol review committees. These details are reported elsewhere [14,15].

3.5. Monitoring of compliance

Compliance is a fundamental issue facing researchers worldwide undertaking QOL studies [26]. There are numerous published studies and systematic reviews reporting considerable difficulties in collecting QOL data [19,27]. Without a doubt, this problem becomes even more complex when working in an international setting [2]. Therefore, the EORTC has suggested the following approaches:

1. The EORTC has implemented a system of monitoring QOL compliance by means of bi-annual compliance reports [17]. These specify directly the compliance rate by institution for each study. Where possible, at a Group's bi-annual meeting these reports are presented and discussed. Discussions address ways to improve compliance, or specific reasons why certain institutions' compliance may be lower than expected.
2. The EORTC QOL Unit acts as a central educational resource for investigators and data managers on all aspects of QOL data collection. For example, it can provide advice to local investigators on how patients should complete questionnaires, the availability of translations, advice on improving compliance, etc.
3. In future EORTC trials, a baseline QOL assessment will be mandatory to allow patients to be

- Appointing a responsible person for QOL data collection in each institution.
- Ensuring that the people responsible for the on-site data collection have a protocol copy at their disposal.
- Instructions to be given to the patient before completion of the questionnaire.
- Reviewing of the completed questionnaire by the person administering the questionnaire to the patient: check for omissions, incorrectly completed questions, and note reasons for unwillingness to answer or additional comments on the form; stating reasons for not completing the questionnaires.

Fig. 2. Guidelines for collecting QOL data.

Has the patient completed the quality of life of form? Yes/No

If no, please state the main reason:
- patient felt too ill;
- clinician or nurse felt the patient was too ill;
- patient felt it was inconvenient or takes too much time;
- patient felt it was a violation of privacy;
- patient didn't understand the actual language / illiterate;
- administrative failure to distribute the questionnaire;
- not required at this point;
- other (to be specified);
- unknown.

Fig. 3. QOL questionnaire completion module.

eligible for registration or randomisation before initiation of treatment. The only exception to this will be when patients are not fluent in the language of the questionnaire. In this case, QOL assessment can be waived and the patient, if otherwise eligible for the study, can be enrolled. This approach is characteristic of other research groups, including the NCI-C [28].

4. The EORTC is considering a minimum QOL compliance level to close QOL studies where data does not meet compliance standards. This is clearly difficult, as each protocol has different aims, some emphasising long-term compliance and others stressing mainly treatment-related compliance, depending on the expected QOL implications. In addition, over time, compliance could improve. Therefore, it may be useful to establish minimum and final levels of compliance. For example, there can be little point in continuing a study where follow-up compliance falls below 50%, as in survey methodology generally a response rate below 50% is no longer considered adequate [29]. Such low response rates would most likely influence the power of the QOL study, and one may be left wondering just how representative the results would be to any population.
5. The EORTC is pilot testing data management allocations to the monitoring of QOL studies within clinical trials. This includes developing centralised dynamic reminders to investigators at each assessment point, along with a QOL schedule checklist once patients are registered. Regular reminders and clearly-established time sheets aim to improve compliance.
6. Sponsored trials should provide sufficient financial resources to ensure adequate infrastructure to help manage the collection of QOL data [17], ensuring staff have adequate time for this important function. One example of a trial with such sponsorship (EORTC 10921), which was conducted in locally advanced breast cancer patients, achieved 80% compliance during treatment. Other trials, also in breast cancer patients, are ongoing with sponsorship (e.g. EORTC trial 10001-16010). Hopefully, high levels of compliance will occur within such trials. Guaranteeing sufficient resources and support for QOL data collection in this way is considered an important component in selected future EORTC trials.
7. The EORTC is considering establishing a QOL Clinical Trials Implementation Committee, consisting of members of the QOL Group, the QOL Unit and EORTC Data Center staff. Significant resources will be made available to members. The idea is to annually oversee levels of compliance across all Groups and trials with QOL making recommendations regarding specific approaches to adopt.

3.6. Analysis of EORTC studies

As the analysis of QOL studies is often a matter of debate [22], considerable attention is paid to both levels of missing data and patterns of patient drop out [30]. While one QOL method will not fit all studies, several attempts have been made to standardise the way QOL data is analysed. These include the development of standard QOL macros and, more recently, the initial development of a standard operating procedure for the analysis of EORTC QOL data.

3.7. Reporting QOL studies in EORTC clinical trials

Reporting of QOL data in cancer clinical trials has been under considerable criticism over recent years [19,20,31]. In many respects, this criticism can be justified and fairly directed at QOL research. However, within the EORTC both the liaison experts and the QOL Unit staff must be involved in the analysis and final writing of any publication containing QOL aspects, thereby helping to ensure quality. To ensure standardisation across all groups and studies, the QOL Unit is presently preparing minimum standards for the reporting of QOL studies in EORTC clinical trials. This will, for example, require as a minimum: a statement of the rationale for including QOL research in the trial, specification of the hypothesis, details of population, instruments, timing of assessments, methods of collection and analysis of data, and explicit details on compliance and methods of handling missing data, with a focus on the clinical significance of QOL results.

4. Conclusions

It is clear from this review that QOL is now a well-integrated aspect of EORTC clinical trials. The level of QOL implementation has risen dramatically over the last 5 years. The majority of trials incorporating QOL are phase III studies. Presently, all of these studies have QOL as a secondary endpoint.

It is clear that in some cases the collection of QOL data requires considerable effort. This is a reflection of what has been seen worldwide and previously reported by international researchers [1]. However, a number of approaches outlined within this paper have helped to improve the quality of QOL reporting and compliance. These include monitoring, providing feedback, education, training and planning.

Ongoing initiatives will continue to improve compliance. Hopefully, in the near future, the EORTC will

eradicate the problems that can plague many cancer clinical trials. The expectation is that with significant resources, time and commitment from clinicians and researchers, all EORTC QOL studies will significantly impact upon the future treatment and care of patients.

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