PERGAMON

European Journal of Cancer 36 (2000) 821–825

European Journal of Cancer

www.elsevier.com/locate/ejconline

Special Paper

Quality of life evaluation in oncological clinical trials — the EORTC model

J. de Haes [a,*], D. Curran [b], T. Young [c], A. Bottomley [b], H. Flechtner [d], N. Aaronson [e], J. Blazeby [f], K. Bjordal [g], Y. Brandberg [h], E. Greimel [i], J. Maher [c], M. Sprangers [j], A. Cull [k] for the EORTC Quality of Life Study Group

[a] *Department of Medical Psychology, Academic Medical Centre, PO Box 22660, 1100 DD Amsterdam, The Netherlands*
[b] *EORTC Quality of Life Unit, Brussels, Belgium*
[c] *Mount Vernon Hospital, Middlesex, UK*
[d] *Klinik for Psychiatrie und Psychotherapie, Kóln, Germany*
[e] *Netherlands Cancer Institute, Amsterdam, The Netherlands*
[f] *Bristol Royal Infirmary, Bristol, UK*
[g] *National Hospital of Norway, Oslo, Norway*
[h] *Karolinska Hospital, Stockholm, Sweden*
[i] *University of Graz, Graz, Austria*
[j] *Academic Medical Hospital, Amsterdam, The Netherlands*
[k] *Western General Hospital, Edinburgh, UK*

Received 7 July 1999; received in revised form 8 November 1999; accepted 4 January 2000

Abstract

The European Organization for Research and Treatment of Cancer (EORTC) has taken a leading role in the development of the methodology of quality of life (QL) measurement. In the EORTC Quality of Life Study Group (QLSG) valid instruments to assess QL in a general manner and disease-specific modules have been developed to be used in oncological clinical trials. Statistical and methodological aspects of QL research are discussed. The application of QL assessments in clinical trials represents a subsequent challenge. To improve the practice of QL assessment in clinical trials an 'EORTC model' has been developed. This model requires the collaboration of liaison persons, the EORTC Cooperative Tumour Groups and the EORTC Data Centre Quality of Life Unit (QL Unit). Cooperation between these parties, protocol development and advantages and concerns of the model are mentioned in this paper. Finally, suggestions for improvement are proposed.

Keywords: Quality of life assessment; Liaison function; Protocol development

1. Introduction

Improvement in survival, disease-free survival or response rates to therapy are still the most important endpoints in clinical cancer research. The impact of therapy on disease progression, however, is often uncertain and the side-effects of treatment, whether surgery, radiotherapy, hormonal- or chemo-therapy, may be substantial. Symptom control, reduction of treatment toxicity and of patients' distress have become more relevant objectives in the evaluation of cancer treatment [1]. As a result, quality of life (QL) studies have been increasingly undertaken in oncology over the past decade.

Information from QL studies may (a) help to decide about the relative effectiveness of cancer treatment; (b) enhance patients' decision making by providing them with data regarding the side-effects of such treatment; (c) improve the organisation and quality of cancer care; and (d) be used in a prognostic factor analysis.

The European Organization for Research and Treatment of Cancer (EORTC) has taken a leading role in the development of the methodology of QL measurement. In the EORTC Quality of Life Study Group (QLSG) valid instruments have been devised to assess

* Corresponding author. Tel.: +31-20-566-4661; fax: +31-20-566-9104.
E-mail address: e.m.verkooijen@amc.uva.nl (J. de Haes).

0959-8049/00/$ - see front matter
PII: S0959-8049(00)00007-1

QL generally [2]. In addition, disease-specific modules are being developed to be used in clinical trials involving different tumour sites [3,4]. Furthermore, statistical and methodological aspects of QL research are being defined in the group.

Having established a firm methodology, the application of QL assessments in clinical trials and the clinical use of research findings represent subsequent challenges. To improve the practice of QL assessment in clinical trials, an 'EORTC model' has been developed. This model requires the collaboration of three parties. Liaison persons and experts in QL measurement are involved, as well as the EORTC Cooperative Tumour Groups and the EORTC Data Centre Quality of Life Unit (QL Unit). Both cooperation between the parties involved and protocol development will be described. Advantages and concerns related to the model are also outlined and suggestions to overcome the latter proposed.

2. The different parties involved

2.1. EORTC Cooperative Tumour Groups

'The ultimate goal of the EORTC is to improve the standard of cancer treatment in Europe through the development of new drugs and other innovative approaches as well as the testing of new therapeutic regimens, using drugs which are already commercially available, with or without surgery or radiotherapy.' [5]. Research within the EORTC has been primarily accomplished within the different EORTC Cooperative Tumour Groups. Through such cooperative groups (a) a research agenda is developed for the specific field; (b) study protocols are prepared; (c) large, multicentre oncological clinical trials are carried out amongst the members of the group; and (d) results are reported. If the cooperative group judges a proposed study interesting and relevant and approves of the proposed study design, a study protocol is written by a writing committee with the main input coming from the study coordinator. Nowadays, QL assessment is included in many of the cooperative groups' studies.

2.2. QL liaison function

As the study coordinator is usually not an expert in the field of QL assessment, he/she may seek input from a liaison person. This person is an active member of the EORTC quality of life study group (QLSG) and an expert in QL assessment within a specific field of oncology. Ideally, they have a 'state of the art' knowledge of assessment methodology and some background in the relevant tumour type. Each liaison person is attached to one of the EORTC Cooperative Groups and attends the meetings of these groups on a regular basis.

The QL liaison is meant to support the cooperative group and the study coordinator in:

1. Generating interest in QL within the cooperative group by presenting relevant QL research.
2. Establishing whether QL assessment is appropriate in a given trial.
3. Writing parts of the study outline to be submitted to the Protocol Review Committee (PRC).
4. Supporting the writing of the full protocol.
5. Establishing contact with the QL Unit in between cooperative group meetings to enable reporting on the QL data collection during the course of the trial.
6. Collaborating with the QL Unit when QL data are being analysed.
7. Preparing, in close collaboration with the study coordinator and the QL Unit, publication of the results.

The liaison persons from the different cooperative groups meet at the bi-annual QLSG meeting in the 'liaison subcommittee'. A representative of the EORTC QL Unit is also present at these meetings. In this committee, the liaison persons generally report on the ongoing work within their respective cooperative groups. In addition, the common strategy as well as problems encountered can be discussed. A set of 'Guidelines for assessing quality of life in EORTC clinical trials' has been developed recently within the QLSG in close cooperation with the QL Unit at the EORTC Data Centre [6]. These guidelines allow for a systematic approach in all EORTC clinical trials. Internal report, EORTC, Brussels, 1999. These guidelines can be obtained from the EORTC QL Unit, Ave E. Mounier 83/Bte11, 1200 Brussels, Belgium.

2.3. The QL Unit

The rapid growth of the number of studies assessing QL has emphasised the need for the establishment of a QL Unit within the EORTC Data Centre. The QL Unit staff include a coordinator, a statistician, a data manager, a psychologist and an administrative assistant. The Unit's objective is to coordinate QL research within the EORTC. It has established an adequate infrastructure for data collection in clinical trials and the analysis of QL data.

The QL Unit is involved in studies across EORTC Cooperative Groups, in different phases of study development. It is involved in the review of outlines and protocols, supervises data collection and encourages a standard approach to optimise research quality. To maintain a high level of compliance, standards and procedures are developed for data management. These may include training of data managers and providing feedback about compliance to trial participants. The

analysis of data is coordinated and sometimes performed within the QL Unit. These activities facilitate the coordination of QL assessment in international, multicentre clinical trials throughout Europe.

3. Protocol development

3.1. Submission procedures

Within the EORTC, study proposals are reviewed by the New Treatment Committee (NTC) and the PRC. The NTC and the PRC comprise clinical trial experts including medical doctors, statisticians and a QL expert. The PRC may also co-opt the help of external individuals who are specialists in a given field and to whom protocols may be submitted for external review. The NTC reviews and approves the concept of EORTC trials with non-registered modalities on the basis of their scientific background, interest and feasibility, whereas the PRC reviews and approves EORTC protocols on such a basis for studies without non-registered modalities and on methodology for all studies. It also verifies that important scientific, methodological, collaborative and administrative issues are in agreement with general EORTC operating procedures. Only protocols which are approved by the EORTC PRC may be handled by the EORTC Data Centre and bear the EORTC label in publications.

As mentioned, for all new study proposals a study outline describing the design of the study is submitted to the PRC. The study outline template as well as guidelines for submission are available on the EORTC Website (www.eortc.be). A study outline may be accepted, accepted pending modification, may have to be revised and resubmitted, or may be rejected. Based on an accepted study outline a full protocol is developed.

Full protocols are developed by the EORTC cooperative groups. Writing committees consist of the study coordinator, other interested members of the cooperative group, an EORTC statistician, a data manager and, if applicable, the QL liaison person. Both the liaison person and the QL Unit are thus involved when QL is assessed, in the preparation of study outlines and full protocols.

During the process of protocol writing the liaison person, the QL Unit and the study coordinator work together. An overview of the procedure is given in Fig. 1. First, the study outline may be discussed between the study coordinator and the QL liaison person. Before being submitted to the PRC, the outlines are also reviewed internally in the EORTC Data Centre. The QL Unit's staff reviews the study outline to see that all the requirements are met. Comments are sent to the study coordinator. When the comments of the Data Centre are taken into account the revised study outline is sent to the PRC.

The decision of the PRC is conveyed to the study coordinator together with comments made by the committee and its external reviewers. After resubmission and acceptance of the study outline, the study coordinator is invited to write a full protocol. The QL liaison person will prepare the sections that refer to the QL part of the study. The text will then be sent to the QL Unit for further approval. After agreement is reached between all parties, the text regarding QL assessment is incorporated into the full protocol. Protocols are then submitted to the PRC. After approval the Data Centre will support the data collection and analysis.

For phase II studies a 'quick procedure' may be employed. However, QL is generally not assessed in these studies.

3.2. Protocol writing requirements

The success of a clinical trial depends on the thoughtful preparation of its protocol. Careful decision making before initiating a research project facilitates the conduct of a study as well as the reporting of results. The protocol must also be detailed enough to ensure that all participants carry out the study in a uniform manner.

In any study outline required by the PRC a statement regarding the appropriateness of the QL measurement in the trial should be given. If QL is considered a relevant endpoint, the rationale for including such assessment should be identified. In addition, the main outcome variables need to be stated, as well as the

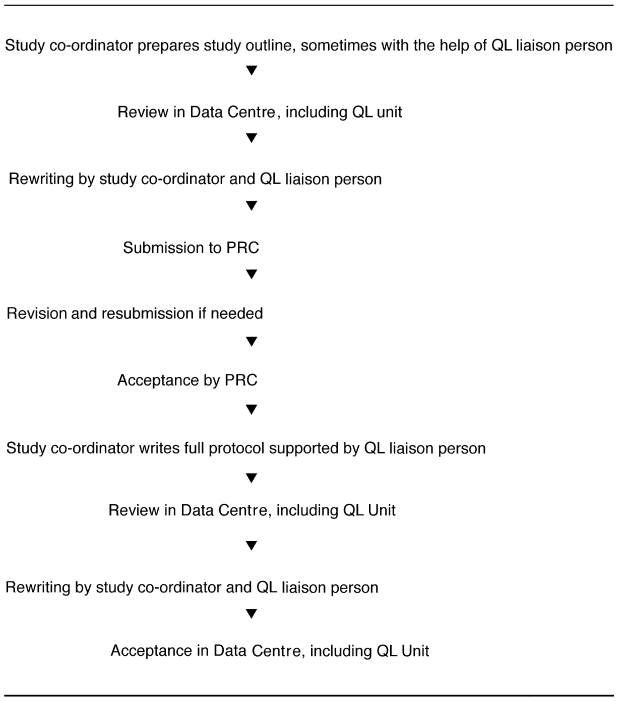

Fig. 1. Protocol development procedures.

instruments selected to measure these. The following questions are asked at the outline stage: (a) 'Do you intend to assess QL in the study (yes/no)? If yes, have you contacted the QL study group (liaison person)? (b) What is the rationale for including QL in the study? and (c) Which QL instruments will be used in the study?

In the full protocol the explanation of the procedures adopted should be further elaborated. The 'Guidelines' cover all relevant aspects [6].

1. The description of the rationale for measuring QL should be detailed. The need for QL assessment will be more pronounced when (a) the prognosis of the patients to be studied is unfavourable; (b) the expected impact of the treatment on QL is large; and (c) the expected impact of the treatment on clinical effectiveness is small. Nowadays, in a number of studies QL may be the main outcome parameter. This is the case especially in equivalence studies where the trial arms are expected to have an equal effect on clinical efficacy. Hypotheses regarding QL outcomes should be explicit.
2. Based on this rationale, the QL variables considered relevant are to be outlined.
3. A detailed description of the study design should be given.
4. Patient eligibility criteria for QL assessment should be formulated, if different from the eligibility criteria in the trial.
5. The choice of valid instruments proposed to measure the relevant study variables must be mentioned: which instruments are selected and why they are considered appropriate.
6. The timing of assessments should be detailed in advance. Measurement points have to be chosen in such manner that the research question can be answered adequately. Preferably, they will coincide with the clinical follow-up schedule for practical reasons.
7. The method of data collection should be outlined, e.g. whether assessments are done in person or by mail.
8. Statistical considerations should include the hypotheses to test, the expected effect size, sample size and the analysis plan. It is emphasised that making QL assessment an optional part of the trial is unacceptable to prevent selection bias and for reasons of completeness of data sets. However, it may well be that smaller numbers of patients are required to answer QL questions than the medical questions. One could then envisage that the assessment is done by a subset of participating centres preselected at the start of the trial.
9. The method of handling missing data, as well as procedures to enhance compliance, should be included (guidelines for data collection by nurses and data managers: who is responsible for data collection; who should fill in the questionnaire; what instructions should be given to the patient; where and when is the questionnaire to be filled out; how is the completion reviewed and what is to be done with missing forms).
10. Informed consent procedures must be outlined.
11. Finally, appendices including instruments, patient information sheets and consent forms should be included in the protocol.

4. Advantages and concerns

The model proposed has a number of advantages but is not without concerns.

4.1. Cooperative groups

Interest in and support for the value of QL assessment varies within, as well as between, EORTC cooperative groups. Cooperative groups with a high level of interest in QL assessment have formed subcommittees of clinicians from amongst their members to steer QL studies in their trials. In other groups, designing and conducting studies and, particularly, obtaining good compliance may present a challenge.

Moreover, individual centres participating in cooperative group trials may vary in the amount of resources available to them and thus their ability to participate in QL assessment. Study coordinators may also have variable levels of experience in how to coordinate such studies.

This leads one to suggest not only training in data collection but also towards recommending more selective use of QL assessment. Groups or centres that fail to reach good compliance in QL assessment may have to be sanctioned whereas centres that collect good quality data could be supported in having the necessary staffing to help with this.

4.2. QL liaison function

In committing oneself to the liaison function one may gain an opportunity to publish work from large-scale clinical trials. A liaison person may also have the possibility of establishing relationships with members of the cooperative group and, thus, develop an international professional network. A liaison person can gain experience in protocol writing and review. Liaison function may also provide the opportunity of travelling and presenting work throughout Europe. Finally, when genuine collaboration is established, the model offers opportunities to address questions relevant to the basic science of QL assessment in the context of clinical trials along with the clinical research questions addressed.

However, to deal effectively with the responsibilities, a substantial input of time is needed. Liaisons may, moreover, find that time spent in the cooperative group meetings is used less effectively when studies are discussed in which QL is not assessed. In addition, the role that has to be taken may be diffuse. The success of a liaison function depends, like all consultation work, not only on expertise but also on establishing good relationships. Members of the cooperative groups may not always be open to QL assessment. If so, it becomes more difficult to deliver good quality work and find contentment in the liaison role.

4.3. The QL Unit

From the perspective of the QL Unit, having liaison persons is helpful. Because (a) as many as 15 cooperative groups are involved in QL assessment within the EORTC; (b) the studies are divided by disease site, tumour type or treatment method and, therefore, specific knowledge is an asset; and (c) meetings are being held at different times at different locations. It would be practically impossible to perform all the work involved by the officers working at the QL Unit only.

The QL Unit does have the advantage of being easily accessible and working efficiently in a centralised and professionally organised body. However, one needs to avoid mixing of roles and responsibilities. Being the reviewer of protocols, the QL Unit might not be in the ideal position to serve as a consultant at the same time.

5. Conclusions

Different research groups in the world now include QL assessment in some of their studies. They sometimes work with a QL committee or with a fixed group of experts [7]. The EORTC has so far chosen a decentralised approach. Liaison persons have become active in the Cooperative Breast Group, Gastrointestinal (GI) Group, Gastro-urinary (GU) Group, Gynaecology Group, Head and Neck Group, Lung Group, Lymphoma Group and the Osteosarcoma Group of the EORTC. By standardising procedures and setting guidelines for QL assessment in EORTC clinical trials, the best methods of data collection can be developed and therefore optimal use of results can be reached.

In a number of studies good compliance rates have been shown. For example, in a recent study an 85% compliance rate was reached at baseline and a 70% rate thereafter [8]. However, although much progress has been made regarding the integration of QL as an endpoint in oncological clinical trials during the last decade, our early studies also point out the difficulties related to this field of research. Poor compliance poses one of the most severe drawbacks in the successful implementation of QL research. QL forms should be collected with the same rigour as other study forms. To overcome problems in compliance, the number of new studies should be restricted to those where quality of life is an endpoint of evident relevance. Moreover, those centres with a good record of quality of life assessment may be supported whilst those that are unable to fulfil the requirements of appropriate data collection may have to be sanctioned. As mentioned earlier, guidelines and procedures have recently been developed and put in place, e.g. guidelines for assessing QL in EORTC clinical trials including detailed instructions for data collection, to improve data compliance and data quality [6]. Finally, a European Unit grant has recently been provided to the EORTC QLSG and QL Unit, enabling them to run a training course in the year 2000 to promote data collection and data handling. Since these developments are quite recent, the benefit of most of these changes has still to be proven.

The EORTC model can, in our view, lead to high quality research in oncological clinical trials throughout Europe. When the approach works effectively, optimal use of the expertise available is ensured as experts specialised in specific tumour types are involved in all studies. As a result, cooperative groups have access to 'state of the art' knowledge of QL assessment within a particular cancer field. Moreover, as liaison persons meet on a regular basis, feedback is possible and a standardised approach can be developed for different studies.

References

1. Kiebert GM. Quality of life: an additional value in cancer clinical trials? *Eur Cancer News* 1997, **9**, 11–12.
2. Aaronson NK, Ahmedzai S, Bergman B, *et al*. The European Organization for Research and Treatment of Cancer QLO-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993, **85**, 365–376.
3. Aaronson NK, Cull A, Kaasa S, Sprangers MAG. The EORTC modular approach to quality of life assessment in oncology. *Int J Mental Health* 1994, **23**, 75–96.
4. Sprangers MAG, Cull A, Groenvold M, Bjordal K, Blazeby J, Aaronson NK. The European Organisation for Research and Treatment of Cancer approach to developing questionnaire modules: an update and overview. *Qual Life Res* 1998, **7**, 291–300.
5. EORTC. Organization, activities, and current research 1997–1998 (internal report). Brussels, EORTC, 1997.
6. Young T, de Haes JCJM, Curran D. Guidelines for assessing quality of life in EORTC clinical trials (internal report). Brussels, EORTC, 1999.
7. Osoba D. The Quality of Life Committee of the Clinical Trials Group of the National Cancer Institute of Canada: organizations and functions. *Qual Life Res* 1992, **1**, 211–218.
8. Curran D, Aaronson N, Standaert B, *et al*. Summary measures and statistics in the analysis of quality of life data: an example from an EORTC-NCIC-SAKK locally advanced breast cancer study. *Eur J Cancer* 2000, **36**, 834–844.