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Quality of Life as an Outcome in EORTC Clinical Trials

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INTRODUCTION by Gwendoline M. Kiebert

In the past decade, increasing attention is being given to more systematic and quantitative ways to evaluate explicitly the impact of diseases and medical interventions on quality of life. A substantial part of this research pertains to the field of cancer where cure is not always possible and treatments are mostly intrusive. In recent years it has become more acceptable to include a quality of life (mostly as a secondary) outcome measure in cancer clinical trials. It is for this reason that quality of life as an outcome measure was discussed at the conference on 'Cancer Research and Treatment —Towards the 21st Century' in Heidelberg. The presentation highlighted the present situation, current problems, and future perspectives of quality of life research in cancer care within Europe. The following text is a section from '*A Practical Guide to EORTC Studies*', which describes some of the issues involved in the use of quality of life assessment in clinical trials from the perspective of the EORTC. © 1997 Published by Elsevier Science Ltd.

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ALTHOUGH THERE is some disagreement among quality of life researchers with respect to the definition of quality of life, there are a number of issues on which they agree. The first area of agreement is that quality of life contains *four* basic components or dimensions which are physical state, psychological well-being, social relations, and functional capacity. Although additional components to the general concept (e.g. role performance, economic status, and spirituality) or subcomponents to the main components are often suggested (e.g. sexuality, body-image, self-esteem), these four basic components are generally considered to provide the core elements of the conceptual framework of quality of life research. In addition to the information that has to be gathered on the various dimensions, it is also recommended that an overall value of global quality of life is obtained. This global concept refers to life as a whole, which is more than the sum of its parts. The advantage of including a global overall evaluation is that this quantification can be used as an index. Comparison of indices can broaden the application of quality of life evaluation without losing the diversity of information regarding specific components or dimensions. The second issue researchers agree upon is that quality of life is a *subjective* evaluation and that patients themselves are the best judges of their own quality of life. The third agreed issue is that quality of life is not a static, but a *dynamic* entity. It changes as a function of time and is susceptible to numerous medical as well as psychosocial influences. In other words, quality of life is more a transient time-dependent process than a final outcome.

The general purpose of quality of life assessment in medicine is to provide more accurate estimation of the well-being of individuals or groups of patients and of the benefits and losses that may result from medical intervention. There are three fundamental purposes of measurement: predictive (predicting a future outcome); discriminative (differentiating between people at a single point in time); and evaluative (measuring change over time). In cancer clinical trials the focus of study is mainly to compare quality of life in different treatment arms and therefore it is mainly evaluative. It would be unrealistic to suggest that quality of life evaluation should be incorporated as a standard approach in all clinical research. Quality of life research requires manpower and therefore money, and the necessary resources may not always be available. Moreover, it is obvious that information on quality of life is more relevant in some cases than in others. A number of criteria can be formulated in which quality of life should be considered as a relevant study endpoint. These criteria are:

(i) if important improvements of overall, recurrence-free, or disease-free survival realistically cannot be expected to occur as a result of treatment, but significant changes or differences in at least one aspect of quality of life are expected to occur;
(ii) if one treatment demonstrates a better survival, but produces more severe toxic effects;

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(iii) if with or without treatment the disease site is associated with an extremely poor prognosis;
(iv) if a treatment is known to be burdensome for patients;
(v) if a new (invasive) treatment is to be evaluated.

In either of these circumstances quality of life can be a primary or a secondary endpoint and in most cases it concerns randomised phase III trials.

In principle, quality of life is not considered as a relevant endpoint in phase II trials, since the primary aim of such a study is to determine anticancer activity and the treatment-related toxicity. However, previous studies have shown that patients and their physicians can differ in their rating of toxicities and burden of treatment. Moreover, the clinical evaluation of toxicity mainly focuses on its occurrence and severity and not on the duration of toxicity or on the relative burden of side-effects for patients. For these reasons it may be important to include the patient's evaluation of these factors in phase II studies. This may provide not only important information and thus increase our understanding of the frequency, severity, and burden of the side-effects, but it may also provide valuable information for deciding on the design of a subsequent phase III trial. It can yield a better indication of which aspects of quality of life should be examined, and it could be used to determine which interventions should be made early on in the phase III trial in order to minimise symptoms and dysfunction. However, it should be noted that the subjective evaluation of perceived burden of treatment related side-effects is not to be confused with or regarded as equivalent to the 'classical' approach to the evaluation of quality of life. The latter entails more than just the assessment of treatment-related symptoms. There is one exception to the general rule of not measuring quality of life in a phase II study. This exception concerns randomised phase II studies that may continue as a randomised phase III trial, in which quality of life is regarded to be an important outcome measure, since the data of patients entered in a randomised phase II study will be included in the phase III comparison. It is important to test quality of life instruments in pilot studies before they are applied on a large scale in a randomised phase III trial. The objective then is, for example, to see if all the relevant issues are being addressed adequately or to test certain psychometric properties.

If quality of life is considered to be a relevant outcome parameter in a clinical trial, then a number of decisions have to be made concerning the design of the study and the methodology of assessment. These decisions relate to: (a) the domains or components of quality of life to be evaluated; (b) the choice of subjects; (c) the instrument(s) to measure the relevant components; and (d) the timing of measurement.

Components of quality of life

As stated earlier, the basic quality of life assessment includes the evaluation of four components (functional status, physical, psychological, and social well-being). In addition, other components or subcomponents can be considered relevant outcomes, depending on the specific context and objectives of the study. The selection of these additional (sub)components can be based on expert opinion, clinical experience, patient interviews, pilot studies, reports in the literature, or can be selected based on face value. An additional argument can be the availability of appropriate and sound instrument to measure this aspect. The development of a sound instrument is a time consuming and costly endeavour. In many cases both may be lacking. Although reinventing the wheel as well as the use of *ad hoc* questionnaires should be avoided as much as possible, in some cases it is unavoidable. For instance, domain-specific questionnaires may not be available, or they may be unsuitable for certain studies.

Selection of instruments

There is no gold standard with respect to instruments to measure quality of life. Instruments that have been proved to meet all the criteria when used in one application may be less appropriate or even inappropriate in another. Nevertheless, there is consensus about some general criteria an instrument has to meet. In a multicentre clinical trial it is not feasible, in general, to perform any other quality of life evaluation other than by means of a written questionnaire. The questionnaire should have proven, good psychometric properties with respect to validity, reliability, and responsiveness to change. Responsiveness refers to a combination of both reproducibility (i.e. identical scores in stable subjects over time), and sensitivity (i.e. the ability to demonstrate changes when the subject's state of health improves or deteriorates). This latter characteristic is particularly important in a clinical trial setting. The questionnaire should also be simple, brief, and easy to administer. These properties enhance both participation and compliance, and they reduce the burden for both patient and staff.

There are two basic types of instruments: generic and disease-specific. Generic instruments focus on the main components that constitute quality of life, and they are intended to be applied in a wide range of populations and health states. Disease-specific instruments have been developed especially to detect subtle, disease and/or treatment-related effects.

The EORTC Study group on Quality of Life developed a questionnaire (QLQ-C30) which is now widely used both within and outside the EORTC. This core questionnaire consists of 30 items assessing five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain, nausea, and vomiting), a global health status/quality of life scale, perceived financial impact of the disease and a number of single items assessing additional symptoms. The instrument is reported to possess good psychometric properties and it is brief and easy to administer. For this reason it is the standard instrument to be used in EORTC clinical trials. It is available in 20 languages. The QLQ-C30 or core questionnaire can be supplemented by disease or treatment-specific modules. At present, the lung and the breast cancer modules have been tested and are available. Other modules are in various stages of development, but most of them can be used in EORTC trials if permission is obtained from the member of the Study group on Quality of Life who is responsible for its development.

Timing of measurement

The timing of assessment of quality of life must be carefully scheduled in order to optimally detect possible treatment differences. In general, a minimum of three assessments are required to capture relevant changes in quality of life over time in a clinical trial. The first assessment is one that should take place prior to the start of treatment, and preferably prior to randomisation. This assessment, although not a baseline in the true sense of the word, serves as such (a true baseline would be an assessment prior to the diagnosis of cancer). The

second assessment is during treatment, when treatment related side-effects are expected to be at their height. The third assessment is at the time that the therapeutic benefit is expected to be maximal. Eventually, the quality of life evaluation can be expanded to additional assessments to capture long-term effects at follow-up. It is important that the intervals of assessment correspond to the natural changes that may occur during the process of disease and adaptation to treatment. It is also important that timing of assessments is the same in all treatment arms.

Hypothesis testing

Even if quality of life is a secondary endpoint in a clinical trial it is important to formulate at least one *a priori* hypothesis to minimise the risk of a type I error (false-positive findings). Since comparison of multiple outcome scores implies the repeated use of significance tests, the probability of such type I error is automatically increased. For this reason it is important to identify the major issues in the study. It is also important that these major issues are identified in advance of the study activation and not after the data are collected.

Hypotheses should be defined in a precise and operational manner. Statements like 'to test if there is a difference in quality of life between the two treatment arms' are clearly too vague and insufficient. The direction of expected differences should be defined as well as the domains in which one expects these differences to occur.

Collection of quality of life data

If quality of life is an endpoint in a cancer clinical trial then data-collection will be performed alongside the recording of the biomedical parameters. It is of great importance that the collection of quality of life data coincides with the collection of clinical data, not only from a practical perspective, but also from the analytical perspective. Statistical analysis of quality of life data has to be performed in conjunction with the clinical data.

There are a number of measures that can be taken to minimise the workload and to optimise compliance in both patients and institutions (clinicians, nurses, data managers).

A. If quality of life is an endpoint in a multicentre clinical trial then it is to be preferred that it is not optional, but that all centres participating in the trial also perform the evaluation. Optional assessment or quality of life assessment in a selection of countries or centres introduces the possibility of both sample and selection bias, which is hard to control for.

B. To minimise the additional workload it is necessary to limit the number of quality of life assessments and to keep the assessments as simple and brief as possible.

C. A third measure is to limit the number of studies in which quality of life is evaluated. If in a centre, a country, or in a cooperative group various studies are being conducted at the same time, the standard inclusion of an additional outcome measure such as quality of life may not be feasible because of the additional burden it entails. Sometimes it can be necessary to limit the number of ongoing studies that include quality of life as an endpoint to prioritise studies.

Measures to limit low quality data and to enhance compliance

An elementary characteristic of quality of life evaluation is that it is impossible to correct for missing data by collecting data retrospectively. Therefore, one of the most important and crucial elements of quality of life research in cancer clinical trials is that the logistics of data collection have to be very well organised. If the proper instrument is not present at the right moment and the right place then obviously data cannot and will not be collected. There are a number of measures that can be taken fairly easily in order to limit the number of failures, to improve the quality of data, and to enhance compliance in multicentre clinical trials. These measures are:

(i) identify one person in each centre who is responsible for the logistics of data-collection;
(ii) ensure that the protocol is available to those persons who collect data;
(iii) provide regular feedback on the progress of the study with respect to the evaluation of quality of life;
(iv) send out reminders when questionnaires are due to be filled out;
(v) provide detailed explanation of study objectives, the importance of quality of life evaluation, and instructions for data collection to both the person responsible at each centre, as well as the patient;
(vi) collect questionnaires when completed; check for omissions; check for incorrectly completed questions; and check for inconsistent answers.

Protocol requirements

Each protocol must contain a statement as to whether or not quality of life will be an outcome measure. If quality of life is an endpoint in a cancer clinical trial then the protocol should contain information on a number of issues. These issues are listed in Table 1. Before a protocol is submitted to

Table 1. Quality of life as an endpoint in EORTC clinical trials: protocol requirements

The protocol should contain:
(i) A description of the rationale of measuring quality of life;
(ii) A statement of the objectives of the quality of life evaluation and formulation of hypotheses that will be tested;
(iii) A detailed description of the design of the study:
— patient eligibility criteria
— mode of data collection
— instruments of measurements (which and why)
— timing of assessments
— plan of implementation and logistics
— statistical considerations (effect size; sample size calculation; statistical methods used)
— informed consent procedure
— instruments and patient information leaflet as appendices.

the Protocol Review Committee, it will be reviewed by the Quality of Life Unit at the EORTC Data Centre. If quality of life is an endpoint protocol will be reviewed according to the requirements as described in Table 1. Since quality of life is a relatively new field of research, and mainly developed and conducted by social scientists, many clinicians have limited experience in the conduct of quality of life evaluation. It is helpful to obtain advice on the appropriateness of quality of life as an endpoint in a certain study and/or on the optimal approach on how to perform such an assessment. Some EORTC Co-operative groups have a liaison person who is a member of the EORTC Study group on Quality of Life and whose primary task is to consult on these issues. If such a liaison person is not available within a Co-operative Group then the Quality of Life Unit at the EORTC Data Centre can be consulted. It is strongly advised to consult with and involve these persons in an early phase of the development of the protocol.