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Special report

Report from a National Cancer Institute (USA) workshop on quality of life assessment in cancer clinical trials

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To promote the inclusion of quality of life (QOL) end-points in clinical research on cancer, the National Cancer Institute (USA) sponsored a workshop on QOL assessment in cancer clinical trials in July, 1990. Experts in clinical trials and QOL research formed four working groups to identify current areas of cancer treatment in which QOL end-points are most important; to discuss methodologic problems in QOL assessment; to address common problems in implementing clinical studies with QOL end-points; and to consider statistical issues in design, implementation, and data analysis. Recommendations made by the working groups are summarized in this paper.

Key words: Assessment methods, cancer, clinical trials, quality of life.

The concept of quality of life (QOL) has been a major area of interest and research during the last decade, as patients and physicians have become more aware of the impact of treatment on quality of survival.[1,2] The US Food and Drug Administration (FDA) recognizes benefit of QOL (as well as improved survival) as a basis for approval of new anticancer drugs[3] and some of the Cooperative Clinical Trials Groups have included QOL assessment, along with traditional end-points of tumour response, survival, and toxicities of therapy, in Phase III protocols.[4,5] Although there have been considerable advances in methods for assessing QOL, there has been only modest integration of QOL outcomes into clinical trials. Reasons for this are unclear but might include clinicians' lack of familiarity with QOL scales, practical problems in implementing QOL assessment and difficulties in addressing data analysis.

On 16 and 17 July 1990, the National Cancer Institute (NCI) and the Office of Medical Applications of Research (OMAR) co-sponsored a workshop on Quality of Life Assessment in Cancer Clinical Trials. The purposes of the meeting were to define elements of QOL that are relevant to clinical decision-making and serve as end-points in cancer clinical trials; to discuss strategies for implementation of QOL assessment in clinical trials; to identify site-specific questions of high priority; to examine issues regarding the integration of findings from therapeutic evaluations and QOL measurements. National and international experts with diverse scientific backgrounds in clinical trials and QOL research formed four working groups to explore and debate issues concerning selection of appropriate clinical trials, assessment implementation and analysis.

A major theme for workshop participants was the importance of cooperation among social scientists and clinicians. Discussion of the relevant issues from diverse scientific viewpoints was encouraged. Recommendations made by the working groups are summarized below.

This article summarizes recommendations from the four working groups that comprised the workshop. Copies of the full reports are available from Dr Nayfield at the address above.

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Which treatment trials

The Integration Working Group (comprised of members from Cooperative Clinical Trials Groups, NCI-supported cancer centres and pharmaceutical companies) identified current areas of cancer treatment research in which QOL end-points would be most important.

Information on QOL aspects of different treatment options is especially important in clinical decision-making when treatments are associated with similar survival but different toxicities, or when one treatment demonstrates better survival but more severe toxic effects.[6] This working group pointed out that patients' reports of toxicities have been used routinely to identify side-effects such as nausea, anorexia and fatigue, which may not be associated with specific abnormalities in laboratory studies or physical examination. In contrast, the patients' subjective assessment of QOL includes dimensions beyond toxicity, such as physical, physiological, emotional and social function and can be a complementary end-point to response, survival and toxicity. The group also addressed specific clinical problems in Phase III clinical trials for which the impacts of treatment toxicities on QOL were especially important research questions. These are presented in Table 1. Although QOL assessment may be just as important an issue (or more important) in Phase I and Phase II studies, the group concluded that systematic assessment efforts can profit from the comparative focus of Phase III trials.

Table 1. Phase III clinical trials with QOL issues

Primary site	Treatment comparison	QOL issue
Organ sparing procedures:		
Prostate (B1 and B2)	Surgery vs. radiotherapy	Impotence vs. proctitis
Bladder	Surgery vs. radiotherapy	Ileal conduit vs. proctitis
Lung (non-small cell)	Surgery vs. radiotherapy	Pain, etc vs. oesophagitis
Larynx	Surgery vs. radiotherapy	Degrees of impairment and disfigurement
Adjuvant breast cancer studies:		
Breast	High-intensity, short duration chemotherapy vs. standard chemotherapy	Inpatient vs. outpatient treatment setting
Breast	Standard chemotherapy ± maintenance hormonal therapy (Tamoxifen)	Therapy after remission (positive or negative effects on QOL)
Breast	Tamoxifen ± standard chemotherapy	QOL effects of chemotherapy
Gynaecologic malignancies:		
Ovary	Cisplatin/cyclophosphamide vs. cisplatin/taxol	Neurotoxicity
Endometrium	Surgery ± radiotherapy	Chronic toxicities
Haematologic malignancies:		
Hodgkin's disease (Stage I–II)	Chemotherapy vs. radiotherapy	Effects of toxicity
Bone marrow support for intensive therapy:		
Adult AML	Standard chemotherapy vs. intensive chemotherapy with bone marrow support	Daily living, hospital days, work attendance
Childhood neuroblastoma	Standard chemotherapy vs. intensive chemotherapy with bone marrow support	Hospital days, school attendance, social interaction, family life
Paediatric tumours:		
Low risk ALL	Inpatient vs. outpatient consolidation	Cost, effect on family
Brain tumours	Immediate vs. delayed radiotherapy	Psychological, intellectual and neurological functioning
Primary sites with extended survival	Long-term treatment effects	Chronic toxicity; long-term social, intellectual, sexual, and psychological functioning
Symptom control:		
Small Cell Lung Cancer	Standard chemotherapy ± megestrol acetate	Effects of increased appetite and weight gain

Assessment issues

The Assessment Working Group (comprised of clinicians, social science researchers, FDA personnel and cancer QOL researchers) discussed a range of issues including who should assess QOL (patient or clinical observer), QOL dimensions relevant to cancer clinical trials, criteria for selection of QOL instruments and components of a minimum set of demographic data. Each topic will be reviewed below.

Perspective

This working group concluded that patient report provided the best scientific and clinically relevant data for evaluating the impact of cancer treatments on patient QOL. Proxy measures (provided either by physicians or family members) should not be used as substitutes for patient QOL ratings because they generally lack good agreement with patient report.[7-9] Observer or proxy ratings could be useful in the following ways:

1. as supplements to patient report of QOL (e.g. physician-rated toxicity or performance status);
2. in trials where cognitive or physical function is expected to deteriorate over time and high agreement between patient and proxy ratings has been demonstrated prior to the deterioration;
3. as part of the validation of new QOL instruments;
4. when a trial has the additional objective of assessing the burden of cancer treatment on the family, family members can assess both their own QOL and that of the patient.

Dimensions

The Assessment Working Group restricted its definition of QOL to health-related QOL.[10-15] Health-related QOL refers to those aspects or dimensions of a person's life likely to be affected by his health or treatment of his health. This definition is relevant for clinical trials research and narrows considerably the areas of a person's life that should be addressed (e.g. satisfaction with housing can be eliminated). Most researchers agree that QOL is a multidimensional construct and that, while there may be some disagreement about the number of critical dimensions required to assess health-related QOL, there is substantial overlap among the components considered essential by various researchers.[16-18] This working group recommended that, as a minimum, QOL assessment in cancer clinical trials should include: physical, emotional and social functioning; somatic/physiological complaints (symptoms and side-effects associated with treatment); a global, self-perceived description of QOL (alternatively, self-perception of wellness or its absence). Patient satisfaction with treatment or perception of the health care system was identified as an important variable; however, working group members could not agree that it should always be measured. Additional research is needed to develop methods for determining the relative importance or weight of particular QOL dimensions for individual patients and incorporating these weights into the assessment of the extent to which QOL is affected by treatment for cancer.

Instrument selection

For selection of QOL measures to be used in a clinical trial, the working group recommended use of a core instrument (or set of instruments) to assess the basic dimensions of QOL in a generic manner and a disease- or treatment-specific module dictated by the nature and objectives of the trial. Criteria for instrument selection include: (a) content assessing the dimensions listed above, and (b) published evidence of psychometric evaluation with respect to reliability, validity, and responsiveness to change. The working group preferred brief and simple assessments to reduce patient and staff burdens. However, there must be adequate coverage of key dimensions and adequate item coverage within dimensions to assure both validity and reliability. Thus, with the exception of global QOL assessment, one-item measure of QOL dimensions should not be used. The working group could not select a best measure of QOL but suggested a number of candidate instruments that meet these criteria (Table 2).

The selected instrument should be appropriate to answer the QOL questions of interest in a trial and appropriate for patients with cancer. The group recommended pilot testing with patients having the same disease site and stage as those to be enrolled on the trial to determine whether the items are relevant for the study sample and to evaluate implementation problems. Investigators wishing to include QOL end-points in a clinical

Table 2. Examples of QOL instruments

Generic instruments: general medical conditions
*Medical Outcomes Study (MOS) Short Form (SF) (SF-20 and SF-36 versions)[23,24]
Generic instruments: cancer
CAncer Rehabilitation Evaluation System (CARES) – Short Form (59 items), Research Form[25–27]
Functional Living Index—Cancer (FLIC)[28,29]
**EORTC Core Quality of Life Questionnaire[30]
Disease/site-specific instruments
Breast Cancer Chemotherapy Questionnaire (BCQ)[31]
EORTC Modules for Disease Sites
Dimension-specific instruments
***Psychosocial Adjustment to Illness Scale—Self-Report version (PAIS-SR): All medical conditions[32,33]
Symptom Distress Scale: Cancer[34–38]
Rotterdam Symptom Checklist (RSCL): Cancer[39–42]

*Use requires notification to Dr Ware and his colleagues.
**Still undergoing development; use requires permission from Dr Aaronson.
***Not in public domain; use requires purchase of forms and scoring manuals.

trial should consult individuals with expertise in QOL instrument selection and implementation at the planning stages of the protocol.

Variables that moderate or modify QOL

Research has documented the relationship between socioeconomic factors and cancer survival[16–18] and sociodemographic factors are frequently related to the quality of life of cancer patients and survivors.[19–21] Thus the working group supported NCI efforts to develop standardized questions on sociodemographic variables for routine collection in cooperative group trials. It was felt that data such as age, ethnicity, gender, marital status, educational level and employment status could be obtained without additional burden in most NCI-sponsored clinical trials.

Coexistence of other health conditions may have an impact on QOL outcomes in addition to the protocol treatment effect on QOL. Collection of information on comorbidity is recommended in all cancer clinical trials, espcially those including QOL outcomes.

Implementation methods

The Implementation Working Group (comprised of data managers, operations and statistical centre experts, social scientists, and medical and nursing clinicians) addressed issues linked to collection and management of QOL data in the setting of multi-institutional clinical results. This group examined strategies for selecting assessment times and implementing multiple assessments over time, establishing data collection methods, and modifying quality control mechanisms for treatment trials appropriate for QOL data.

Times of measurement

This working group determined that, in general, a minimum of two measurements (baseline and at least one follow-up) is required to evaluate changes in QOL over time. (The Assessment Working Group recommended a minimum of three assessments.) Baseline measurement is essential and should be performed prior to randomization if possible, but always prior to treatment.

The timing of follow-up assessments depends on study objectives, the natural history of disease and characteristics of the treatment regimen (e.g. cycle length, expected response patterns for different arms, etc). In general, investigators should use as few measurement times as possible to minimize respondent burden. Possible points for follow-up assessments include:

1. during treatment;
2. at completion or discontinuation of treatment;

3. at completion of the study.

Clinical trials comparing different treatments may require QOL assessment at each of these times in addition to the baseline measurement. Because treatment regimens often differ in cycle length, time to maximum response and duration of response, assessments must be planned at times that will allow a 'fair' evaluation of each treatment arm.

Assessments during the treatment period should be obtained prior to delivery of treatment (unless immediate toxic effects are of interest) in order to maximize patient objectivity and ensure consistency of data. Adherence to QOL study demands can be enhanced by planning for subsequent data collections to be shorter and less demanding than baseline measurement.

Group members emphasized the importance of continuing QOL assessments until the end of the study, to ensure appropriate comparisons between study arms, regardless of the treatment status of the patient. 'Off treatment' should not mean 'off study' for QOL measurements.

Data collection

This group concurred with the recommendation of the Assessment Group that self-report data are preferable to observer data, because of the subjective nature of the QOL construct. Obtaining both types of data can be quite valuable, since they are often independent and complementary in their ability to predict other health-related outcomes such as response and survival. Although this group concluded that interview-generated data are superior in quality to data collected with self-administered methods, they acknowledged the logistical constraints that prohibit the collection of interview data in clinical trial settings. An acceptable alternative to the clinical interview is a system of carefully monitored self-administered assessments currently under way in some cooperative groups (e.g. SWOG). Standardized back-up methods for obtaining data (e.g. telephone interviews) can help avoid missing data. It is important to obtain the data via the back-up methods within a short time (1 week) of the scheduled data collection. Additionally, a mechanism for checking the quality of the retrieved data (e.g. comparison of patient responses to the same set of items obtained in the clinic vs. a telephone interview) should be implemented.

Quality control

The working group emphasized that QOL protocol design should minimize burden on the patient, staff, institution and cooperative group. Prior to submission for final approval, studies with a QOL end-point should be reviewed by all involved disciplines (including nurses and data managers) to identify and address potential implementation and quality control problems.

The group recommended that specialized quality control procedures should be instituted for the QOL components of a clinical trial. A staff member and a biostatistician should be designated by each cooperative group for QOL implementation and analysis, and each group should develop a policies and procedures manual for conducting QOL research within its unique structure. Each cooperative group must have adequate resources to conduct QOL research. These recommendations also apply to cancer centres that are conducting trials in multiple institutions.

Each institution should identify a site coordinator responsible for the QOL component of its studies and for training of new staff. Special training sessions should be conducted to educate data managers and nurses prior to activation of a multi-institutional QOL study. The training should include information about the QOL instrument, standardized administration and scoring guidelines, the assessment schedule and data submission procedures. 'Booster' training sessions should be scheduled to ensure conformity with study aims, to resolve unanticipated problems and to renew enthusiasm for the QOL study.

Statistical considerations

The Statistics Working Group addressed statistical considerations in QOL research at levels of study design, implementation, and analysis.

Design

The working group recommended that a small number (in most cases, three or less) of primary QOL hypotheses or research questions should be specified in the protocol and advised that the significance level for the statistical test of each primary hypothesis should be reduced to control the overall QOL significance level. Additional QOL questions or hypotheses should be regarded

as secondary and their analyses regarded as exploratory, requiring confirmation in subsequent trials. The working group emphasized that there are important statistical arguments for choosing the least complex QOL measure that will answer the study questions, and that it be administered a minimum number of times.

Anticipating difficulties with missing data in QOL research, working group members recommended that QOL measures and their associated administration schedules be chosen to minimize the chance of missing data. Furthermore, when several analysis strategies can address a QOL question, the anticipated number of unavailable cases should be an important factor in choosing from them. Power computations should include realistic estimates of the numbers of patients likely to be ineligible due to language or cultural difficulties, and lost to follow-up because of disease progression, toxicity, or death.

Clinical trials requiring large numbers of patients to answer treatment questions can provide a superabundance of power for QOL hypotheses; in this situation it may be possible to select a subset of the total patients in the treatment study to be followed on QOL end-points when an unbiased strategy for selecting the subset is planned. The statistical considerations section of QOL protocols should include information about the QOL issues that influenced the study design as well as a discussion of potential influence on the interpretation of the trial's results.

Conduct

To minimize the extent and adverse consequences of missing data, the working group stressed that all concerned with the trial be made aware of the importance of obtaining complete QOL data by expanding training programmes or increasing the number of data collection personnel at the institution level. They recommended that incoming QOL data forms should be edited as soon as they are received, and noted that additional data entry staff may be required at Cooperative Group data management centres to handle the increase in data quantity and the complexity of QOL assessment.

Analysis

The working group emphasized that analysis of QOL data must consider informative censoring (loss of data due to patient death, recurrence, or toxicity). Simple comparisons of mean scores are not appropriate when, for example, survival distributions are different for the treatment arms. Some strategies for analysing univariate end-points in the presence of informative censoring include:

1. performing survival analysis on time-to-event data generated by defining the event to be a QOL end-point of interest (e.g. decrease in QOL score below a certain value) or death, whichever comes first;
2. adopting the Q-TWiST strategy for analysis of QOL end-points;[22]
3. calculating the slope of QOL scores over time, with some low score assigned at time-points with informatively censored data;
4. calculating mean QOL values for treatment arms after assigning low QOL scores to patients with informatively censored data.

Potential biases should be assessed so that analyses can be adjusted if needed, and adjustments should be made for comorbid conditions. Most Cooperative Group statisticians have had relatively little experience of analysing multivariate outcome statistics in repeated measures situations with informative censoring of data. The working group recommended consultation with statistical colleagues skilled in these areas who can provide help with study design and analysis, and communication of results to clinicians and lay persons.

Conclusions

The NCI Workshop of Quality of Life Research in Cancer Clinical Trials represents an important step in fostering the incorporation of QOL end-points into cancer clinical trials. The recommendations summarized in this report represent the current best thinking of experts in multiple disciplines. They provide a guide for the systematic collection of QOL data by large numbers of investigators involved in clinical trials research. In this way, data can be collected, analysed, and reported in consistent ways across multiple studies. Such consistency will allow necessary comparisons among studies and various patient groups that provide a framework for evaluating QOL end-points in specific studies and for integrating QOL considerations in clinical treatment decisions.

At the conclusion of the workshop, preliminary recommendations were presented from each working group. Agreement on key issues was apparent:

1. quality of life is a multidimensional concept that should be evaluated by a set of instruments addressing broad areas of patient functioning as well as disease- and treatment-specific phenomena;
2. the patient is the best information source for most QOL questions;
3. more than one measurement time is necessary and selection of times shoul be trial-specific;
4. significant research questions should be distilled into a limited number of main hypotheses;
5. special training and skills in QOL research is necessary in both the participating institution and in the central trials office; and
6. statistical expertise is important early in trial design and groups may need consultation with statisticians who are experienced in analysing QOL data.

Finally, participants agreed that continued dialogue among scientists in many disciplines provides the best promise for the meaningful evaluation of QOL in clinical trials and its refinement for many aspects of clinical evaluation.

Although there was significant consensus on many QOL issues, some participants expressed sentiments that the exact role of QOL assessment in cancer clinical trials has not been established. Many workshop participants agreed that QOL should be as important as other end-points in specific cancer clinical trials, since joint consideration of all end-points can provide a more complete evaluation of cancer treatment in clinical trials. However, participants acknowledged that the use of QOL data in clinical decision-making will not routinely occur until the cooperative groups have had more experience in collecting data and have developed models for integrating medical and QOL information.

Cancer treatment clinical trials with traditional survival-based end-points have been used to assess differences in disease response for approximately 30 years. The inclusion of QOL end-points is a very recent phenomenon and has yet to gain wide acceptance among scientists and clinicians in general. The purpose of this workshop report is to encourage and facilitate integration of QOL issues into cancer treatment trials and to enhance the endorsement of QOL end-points as integral components in clinical decision-making.

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