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Original Paper

What has been Learned from Measuring Health-related Quality of Life in Clinical Oncology

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The measurement of health-related quality of life (HRQL) in oncology clinical trials has come of age. Most cooperative clinical trials groups as well as individual institutions have either been measuring, or are starting to measure, HRQL. Over the past decade, much has been learned about how to incorporate HRQL components into multicentre, randomised controlled (phase III) trials and how to collect the data with reasonably low levels of missing information. A selective review, focused primarily on phase III studies, shows that HRQL data are useful for deciding which treatment is preferable when survival rates are similar and for determining whether changes in HRQL, as compared with baseline levels, are related to a treatment or intervention. HRQL information is improving our knowledge of the effects of diseases and their treatments on the patient's ability to function and sense of well-being, and HRQL status is proving to be a more accurate predictor of survival than is performance status. Much more remains to be done, but it is apparent that the inclusion of HRQL in clinical trials has been informative and useful. The increasing frequency of HRQL assessment in clinical trials is evidence of the emergence of a patient-centred philosophy in clinical medicine which, in time, will modify the disease-oriented paradigm under which medical professionals have functioned for the past century. © **1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

THE PACE of research in health-related quality of life (HRQL) pertaining to clinical oncology has increased rapidly over the past 5–10 years. It is now possible to demonstrate that measurement of HRQL in clinical trials is useful for several reasons. The purpose of this brief review is to cite examples of such evidence. Emphasis will be placed on the results of multicentre, randomised, controlled clinical trials (phase III) since these are the most likely to provide level 1 evidence and, thus, are least likely to be proved to be erroneous on further study. Some informative evidence from phase II studies will also be mentioned. However, it has been necessary to be selective rather than comprehensive when choosing the examples, because of unavoidable constraints on the space available. There are at least three broad topic areas under which clinical lessons learned from HRQL research may be discussed. These are related to: (1) methodology, particularly that which pertains to measuring HRQL in multicentre clinical trials; (2) new and useful information derived from clinical trials incorporating HRQL assessment; and (3) what changes in HRQL scores mean to both the patients and to the investigators who are interpreting them. Finally, some examples of what we still need to learn will be listed.

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MEASURING HRQL IN MULTICENTRE CLINICAL TRIALS

Initially, there was concern that measuring HRQL in large, multicentre phase III trials would prove to be very difficult, if not impossible. However, the difficulties were found to stem primarily from practical issues, not scientific ones, and have been overcome in most centres. Meanwhile, we have learned several valuable lessons about the conduct of HRQL measurements in clinical trials.

Clinical trial protocol should incorporate the rationale and instructions for HRQL assessment

Protocols commonly contain all the necessary elements for conducting the trial. As such they also explain why, how and

when HRQL assessments will be completed, provide a justification of the instrument(s) which will be used and how the data will be analysed. Initially, HRQL assessment was added in companion studies, and this led to the perception that HRQL assessment was an add-on rather than an integral part of the trial (and thus less important) [1]. Today, HRQL components are usually a part of the main protocol. Recently, there has also been a move towards specifying the exact HRQL hypotheses in a trial and how the results will be interpreted.

A modular approach to questionnaire construction is desirable

This method has been adopted by many investigators; some self-rating questionnaires are designed, from the outset, to benefit from the advantages this approach offers [2, 3]. The modular approach allows the addition of brief, disease-specific or situation-specific modules [4] or checklists [5] to general condition-specific questionnaires (for example the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, FACT-3). The result is a more detailed assessment of the particular effects that a given disease (e.g. breast cancer) or therapy (e.g. chemotherapy) may have in the population of patients being studied than is possible when only a general questionnaire is used.

Using self-administered questionnaires is efficient and relatively inexpensive

Clinical trials may enrol hundreds or thousands of patients and involve many diverse, participating centres. At the Clinical Trials Group of the National Cancer Institute of Canada (NCIC), HRQL data are collected by clinical research associates (nurses and others) in the course of collecting the data for all parts of a clinical trial. Collecting the HRQL data takes approximately 15 min of additional time per patient. There is an increment in cost for data processing at the CTG central office, but this is a small fraction of the cost of overall data processing at the CTG (data not shown).

Data collection and processing may become less costly and more efficient with the advent of new tools such as touch-sensitive video monitors attached to small personal computers [6]. Although there is an initial capital cost for the participating centre, this may be smaller than paper and pencil methods when averaged out over many years. It would appear that such methodology will lead to less randomly missing data and should prove to be cost-effective at the data processing office, where processing and analysis should be less labour-intensive.

High completion (compliance) rates are achievable

They can be attributed to three factors: the training of data-collection personnel (both at the participating centres and the central office) at an early stage of trial development; the incorporation of clear instructions in the protocol, and the growing realisation that assessing HRQL is an important and integral part of a trial [7–11]. All of these have added to the motivation and enthusiasm of personnel at both the data collection and data processing centres. In some instances, e.g. the Clinical Trials Group of the NCIC [12] and at the NSABP [13] very high completion rates are achievable. In general, there has been a great improvement in the collection of HRQL data today, and many centres are achieving acceptable completion rates [14–16].

Time frames of items and the timing of assessments are dependent on the purposes of HRQL assessment

One study has suggested that time frames of more than one week for questionnaire items may fail to provide a clear distinction between trait and state [17]. Thus, some questionnaires that have open-ended time frames or time frames of 2 weeks or a month may not be relevant to the patient's state of HRQL. At the other end of the scale, the results of questionnaires that ask about this moment or the past day show random variations due to day-to-day instability.

The use of open-ended time frames that do not specify a particular time should be discouraged. There is no way of knowing whether the respondents had this moment, today, yesterday, last week, last month or last year in mind when they answered the questions. There is evidence that patients do recognise and respond to specific time frames. For example, in a recent NCIC Clinical Trials Group study of the efficacy of anti-emetics for the control of postchemotherapy nausea and vomiting, the responses to the QLQ-C30 clearly indicated that patients experienced more difficulties during the initial 3-day time period than they did over the entire 7-day period after chemotherapy [18]. This was in keeping with the incidence and severity of postchemotherapy nausea and vomiting as indicated independently in a daily diary.

The timing of HRQL assessments during the course of a clinical trial depends upon the purpose of assessment. All patients accrued to a trial should have a baseline assessment before randomisation and/or treatment begins [19], since responses after randomisation may be influenced by knowledge of group assignment. If such an assessment is not carried out, it will not be possible to compare HRQL scores obtained while on treatment or after the cessation of treatment (follow-up) with before-treatment scores. The baseline scores also allow a check of the treatment groups for balance between HRQL characteristics. The timing of on-treatment assessments will vary according to whether the prime purpose is to determine the impact of toxicity on HRQL, or to determine whether treatment is having an impact on disease-related HRQL. In the former, HRQL measurement should occur at the peak of expected toxicity-related effects; in the latter, it should be when toxicity is fading; and in the case of chemotherapy, just before the next treatment cycle is given. Both purposes may be achieved in the same trial. The frequency of follow-up HRQL assessments during follow-up and after treatment completion will depend upon the pattern of the disease trajectory. For example, in diseases with rapid recurrence rates and short survival times, assessments will need to be more frequent than if survival is measured in 2 or 3 years or more. Measurement of HRQL at the time of disease recurrence and/or progression is very important if the effects of increasing disease burden are to be known.

NEW AND USEFUL INFORMATION DERIVED FROM HRQL MEASUREMENT

The results of HRQL measurement have several clinical uses and the application of HRQL assessment is important under a variety of clinical settings such as symptom control (either disease- or treatment-related), cancers with poor prognosis, treatment arms with small survival differences and for supportive care intervention. What we have learned from HRQL assessment in a variety of circumstances will be reviewed with an emphasis on phase III trials.

Deciding whether one treatment (or intervention) is preferable to another being tested in phase III clinical trials may depend on the HRQL results when the survival or progression-free outcomes do not demonstrate significant differences between treatment groups. Many phase III studies are intended to show differences with respect to a primary outcome, for example, survival or progression-free interval, and HRQL outcomes are given as secondary outcomes of interest. Frequently, however, there are no convincing differences between groups in the primary outcomes. In such cases differences in HRQL outcomes—owing to differing toxicities of the treatments under study—become important.

HRQL was assessed by the Rotterdam Symptom Checklist and the Hospital Anxiety and Depression Scale in a study of 161 out of 280 chemotherapy-naïve patients with progressive and inoperable recurrent or metastatic colorectal cancer who were randomised to either 5-fluorouracil and leucovorin ± interferon α-2a [20]. There were no differences in tumour response, progression-free and overall rates between the two arms of the study. Nevertheless, during the first 12 weeks of treatment, twice as many patients who were receiving interferon reported deterioration of symptoms as did patients receiving 5-fluorouracil alone. Furthermore, those on interferon were less likely to report improvements in pretreatment scores for physical and psychological symptoms as compared with those not receiving interferon. Thus, interferon did not improve survival and had a deleterious impact on symptom scores. It should not be recommended for use in the same dosage and schedule as used in this study.

One of the earliest large studies showing HRQL benefits in one treatment arm over another was in metastatic breast cancer [21]. Women were randomised to receive cycles of chemotherapy either repeatedly every 3 weeks until disease progression or toxicity resulted (continuous therapy), or to receive three cycles of chemotherapy followed by no further chemotherapy until relapse or progression (intermittent therapy). A 9-item linear analogue self-assessment (LASA) scale was used to measure HRQL. The hypothesis being tested was that the intermittent therapy group would have better HRQL than the continuous therapy group because there would be less of a burden from treatment toxicity in the former. Contrary to these expectations, the continuous therapy group experienced improvement in 7 of the 9 LASA scales (with the exception of nausea and vomiting and pain) when compared with the intermittent therapy group. In addition, when all the data from the study were analysed, it became clear that survival in the continuous therapy arm was significantly longer than in the intermittent therapy arm. It was concluded that HRQL benefits were greater after continuous chemotherapy than intermittent therapy.

The value of post-treatment follow-up by general practitioners close to patients' homes, versus follow-up at major treatment centres, was studied in 286 treated, asymptomatic breast cancer patients in England [22]. The patients were randomised to either hospital or general practice follow-up. They completed the SF-36, EORTC QLQ-C30 and Hospital Anxiety and Depression Scale at baseline, part way through and at the end of 18 months of follow-up. There were no statistically significant differences in incidence of recurrence, time to confirmation of recurrence, or mortality between the two groups. There were also no differences in HRQL scores except that both groups had some deterioration at the time of recurrence. Thus, follow-up in large hospital treatment centres is probably not necessary for this group of patients.

HRQL measurement in several other clinical trials has also been helpful in determining whether one treatment is preferable to another, for example comparing two chemotherapy regimens in poor-prognosis small cell lung cancer [23, 24], chemotherapy versus supportive care in non-small cell lung cancer [25, 26], strontium-89 and local radiotherapy for bone metastases from hormone-resistant metastatic prostate cancer [27], hepatic artery infusion versus conventional palliation for liver metastases [28], and choice of anti-emetics for control of chemotherapy induced nausea and vomiting [29].

There has been controversy over the value of treatment with medroxyprogesterone for weight loss and anorexia in advanced stages of cancer. Recently, three phase III studies have included HRQL assessment since it is not certain if HRQL is improved if patients' appetite is better and weight loss arrested [30–32]. In all three studies, appetite improved and weight loss decreased, but in only one of them (a cross-over design study) was there improvement in physical activity, fatigue and well-being [33]. In the latter study, 30 of 55 patients preferred medroxyprogesterone, 15 preferred the placebo and 10 had no preference. However, the period of treatment before cross-over was short. There were several differences in design, numbers of enrolled patients, dose and schedule of medroxyprogesterone and the instruments used to measure HRQL between these three studies. Thus, it is still uncertain as to how beneficial medroxyprogesterone is in improving HRQL.

Determining whether a treatment (or intervention) improved HRQL over baseline is most likely to be helpful in phase II studies, but can also provide important information when applied to each of the treatment groups in phase III trials. For example, a clinical trial of mitoxantrone and prednisone versus prednisone alone in hormone-resistant metastatic prostate cancer was designed to achieve a reduction in pain without increased analgesic use as a primary endpoint, and change in HRQL as a secondary endpoint. Patients randomised to the prednisone only arm could have mitoxantrone added after 6 weeks if pain was not controlled by prednisone. Survival was expected to be the same in both arms. A total of 161 men were randomised, 81 to prednisone alone and 80 to mitoxantrone and prednisone. There was significant improvement in pain in a higher proportion of men in the mitoxantrone and prednisone group (29%) than in the prednisone group (12%) ($P = 0.01$) and it lasted more than twice as long (43 weeks) as in the prednisone alone group (18 weeks) ($P = 0.0001$). HRQL, as measured by the QLQ-C30 and a Prostate Cancer Quality of Life Index (POSQOLI), improved with respect to several domains. In addition, when the scores of patients in each arm during treatment were compared with their own baselines, HRQL scores for patients in both arms improved during the first 6 weeks, whereas after 6 weeks only the mitoxantrone plus prednisone arm continued to show improvement in several domains. Improvement in this group lasted longer than in the prednisone alone group. When mitoxantrone was added to prednisone after 6 weeks, there was improvement in pain, pain impact and relief, insomnia and global quality of life [34].

In another study designed to evaluate the potential benefits of treatment with oral temozolomide for recurrent anaplastic astrocytoma, HRQL, as measured by the QLQ-C30 and Brain Cancer Module (BCM20), improved over baseline in

three or more of seven preselected domains in 58% of patients. The highest proportion (82%) of patients with improvement was seen in those with either a complete or partial response, but 59% with stable disease also showed improvement [35]. Thus, comparing HRQL during treatment with baseline scores in phase II trials provides useful information and should be used more often than it is currently.

Describing the effects of a disease and/or its treatment has been a frequent application of HRQL measurement. Many clinical trials groups and others have been active in this area; only a few examples will be mentioned. They range from determining the concerns of women receiving chemotherapy for metastatic breast cancer [36] and of men with prostate cancer [37], the effects of adjuvant chemotherapy or hormonal therapy for breast cancer [38], the effects of recurrence in breast cancer [39], and the effects of postchemotherapy nausea and vomiting [39–41]. These and other studies are increasing our knowledge about patient-centred outcomes and, thereby, have the potential of improving communication between patients and healthcare professionals within the healthcare profession.

The provision of prognostic and predictive information by the results of HRQL measurement has been something of a surprise in oncology, and there is a growing indication that some of the standard prognostic indicators for survival, such as performance status, may be less informative than HRQL status. For example, in metastatic breast cancer [42], scores on the Spitzer Quality of Life index and the physical well-being scale of the LASA questionnaire replaced the ECOG performance scale in providing prognostic information for survival. The presence of liver metastases was the third variable remaining in the final model. The prognostic value of HRQL scores remained significant even after allowance for treatment group, performance status and tumour response. A similar pattern was found in patients with metastatic malignant melanoma [43]. Using another questionnaire, the QLQ-C30, in a group of patients with heterogeneous cancers (mainly breast, lung and ovarian), scores at or above the median global quality of life scores were associated with longer survival not only in patients with distant metastases but also in the entire population which included a significant proportion of patients with local-regional disease [44]. Similar results have been seen in another population with heterogeneous cancer diagnoses [45]. HRQL status before therapy has also been shown to be prognostic for survival in non-small cell lung cancer [46–48], and in colorectoral cancer [49].

Baseline HRQL status, before the beginning of treatment, may also have predictive value for how patients will fare on treatment. For example, in a study of patients with malignant melanoma who were at high risk for recurrence after the surgical resection of the primary lesion with or without regional lymph node dissection, on-treatment global quality of life (QLQ-C30) scores were predicted by: baseline global quality of life, the treatment group to which patients had been randomised, and whether they had stage I or II disease [50]. In a study of HT_3 receptor-antagonist anti-emetics with or without dexamethasone for the prevention of post-chemotherapy nausea and vomiting, it was found in multivariate analyses that the pre-chemotherapy scores for social functioning provided predictive information additional to that provided by emetogenicity of the chemotherapy, use of maintenance anti-emetics, gender and pre-existing nausea and vomiting. Patients with higher than the group median social functioning scores had less risk of postchemotherapy vomiting than did patients with lower than the median scores [51].

The ability to provide more accurate prognosis and predictive information will not only improve communication with patients and families but also will allow the design of treatment that is better suited to various patient populations. Such patient variables may, eventually, replace performance status as an eligibility requirement and/or stratification variable in clinical trials.

MEANINGFULNESS OF CHANGES IN HRQL SCORES

Small numerical changes (for example 5 points on a 0–100 scale) in HRQL scores may reach high levels of statistical significance (for example $P = 0.001$) when the number of subjects is large (several hundred). Clinicians who see such data often ask whether such an apparently small change is meaningful to either patients or to themselves. The relevance of changes in HRQL scores depends upon the perspective of the potential user of HRQL information. For example, small numerical changes affecting very large populations may be of interest to epidemiologists and policy-makers, whereas clinicians may require larger changes before considering alteration or cessation of a treatment. One approach to this dilemma has been to assess the amount of change that is perceptible and important to the subjects themselves. Clinicians should always be aware of such subjective significance, whether or not it will alter their management or treatment plans. Since patients are the source of information in a patient-centred approach, they provide the primary information with which all other information such as the results of physical examination, radiological and laboratory investigation should be integrated.

One of the possible approaches to obtaining subjective significance information in oncology is based on earlier work done in patients with asthma [52, 53]. Patients with metastatic breast or small cell lung cancer were asked to complete a Subjective Significance Questionnaire which asked about the perceived changes (ranging from ''much better'' through ''no change'' to ''much worse'' in a 7-item response categorical scale) over time in three functioning domains (physical, emotional, social) and global quality of life (QLQ-C30) [54]. It was found that patients who perceived ''a little'' change for the better or worse had changes of 5–10 in the above QLQ-C30 scale scores, those with ''moderate'' change had changes of 10–20 and those with ''very much'' change had changes >20. These results allow us to interpret changes in HRQL scores in terms of how much change is perceptible to patients and then to use this information in decision making. Another application of this information is to determine adequate sample sizes in phase II and III clinical trials.

Another approach examined the differences in mean scores between studies of patients with breast cancer in whom the QLQ-C30 had been used [55]. These ranged from adjuvant chemotherapy to chemotherapy for advanced disease. It was concluded that a change of 10 or more was probably clinically significant in that the difference between well-defined clinical groups was approximately 10 points on a 0–100 scale.

Thus, there is congruence between the above two approaches, and similar score differences have been suggested for other instruments [56]. Having a numerical value that appears to classify patients into various groups who are either experiencing benefit or deterioration in HRQL and linking it

Table 1. *What do we still need to learn?*

1.	The design and value of proxy ratings.
2.	Dealing, rationally, with missing data.
3.	Determining specificity and sensitivity of instruments.
4.	Integration of HRQL outcomes with biological outcomes.
5.	Finding a place for both utility and HRQL assessment in the same populations of patients.
6.	Description of HRQL scores and changes therein that are meaningful in individuals.
7.	Using HRQL results as the ''gold standard'' to which other outcomes are compared.
8.	Integration of HRQL measurement in individual patients into routine clinical practice.
9.	Integration of HRQL results with Q-TwiST, EuroQol and other utility measurements (time trade-off and standard gamble).

to classical clinical parameters such as stage of disease, will be of value in providing information to patients and to health-care professionals.

WHAT DO WE STILL NEED TO LEARN?

The short answer is—a great deal! Although great strides have been made in reaching the current position, and some examples of informative studies have been given above (with my apologies to others not mentioned), there are many contentions and challenging areas for work. Several examples are listed in Table 1; many others could be added. The list is not in any order of priority. Prioritisation of which of these needs is most important and should receive the majority of our attention is tempting, but unlikely to be helpful, since researchers are usually most successful when left free to pursue their own 'passions' and find other like-minded researchers for collaboration. Many of these issues are currently being researched [57–69], but more information is still required.

The past two decades of work have shown that HRQL measurement yields valuable clinical information. What was once viewed as the ideal model for clinical trials has changed irreversibly, and HRQL is now frequently an integral part of the design and conduct of trials. More importantly, HRQL assessment is changing the medical paradigm from a disease-centred approach to a patient-centred approach. Change is slow and takes years, if not generations, to accomplish, but the addition of a patient-centred philosophy to western medicine bodes well for future patients.

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