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Review

Quality, interpretation and presentation of European Organisation for Research and Treatment of Cancer quality of life questionnaire core 30 data in randomised controlled trials ☆

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ABSTRACT

Aim: To review reporting standard, presentation and interpretation for quality of life (QOL) outcomes in randomised controlled trials (RCTs) using the European Organisation for Research and Treatment of Cancer quality of life questionnaire core 30 (EORTC QLQ-C30).
Methods: Cancer RCTs reporting EORTC QLQ-C30 data were identified and reviewed against a reporting quality checklist. Interpretation/presentation methods for QOL data were also recorded.
Results: Eighty-two papers were reviewed. Seventy percent met criteria for high quality reporting; 94% reported mean scores; 84% presented results in tables/graphs; 80% reported *p*-values or statistical significance. Clinical significance was addressed in 38%. Where clinical significance was not addressed, reliance was usually on statistical significance to interpret the results.
Discussion: EORTC QLQ-C30 results are generally reported well, although it was common to rely on statistical significance alone for interpreting results. Whilst interpretation in terms of clinical significance has improved in recent years, there is still a lack of robust clinical interpretation of QOL results even in papers reported to a high standard.

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1. Introduction

While a considerable body of evidence about health-related quality of life (QOL) is accruing from cancer clinical trials, the extent of its impact on clinical practice is unclear. One of the barriers is poor communication of the clinical relevance of the results.[1] Reviews of prostate cancer[2] trials, breast cancer trials[3] and surgical oncology trials[4] report that 11%, 33% and 67% were able to inform clinical decision making. Part of this variability in these estimates arose because of differences in how the ability to inform decision making was measured. Regardless of this, it is clear that in order to inform clinical decision making, a QOL study needs to be designed robustly, reported adequately and interpreted appropriately.

The CONSORT statement[5,6] provides a checklist for reporting randomised controlled trials (RCTs). Efficace et al.[2] proposed a checklist specifically for evaluating QOL outcomes, listing criteria for reporting QOL outcomes and identifying the essential issues to be addressed in order for a trial to have reliable QOL outcomes. The checklist comprises 11 items grouped into four categories: conceptual, measurement, methodology and interpretation. The authors define a paper with high quality QOL outcomes as one that meets at least eight of the 11 criteria and these have to include three high-priority concerns ('baseline compliance reported', 'psychometric properties reported' and 'missing data documented').

Osoba et al.[7] and Guyatt and Schunemann[1] recommended that the presentation of QOL data include proportions of patients reporting a QOL benefit. They argued that this provides results meaningful to clinicians and therefore the results are more likely to influence clinical decision making. Osoba et al.[7] recommended 10% of the scale as the cut-off point to define improvement, with a stipulation that this degree of change should persist for a reasonable period. As an additional guide to interpretation Guyatt et al.[1,8] also showed how to generate the number needed to treat for one patient to benefit from therapy.

A number of different approaches have been used to develop interpretation for QOL scores. Some are entirely data driven and some use clinical anchors to interpret differences (over time or between groups). However, there are a number of shortfalls of the current methods and no single method has emerged as a standard for interpretation. Some are not specific to the QOL instrument being used and the validity of these is rarely tested for the specific instrument prior to relying on them for interpretation. It is also common to rely on statistical significance in order to interpret whether differences in scores are clinically significant. However, statistical significance does not necessarily imply a meaningful difference in a clinical context, particularly if the minimum clinically important difference in QOL was not determined *a priori* and used to determine the sample size for the trial.

Several authors provide a comprehensive overview of existing interpretation strategies.[9–12] Various methods have been used to aid interpretation of the European Organisation for Research and Treatment of Cancer quality of life questionnaire core 30 (EORTC QLQ-C30) specifically, which are of interest for our review. King[13] used 14 studies to estimate effect sizes (mean difference divided by standard deviation) using clinical anchors, and compared these to Cohen's guidelines[14] which propose small, medium and large effect sizes are 0.2, 0.5 and 0.8, respectively. King's estimates were about the same as Cohen's guidelines for physical, role and symptom scales, although for the global and psychosocial dimensions of the QLQ-C30, the estimates were smaller. Osoba et al.[15] provided estimates for small, moderate and large changes in scores from the EORTC QLQ-C30 based on retrospective global ratings of change, an approach based on individual patients rating the importance of changes in QOL. These were found to be 5–10 for a small difference, 10–20 for a moderate difference and >20 for a large difference, similar to those yielded by King's analysis.[13,16] This is the basis of Osoba et al.'s[15] recommendation of 10% of the scale as the cut-off point to define a clinically important change.

This review summarises the quality of QOL reporting for cancer RCTs using the EORTC QLQ-C30 and looks at the methods used to present and interpret the QOL data, particularly in papers that score well on the quality checklist. The interpretation methods used across studies are reviewed to assess how widely used current methods are, the extent to which clinical significance is addressed and whether there is a need for additional interpretation guidelines for the EORTC QLQ-C30. A summary of the methods of presenting the data is used to assess whether it is reported clearly and in a way that may be utilised by clinicians.

2. Methods

Potential sources of EORTC QLQ-C30 scores were identified by searching Cinahl, Medline, Embase, Medline-in-process and Psychinfo concurrently via the Ovid interface. The search terms were qlq c30, quality of life questionnaire c30, quality of life questionnaire c30, eortc qlq-c30, qlq c33 and qlq c30+3. References from the EORTC bibliography (http://groups.eortc.be/qol/documentation_bibliography.html) were also added. Duplicates were removed in Ovid or subsequently in Reference Manager.

Papers identified as cancer RCTs using the EORTC QLQ-C30 were reviewed and classified according to the minimum standard checklist for evaluating QOL outcomes.[2] If more than one paper was identified reporting QOL results from the same study then the study report was included rather than a paper reporting any wider issues, for example comparisons of statistical methods. Papers were defined as having high quality QOL outcomes if they met at least eight of the 11 criteria, including the three high-priority concerns ('baseline compliance reported', 'psychometric properties reported' and 'missing data documented'). If any items were evaluated as 'not applicable' then these items were excluded in the evaluation of high quality. K.C. reviewed the identified RCTs and classified them according to the checklist. A second reviewer (J.B.) independently classified a sample of the papers.

Methods used for presenting the data were recorded for all papers in terms of whether text, tables or graphs were used and the type of data presented (e.g. means, medians, effect size, *p*-values and proportion improved). For papers addressing clinical significance, the method of interpretation was recorded.

3. Results

3.1. Identification of papers

As of February 2006, 911 papers had been identified using the search strategy. Papers were included if they presented any data from the EORTC QLQ-C30, were cancer trials and were available in English. Ninety-two papers were identified as cancer RCTs reporting EORTC QLQ-C30 scores.

Ten papers were subsequently excluded from the review. Nine used the data to investigate different statistical techniques, conducted extra analyses or reported long-term follow-up rather than reporting the results from the RCT and the checklist does not seem applicable. Four of these papers also had a trial report for the same study which was included. One paper was excluded as it was a pilot study with a randomised design exploring the feasibility of QOL assessment in a further RCT. Eighty-two RCTs were therefore included in this review.

3.2. Study characteristics

Table 1 shows the characteristics of the 82 studies. Sample sizes ranged from 31 to 1491 patients, with a mean of 272. In total, the papers reported on more than 22,000 patients. The majority of studies involved patients with breast cancer (21%), mixed cancer sites (18%), lung cancer (17%) and colorectal cancer (11%). No other cancer sites represented more than 10% of the sample. Patients were from a wide range of countries, although the majority were European (55 (67%)).

Table 1 – Study characteristics

	Number of studies (%)
Design	
Phase II	7 (9%)
Phase III	25 (30%)
Not specified	50 (61%)
QOL end-point	
Primary	12 (14%)
Secondary	67 (82%)
Not specified	3 (4%)
Number of patients	
Mean (standard deviation)	272 (239.1)
Median (range)	208 (31–1491)
Region/Country where study conducted	
Europe	
Multi-country	6 (7%)
Austria	1 (1%)
Belgium	1 (1%)
Denmark	2 (2%)
France	4 (5%)
Germany	3 (4%)
Italy	6 (7%)
Netherlands	6 (7%)
Norway	6 (7%)
Spain	1 (1%)
Sweden	8 (10%)
UK	11 (13%)
International	
Multi-country	10 (12%)
Australia	2 (2%)
US/Canada	15 (18%)
Cancer site	
Breast	17 (21%)
Mixed sites	15 (18%)
Lung	14 (17%)
Colorectal	9 (11%)
Leukaemia/lymphoma	7 (9%)
Prostate	7 (9%)
Brain	3 (4%)
Oesophageal/stomach	3 (4%)
Gastro-intestinal	2 (2%)
Malignant melanoma	2 (2%)
Head and neck	1 (1%)
Ovarian	1 (1%)
Testicular	1 (1%)

3.3. Quality of reporting

Table 2 shows the level of QOL reporting according to the checklist. As the EORTC QLQ-C30 is a generic instrument designed for all cancer patients and was previously validated in cancer patients, the measurement criteria in the checklist were satisfied for all papers. The main failings of studies were no rationale for using the questionnaire, no details of the administration and not addressing clinical significance of results. The majority of papers (>90%) reported the hypothesis (or stated QOL as an end-point), stated the timing of assessments and included some general presentation of the results. Fifty-seven (70%) papers met the criteria for high quality. Reporting was of slightly higher quality in the 41 papers whose primary end-point was QOL or which reported QOL as the main purpose of the paper rather than reporting the overall results of the trial. Thirty-five (85%) of these papers met the criteria for high quality. However, despite QOL results being the main aim of these papers, still only 22 (54%) addressed clinical significance.

3.4. Presentation of QOL data

Thirty-two (39%) papers used a combination of tables and graphs to summarise the data. Thirteen (16%) used graphical summaries alone and 24 (29%) used tabular displays. Thirteen (16%) reported QOL results in the text with no graphical or tabular summary. A higher proportion 27 (47%) of the papers meeting the standard of high quality reporting used both graphs and tables to display the results.

Fifteen (18%) of papers report the percentage of patients with improved QOL scores as recommended by Osoba et al.[7] and Guyatt et al.[8] and this percentage is similar in the subgroup of high quality papers (12 (21%)). The definition of 'improvement' varied between the reports however, with some papers using >10 points as an improvement (with or without a minimum length of time for this to be sustained) and other papers regarding as any increase in scores as an improvement. No papers reported the number of patients needed to treat in order for one patient to benefit.

The majority of papers reported the mean QOL scores (77 (94%)) and 56 of these also indicated the variation around

Table 2 – Level of reporting according to the minimum standard checklist for evaluating quality of life (QOL) outcomes in cancer clinical trials

QOL issue	All randomised controlled trials (RCTs) (N = 82)	High quality (N = 57)	QOL as primary outcome/aim (N = 41)
Conceptual			
A priori hypothesis stated	77 (96%[a])	57 (100%[a])	40 (98%)
Rationale for instrument reported	25 (30%)	19 (33%)	18 (44%)
Measurement			
Psychometric properties reported	82 (100%)	57 (100%)	41 (100%)
Cultural validity verified	82 (100%)	57 (100%)	41 (100%)
Adequacy of domains covered	82 (100%)	57 (100%)	41 (100%)
Methodology			
Instrument administration reported	39 (48%)	33 (58%)	29 (71%)
Baseline compliance reported	62 (76%)	57 (100%)	36 (88%)
Timing of assessments documented	82 (100%)	57 (100%)	41 (100%)
Missing data documented	64 (78%)	57 (100%)	38 (93%)
Interpretation			
Clinical significance addressed	31 (38%)	25 (44%)	22 (54%)
Presentation of results in general	78 (95%)	56 (98%)	41 (100%)

a N/A for two studies.

the mean (standard deviation, standard error or a confidence interval). Sixty-six (80%) papers reported *p*-values or an indication of the level of statistical significance of QOL differences. Eleven papers reported medians and six papers reported both means and medians. Three papers reported effect sizes. The summary measures used in the subgroup of high quality papers were very similar to the full set of papers.

3.5. *Clinical significance and interpretation of results*

Clinical significance was addressed in 31 (38%) papers (Table 3) and this was only marginally higher (44%) in the high quality papers. The most common method used was a change of >10 points to define a clinically relevant change (18 papers, 22% of all papers). This was usually referenced using Osoba et al.,[15] in which a change of 10–20 is 'moderate'. However, one paper referred to differences of 10 or more as large. Four other papers defined clinically meaningful change as any change from baseline, 5–10 points (not referenced), 8–10 points[17] and 10–15 points,[18] respectively, while three further papers defined different sizes as clinically meaningful depending on the scale. Two of these use a method used for the Uppsala questionnaire[19] and the other uses King's[16] estimates based on evidence-based effect sizes. Other methods of interpretation used were reference populations or norms (three papers) and effect sizes as defined by Cohen[14] or Osoba[15] (three papers). Two papers defined some results as clinically meaningful without defining the criteria used.

Clinical significance was not addressed in 51 (62%) papers; four of these papers contained no discussion of QOL differences and 47 (57% of all papers) relied mainly on statistical significance (or lack of statistical significance) in their discussion of whether there were changes in QOL. These studies ranged in size from 48 to 791 patients (median 205 patients)

Table 3 – Methods of interpretation

Clinical significance addressed	Methods used to assess size of QOL differences between groups or changes over time	Number of papers (% of total)
Yes[a]		31 (38%)
	Use of specified difference in score as clinically relevant:	
	>10 points	18 (22%)
	5–10 points	1 (1%)
	8–10 points	1 (1%)
	10–15 points	1 (1%)
	Subscale-specific	3 (4%)
	Comparison with reference population/norms	3 (4%)
	Effect sizes (<0.2 no change, 0.2–0.5 small, 0.5–0.8 moderate, >0.8 large)	3 (4%)
	Criteria for clinical significance undefined	2 (2%)
	Stable or improved from baseline defined as clinically relevant	1 (1%)
No		51 (62%)
	Statistical significance	47 (57%)
	No discussion of QOL differences	4 (5%)

a Multiple methods used for four papers, therefore numbers do not add to 31.

and it is likely that at least some of these, generally large, studies will have found statistical differences in QOL that were too small to be of clinical relevance. For example, the largest study found that differences in scores as small as 2.1 (physical and social functioning subscales) were statistically significant.

4. Conclusion/discussion

This review shows that RCTs using the EORTC QLQ-C30 report the QOL data to a high standard, with 70% meeting the criteria for high quality QOL outcomes. Similar reviews of QOL reporting in cancer trials have been carried out in prostate cancer,[2,20] advanced breast cancer,[21] colorectal cancer,[22] non-small-cell lung cancer[23] and, more recently, in complementary and alternative oncology medicine.[24] These reviews generally show a lower standard of reporting, in particular the reporting of clinical significance ranged from 12% to 21% compared to the 38% seen here. This may be due to the earlier time period of studies included in previous reviews. Also, as our review was limited to studies using the EORTC QLQ-C30, three of the criteria were automatically met as the questionnaire is well validated, with psychometric properties and cultural validity reported, and a range of QOL domains covered.

The main failings of the papers according to the checklist were not reporting the rationale for using the EORTC QLQ-C30 or the method of administration. These issues also arose in the previous reviews.[2,20–24] In our review, this could be because the EORTC QLQ-C30 is well validated in cancer patients and authors referencing the validity of the questionnaire may regard this, implicitly, as their rationale for using it but without explicitly stating this they fail on this criterion. A more appropriate consideration regarding rationale for the chosen instrument may be whether QOL is relevant in the study at all, which QOL dimensions are important and therefore is the instrument chosen appropriate? The method of administration was only regarded as reported if the setting, e.g. questionnaires given in clinic or posted to patients at home, was reported. It was common to report that the questionnaire was self-reported but this was not considered sufficient to fulfil the criterion. An important aspect of administration is whether the assessments were before or after the clinical consultation, whether the results were confidential or whether they were used as part of the patient's management, which are details unlikely to be included in a paper.

A further finding of this review is that, perhaps not surprisingly, the RCTs meeting more of the criteria on the checklist were those with QOL stated as the primary outcome or reporting QOL as the main purpose of the paper. Papers reporting the full results of a clinical trial with QOL as a secondary outcome will have far less space to report the QOL results and therefore are likely to fail on more of the criteria. Papers reporting QOL alongside the main trial results are important if QOL is to have an impact on clinical decisions and on the results of clinical trials. Therefore, it is unfair to penalise these papers because of the level of reporting of the QOL data when space in the manuscript will be limited. It is possible that there is a need for an even more minimal checklist in order that QOL results can be reported to a high standard despite limited space in the manuscript, otherwise such checklists may encourage separate reporting of the QOL results from the main trial results and could ultimately limit the overall impact of QOL data.

The majority of papers use a table or graph to display QOL results, which is encouraging as this is a good way of presenting QOL results from a number of subscales in a concise and clear way. Papers meeting the criteria for a high standard of reporting according to the checklist were more likely to use both tables and graphs to display the results. Surprisingly, three (5%) papers which met the criteria for high quality reporting used text alone to report QOL results. These papers reported *p*-values for any significant results but little else. Although the checklist contains 'presentation of the results in general' as a criterion, this is based on whether the authors discuss the QOL outcomes giving any comments regardless of the results. This criterion can, therefore, be met by papers reporting very little QOL data resulting in them being classified as 'high quality' when they are clearly uninformative with regards to the QOL results. Eighteen percent of papers presented percentage of patients with improved/deteriorated/stable scores but the definition of an improvement varied. This is of concern, since papers which use any change in score as a 'clinically important change' and/or fail to specify a minimum time period will tend to overestimate the degree of change and therefore the impact of treatment.

Less than half of the papers addressed the clinical significance of QOL results. It is of some concern that half of the papers relied on statistical significance, or lack of statistical significance, rather than interpreting the magnitude of change *per se*. Whilst the minimum standard checklist for evaluating QOL outcomes[2] classes papers according to the robustness of QOL outcomes it is deficient in that it does not assess the appropriateness of the statistical analysis which is key to the QOL results. Given the apparent reliance on statistical significance in order to interpret results, it is important that complex issues such as multiple outcomes, missing data and longitudinal data are dealt with appropriately in the statistical analysis and reported in suitable detail.

Where clinical interpretation was attempted, simple definitions were most common; generally >10 points was regarded as clinically significant. Osoba's work, however, was based on breast and lung cancer patients and the results may not be generalisable to other patient populations. The study was also carried out for specific subscales (global, physical, emotional and social functioning) and therefore these differences may not be applicable to other subscales. Although more detailed guidelines for interpretation are available for the EORTC QLQ-C30[13,16] a universal rule regardless of the subscale may be more attractive due to space limitations in manuscripts and the need for results to be easily understood, but if there are real differences in how to interpret the different subscales, then it is important to take this into account. A universal rule applied to all cancer sites and subscales may miss important differences in QOL or over-interpret differences that actually are of little clinical significance.

This review has highlighted that there are a number of methods of presentation and interpretation of QOL data available for use but that these are being applied regardless of their relevance to the specific QOL instrument or scale and

could therefore be misleading. For accurate interpretation of QOL results, there is also a need to incorporate the adequacy of the statistical analyses in any assessment of the robustness of QOL outcomes. There is a need for further guidelines for the presentation and interpretation of results from the EORTC QLQ-C30 – and other QOL instruments – thus improving the ability of RCTs to influence treatment decisions.

Conflict of interest statement

None declared.

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