Quality of Life (QOL) Results from Clinical Trials

(A primer for New Investigators)

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Queen’s Cancer Research Institute
Cancer Care and Epidemiology Division

Quality of Life Committee Co-Chair
NCIC Clinical Trials Group
Overview: Objectives

• Be familiar with the NCIC CTG structure re: QOL Committee

• Understand the nature of QOL data
  • Philosophy
  • Source Questionnaires
  • Data collection

• Become familiar with Scale/instrument interpretation issues
  • Reliability, validity, responsiveness

• Become familiar with clinical utility of QOL data

• New Directions of CCTG QOL Committee
Brief History

1979: NCIC (now CCSRI) decides to have a formal cooperative clinical trials group

1980: NCIC Clinical Trials Group established at Queen’s University (Dr. Pater)

1982: First Phase III Trial with QOL (BR.5)

1989: Establishment of a QOL committee (Dr. J. Pater)
   • Dr. David Osoba and Dr. Benny Zee
   • Dr. Andrea Bezjak
   • Drs. Jolie Ringash/Michael Brundage
Historical Example: NCIC BR.5


By Edna Rapp, Joseph L. Pater, Andrew Willan, Yvon Cormier, Nevin Murray, William K. Evans, D. Ian Hodson, David A. Clark, Ronald Feld, Andrew M. Arnold, Joseph I. Ayoub, Kenneth S. Wilson, Jean Latreille, Rafel F. Wierzbicki, and Donald P. Hill

*Journal of Clinical Oncology, Vol 6, No 4 (April), 1988: pp 633-641*
BR.5 QOL

• Shortly after the trial started, centres were asked to participate in the QOL component of the trial
  – They were given the option to use both Sickness Impact Profile (SIP) and Functional Living Index – Cancer (FLIC) questionnaires, only FLIC, or not participate
• Almost all centres agreed to participate and most chose to use both instruments
After BR.5

• Low compliance (<25%) with QOL collection in BR.5 was due to many factors

• It was evident that adequate QOL data collection would not just happen
Some High-Impact Trials

• **CE.6** - Temozolomide and Short-Course Radiation in the Treatment of Glioblastoma Multiforme in Elderly Patients. *J Clin Oncol*

• **MA.17R** - Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years. *N Engl J Med*

• **MA.20** - Regional Nodal Irradiation in Early-Stage Breast Cancer. *N Engl J Med*

• **HD.6** - ABVD Alone versus Radiation-Based Therapy in Limited-Stage Hodgkin's Lymphoma. *N Engl J Med*

• **SC.23** - Dexamethasone in the prophylaxis of radiation-induced pain flare after palliative radiotherapy for bone metastases. *Lancet Oncol*

• **PR.7** - Intermittent Androgen Suppression for Rising PSA Level after Radiotherapy. *N Engl J Med*
What is QOL?

**Overall QOL?**

- “the goodness of life” or person’s overall well-being
- Influenced by:
  - patient’s perspective (subjectivity)
  - multi-dimensional (many dimensions of life experience relating to specific “domains”)  
  - Sociocultural context (culture and value systems)

**Health-related QOL?**

- As related to health (not housing, income, environment, etc)
What is health-related QOL?

• “Optimum levels of physical, role and social function, including relationships, and the perception of health, fitness, life satisfaction and well-being.”

Bowling, 1995
• EORTC QLQ-C30+3 Instrument
• Domain: Global quality of life

How would you rate your overall health during the past week?
1 2 3 4 5 6 7
Very poor Excellent

How would you rate your overall quality of life during the past week?
1 2 3 4 5 6 7
Very poor Excellent
<table>
<thead>
<tr>
<th>Quality of Life Data</th>
<th>Toxicity Data / Performance Status</th>
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</thead>
<tbody>
<tr>
<td>Self-reported</td>
<td>HCP/RA-reported</td>
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<tr>
<td>Response-shift?</td>
<td>Rater issues?</td>
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<tr>
<td>Multi-dimensional</td>
<td>Correct dimensions?</td>
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<tr>
<td>Tabulated items</td>
<td>Sufficient?</td>
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<tr>
<td>More complex/Unfamiliar</td>
<td>Less complex/More familiar</td>
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</table>
HRQL vs. Toxicity

Savage et al, ASCO 2005
Measuring QOL
ARTICLE

The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology


Aaronson, JNCI 1993
<table>
<thead>
<tr>
<th>Items*</th>
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<tbody>
<tr>
<td></td>
<td>Physical</td>
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<td>1-5</td>
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<td>29, 30</td>
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<td>Fatigue</td>
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<td>10, 12, 18</td>
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<td>14, 15</td>
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<td>Dyspnea</td>
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<td>Financial impact</td>
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<td>28</td>
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</tbody>
</table>

- Do you have any trouble doing strenuous activities like carrying a heavy shopping...
- Do you have any trouble taking a long walk
- Do you have to stay in bed or a chair for most of the day
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- Do you have any trouble concentrating on things, like reading a newspaper or watching television?
- Have you had difficulty remembering things?
• Has your physical condition or medical treatments interfered with your family life?

• Has your physical condition or medical treatments interfered with your social activities?

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• **Reliability:** Does the questionnaire produce reproducible results?
  
  • Internal – e.g. Chronbach’s alpha
  • Test-retest – repeatability
  • Longer questionnaires generally with higher reliability

• **Validity:** Does the questionnaire *really* measure QOL?
  
  • Face / Content
  • Construct
Why QOL is important

• Different treatments have similar survival
• Treatment improves survival but has severe side effects
• Treatment has no effect on survival but may improve QOL
• Cure is not possible
• Chronic diseases with high survival rates
Clinical Example: Symptomatic Locally Advanced NSCLC (SC.15)

- Disease too extensive for curative therapy
- With or without metastases beyond the thorax
- 2000 cGy in 5 fractions vs 1000 cGy in 1 fraction
Survival according to treatment

Single 18 weeks
Fractionated 26 weeks
p = 0.0492
QLQ-C30 Change Scores (Baseline score to 5 weeks)

- Five Fractions (N=89)
- Single Fraction (N=87)

* $p < 0.05$
Treatment Intent: Improve QOL

QOL Score

Before  
During  
After  

Mean 60.8  
Mean 71.2

Mean 60.8  
Mean 71.2
Treatment Intent: Improve QOL

QOL Score

Before | During | After
QLQ-C30 Change Scores (Baseline score to 5 weeks)

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Before | During | After
---|---|---
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Mean 71.2
Treatment Intent: Improve QOL

QOL Score

Before
During
After
Treatment Intent: Improve QOL

- QOL Score
- Before
- During
- After
Treatment Intent: Improve QOL

QOL Score

Before During After
Treatment Intent: Improve QOL

QOL Score

Before During After
Treatment Intent: Improve QOL

Percent of Patients

After

0%

100%

"Improved"

"Unchanged"

"Worse"
Treatment Intent: Improve QOL

Percent of Patients

- "Improved"
- "Unchanged"
- "Worse"
Interpretation of Changes in Health-related Quality of Life
The Remarkable Universality of Half a Standard Deviation

Geoffrey R. Norman, PhD,* Jeff A. Sloan, PhD,† and Kathleen W. Wyrwich, PhD‡

BACKGROUND. A number of studies have computed the minimally important difference (MID) for health-related quality of life instruments.

OBJECTIVE. To determine whether there is consistency in the magnitude of MID estimates from different instruments.

METHODS. We conducted a systematic review of the literature to identify studies that computed an MID and contained sufficient information to compute an effect size (ES). Thirty-eight studies fulfilled the criteria, resulting in 62 ESs.

RESULTS. For all but 6 studies, the MID estimates were close to one half a SD (mean = 0.495, SD = 0.155). There was no consistent relationship with factors such as disease-specific or generic instrument or the number of response options. Negative changes were not associated with larger ESs. Population-based estimation procedures and brief follow-up were associated with smaller ESs, and acute conditions with larger ESs. An explanation for this consistency is that research in psychology has shown that the limit of people’s ability to discriminate over a wide range of tasks is approximately 1 part in 7, which is very close to half a SD.

CONCLUSION. In most circumstances, the threshold of discrimination for changes in health-related quality of life for chronic diseases appears to be approximately half a SD.

Key words: Quality of life; threshold; interpretation; MID; effect size. (Med Care 2003; 41:582–592)
Interpreting the Significance of Changes in Health-Related Quality-of-Life Scores

By David Osoba, George Rodrigues, James Myles, Benny Zee, and Joseph Pater

Purpose: To determine the significance to patients of changes in health-related quality-of-life (HLQ) scores assessed by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30).

Patients and Methods: A subjective significance questionnaire (SSQ), which asks patients about perceived changes in physical, emotional, and social functioning and in global quality of life (global QL) and the QLQ-C30 were completed by patients who received chemotherapy for either breast cancer or small-cell lung cancer (SCLC). In the SSQ, patients rated their perception of change since the last time they completed the QLQ-C30 using a 7-category scale that ranged from "much worse" through "no change" to "much better." For each category of change in the SSQ, the corresponding differences were calculated in QLQ-C30 mean scores and effect sizes were determined.

Results: For patients who indicated "no change" in the SSQ, the mean change in scores in the corresponding QLQ-C30 domains was not significantly different from 0. For patients who indicated "a little" change either for better or for worse, the mean change in scores was about 5 to 10; for "moderate" change, about 10 to 20; and for "very much" change, greater than 20. Effect sizes increased in concordance with increasing changes in SSQ ratings and QLQ-C30 scores.

Conclusion: The significance of changes in QLQ-C30 scores can be interpreted in terms of small, moderate, or large changes in quality of life as reported by patients in the SSQ. The magnitude of these changes also can be used to calculate the sample sizes required to detect a specified change in clinical trials.

What “difference” is clinically significant?

E.g.: Osoba et al, JCO 1998
- Minimal change: 5-10 points
- Moderate change: 10-20 points
- Large change: >20 points
Cumulative Distribution Function

Physical Function:
Cumulative Percent of Patients Changed at 9 months

Percent of Patients Changed
“Cut-point” for change at 9 months:
Improved at 9 months
Worsened at 9 months

p=0.03
The biggest problem with analyzing QOL information from clinical trials is **missing data**
- are pts whose QOL data are missing different from pts supplying QOL data?
- Or is QOL data missing because pts are sicker than those providing info?

Analysis can try to account for missing data but it is best trying to prevent missing data
Treatment Intent: Improve QOL

- Before
- During
- After

QOL Score

Before | During | After
Treatment Intent: Improve QOL
Treatment Intent: Improve QOL

QOL Score

Before | During | After

0 | 100
1. What are the characteristics of the population of interest?
2. Is the QOL questionnaire relevant, reliable, valid, and responsive to change?
3. Are the timing and frequency of assessment adequate?
4. Is the study adequately powered?
5. How are multiple QOL outcomes addressed in the analyses?
6. How are multiple time points handled?
7. Can alternative explanations account for observed scores?
8. Are missing data handled adequately?
9. Is an observed survival difference accounted for?
10. Was response shift (change in patient’s perspective of QOL) taken into account?
11. Is clinical significance addressed?

Spranger et al, Mayo Clin Proc, 2002; 77: 561-571
Added value of health-related quality of life measurement in cancer clinical trials: the experience of the NCIC CTG


Heather-Jane Au†, Jolie Ringash, Michael Brundage, Michael Palmer, Harriet Richardson and Ralph M Meyer; on behalf of the NCIC CTG Quality of Life Committee

†Author for correspondence

Health-related quality-of-life (HRQoL) data are often included in Phase III clinical trials. We evaluate and classify the value added to Phase III trials by HRQoL outcomes, through a review of the National Cancer Institute of Canada Clinical Trials Group clinical trials experience within various cancer patient populations. HRQoL may add value in a variety of ways, including the provision of data that may contrast with or may support the primary study outcome; or that assess a unique perspective or subgroup, not addressed by the primary outcome. Thus, HRQoL data may change the study's interpretation. Even in situations where HRQoL measurement does not alter the clinical interpretation of a trial, important methodologic advances can be made. A classification of the added value of HRQoL information is provided, which may assist in choosing trials for which measurement of HRQoL outcomes will be beneficial.
Top Ten Examples
10. HRQL results of interest for descriptive purposes

- Head and neck cancer patients
- Women five-years post breast cancer treatment
9. HRQL as a prognostic factor

- Repeatedly illustrated in multiple study contexts
- Stratification / statistical adjustment
8. HRQL in Phase I/II trials

- Detect toxicity or response
- Estimate effect size for phase III
- “Pick the winner”
7. HRQL results that support primary outcome

- Palliative chest radiotherapy for locally advanced lung cancer
- Improvement in nausea and vomiting with effective anti-emetics
6. HRQL results that “conflict” with primary outcome

- Pre-operative vs. post-operative radiotherapy for limb soft-tissue sarcoma
- Wound healing – post-op favoured
- Long-term functioning – pre-op favoured
5. Quantification of treatment-related toxicity

- Adjuvant chemotherapy for early-stage lung cancer
- Significant survival difference
- Some impact of treatment on HRQL
- Recovery of HRQL after treatment
“Added Value”

4. Demonstration of reduced treatment-related toxicity

- Palliative chemotherapy for advanced-stage lung cancer
- No significant difference in global HRQL
- Differences seen in treatment tolerance
3. Measurement of response to treatment

- Mitoxantrone and prednisone for patients with metastatic prostate cancer
  - No significant survival difference
  - Improved symptoms and HRQL
“Added Value”

2. Industry / FDA

- Claims for new drug labelling
2. Industry / FDA

- Claims for new drug labelling

Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact Laurie Burke (CDER) 301-796-0700, Tom Stifano (CBER) 301-827-6190, or Sahar Dawisha (CDRH) 301-594-3090.
“Added Value”

1. Patient Preferences

- Medical decision making
- Other elements of patient education
Preference Ratings

Less useful or helpful

More useful or helpful

0 2 4 6 8 10

Survival Information
Acute Toxicity
Late Toxicity
Global HRQL
Physical Functioning
Emotional Functioning
Cognitive Functioning

Brundage et al, ISOQOL 2005
Some High-Impact Trials

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Future Directions

• PROMIS initiative
• E-PROs
• PRO-CTCAE
Normed Line Graphs

Patient’s Functioning

- **Physical**
  - (line going up means better able to do physical activities)
  - Better than average
  - Average for U.S. adults
  - Worse than average
  - Treatment “X”
  - Treatment “Y”

- **Emotional**
  - (line going up means better emotional well-being)
  - Better than average
  - Average for U.S. adults
  - Worse than average
  - Treatment “X”
  - Treatment “Y”

Patient’s Symptoms

- **Fatigue**
  - (line going up means more fatigue)
  - More than average
  - Average for U.S. adults
  - Less than average
  - Treatment “X”
  - Treatment “Y”

- **Pain**
  - (line going up means more pain)
  - More than average
  - Average for U.S. adults
  - Less than average
  - Treatment “X”
  - Treatment “Y”
E-PROs

“How do you feel today?”
-lousy
-great
PRO-CTCAE

- Subjective toxicity ratings directly from the patient
- Each item (e.g. nausea) with three measures:
  - Frequency
  - Severity
  - Bother
- Ready for “prime-time”
Some Useful Tools

- ISOQOL User’s Guides
  - [www.isoqol.org](http://www.isoqol.org)

- Spirit Project (...coming soon!)
  - Protocol writing for HQOL
  - [www.spirit-statement.org](http://www.spirit-statement.org)

- Consort Project
  - Trial Reporting for HQOL
  - [www.consort-statement.org](http://www.consort-statement.org)