Quality of Life Assessment in Cancer Research

Karen Doyle
Cancer Research UK
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What is Quality of Life?
• An individual’s total wellbeing
  • All emotional, social, and physical aspects of the individual’s life
• In healthcare often referred to as Health Related Quality of Life
  • Often multidimensional
  • Physical, social, emotional, cognitive, work or role related, possibly spiritual aspects
  • Considers the impact on an individual’s wellbeing over time by a disease, a disability, or a disorder

Rapidly growing area…
• Now established area of outcomes research and health technology assessment
• Evaluating cost effectiveness and benefit of new treatments to determine whether associated increases in expenditure is justified

Measuring QoL
You can chose from:
• Generic instruments (e.g. SF-36, Short-Form with 36 questions)
  OR
• Disease or Disorder specific instruments (e.g. the LC-13 Lung Cancer module from the EORTC Quality of Life questionnaire library, or the HADS Hospital Anxiety and Depression Scale).

Translating what makes Quality of Life is complex…
Measuring Quality of Life in Cancer Patients

Mei Calvert, PhD
MRC Midlands Hub Trials Methodology Research,
NIHR West Midlands Research Design Service

Overview
- What are we trying to assess and why?
- Choosing a questionnaire
- Examples
- Where to seek advice

Health-Related Quality of Life

In a clinical setting assessment of quality of life usually concentrates on health-related quality of life (QoL): ‘the way in which physical, emotional and social well-being are affected by a disease or its treatment.’

Fairclough, DL. Design and Analysis of Quality of Life studies in Clinical Trials. 2002. Chapman & Hall/CRC

Why assess QoL in cancer trials?
- Inform future patient choice and consent.
- Particularly when minimal differences in survival or treatments have different toxicities.

Ria Vanden Eynde: Diagnosis

Why assess QoL in cancer trials?
- American Society of Clinical Oncology Statement: Toward Individualized Care for Patients With Advanced Cancer

Patients with advanced incurable cancer face complex physical, psychological, social, and spiritual consequences of disease and its treatment. Care for these patients should include an individualized assessment of the patient’s needs, goals, and preferences throughout the course of illness. Consideration of disease-directed therapy, symptom management, and attention to quality of life are important aspects of quality cancer care. However, emerging evidence suggests that, too often, realistic conversations about prognosis, the potential benefits and limitations of disease-directed therapy, and the potential role of palliative care, either in conjunction with or as an alternative to disease-directed therapy, occur late in the course of illness or not at all. J Clin Oncol 28, 2011

Curative treatments

Cancer patients: We refused to die, now help us cope with living Scotsman, 31/01/2011
- Evaluation of long-term emotional, psychological and physical problems
Why assess QoL in cancer trials?

- Prognostic significance:

  In 36 of 39 studies (N = 13,874), at least one PRO was significantly associated with survival (P < .05) in multivariate analysis, with varying effect sizes. Results indicated that PROs provide distinct prognostic information beyond standard clinical measures in cancer clinical trials. Gotay CC, Kawamoto CT, Bottomley A, Efficace F. The Prognostic Significance of Patient-Reported Outcomes in Cancer Clinical Trials. J Clin Oncol 2008; 26(8): 1355-1363.

Why assess QoL in cancer trials?

- Health utilities may be used to:
  - Generate quality adjusted life years
  - Inform cost-effectiveness analyses
  - Inform health policy (e.g. NICE appraisal)

Trial design issues:

Need to consider:
- Rationale for QoL assessment
- Rationale for choice of instrument.
  - When, how, and where data will be collected.
  - How missing data will be avoided and dealt with.
  - How data will be analysed & results interpreted.

Rationale
- Is QoL primary or secondary outcome?
- Should be specified a priori.

Selecting a questionnaire- Key Considerations:

- Purpose of study
  - Generic vs. condition/disease specific instruments
  - There are hundreds to choose from – useful website: http://www.proqolid.org/
  - Needs to address study aims
  - Content
  - Reliability & validity
  - Recall period
  - Linguistic validity
  - Performance in other studies
  - Interpretability

Patient Reported Outcome and Quality of Life Instruments Database www.proqolid.org
Condition-Specific QoL Instruments

Most commonly used:
- EORTC Quality of Life Questionnaire (QLQ-C30)
- Functional Assessment of Chronic Illness Therapy (FACIT scales e.g. FACT-G)

EORTC QLQ-C30

EORTC Validated modules:
‘specific to tumour site, treatment modality, or a QoL dimension’
To be administered in addition to the core questionnaire:
- Lung
- Breast
- Head & Neck
- Oesophageal
- Gastric
- Multiple Myeloma
- Cervical Cancer
- Head & Neck Gastric
- Colorectal Liver Metastases
- Ovarian
- Colorectal
- Brain
- Information Module
- Endometrial

Functional Assessment of Chronic Illness Therapy

There are over 50 different FACIT scales and symptom indexes.
- General measure e.g. FACT-G
- Cancer specific e.g. FACT-B (Breast Cancer)
- Cancer Specific Symptom Indexes e.g. FAPSI 8 (prostate Cancer)
- Treatment specific measures e.g. FACT-EF: For patients receiving Enteral Feeding
- Symptom specific measures e.g. FACT-An: For patients with Anaemia/Fatigue
- Paediatric measures e.g. Peds-FACT-Br (Brain Cancer)

FACT-G
http://www.facit.org/ [accessed 01/02/2011]

Generic Instruments

Useful for comparisons across patient groups

Health status measures
- For example: Medical Outcomes Study 36-Item Short Form (SF-36)

Preference-based instruments
- EuroQol EQ-5D
- SF-6D
Preference based/utility measures

Developed from a background in economic and decision theory to provide an estimate of patient preferences for different health states.

- Represented as a single numerical score
- Where: 0 = dead and 1 = perfect health
- Can be used to generate Quality adjusted life years

EQ-5D is an example of a preference based measure

Levels of a perceived problem are coded as follows:

- Level 1 is coded as a 1
- Level 2 is coded as a 2
- Level 3 is coded as a 3
- Ambiguity response is coded as an 8
- Missing response is scored as a 9

Scoring EQ-5D health states

In this example EQ-5D health states, defined by the EQ-5D descriptive system, have been converted to a score using a set of UK values to produce an EQ-5D index (Dolan P. Med Care. 1997 Nov;35(11):1095-108.).

Estimation Of A Preference-Based Index From The EORTC QLQ-C30 (EORTC-8D)

- Enables EORTC QLQ-C30 data to be used to directly calculate QALYs for use in economic evaluation.

More than one instrument?

- May be useful to use both a generic and disease specific instrument.
- The development of a preference based index for the EORTC may mean that this becomes the sole instrument of choice for cancer trials (personal opinion!)

In this example, the EQ-5D health states have been converted to a score using a set of UK values to produce an EQ-5D index (Dolan P. Med Care. 1997 Nov;35(11):1095-108.).

To score an EQ-5D health state, you simply add up the corresponding value from a value set.

- In this example, the value set is: 1 2 3 4 5 6 7 8 9 10

Where to seek help and advice:

- NIHR Research Design Service
- MRC Hubs Trials Methodology Research

CONTACT THE WMRDS

Aim: to help NHS researchers, and others working in partnership with the NHS, in the West Midlands area who have a ‘good idea’ and want to turn that into a research proposal for submission to peer-reviewed funding programmes in applied health and social care.

General enquiries: Tel: 0121 414 7113
rdscentre@contacts.bham.ac.uk
Birmingham Hub: rds@contacts.bham.ac.uk
WEB: http://www.wm-rds.bham.ac.uk/

Methodology Advisory Service for Trials (MAST)

- http://www.methodologyhubs.mrc.ac.uk/
- service offered by the MRC Hubs for Trials Methodology Research that aims to provide trials methodology advice to trialists and statisticians who encounter non-standard methodological problems.

Thank you
**Capability: an alternative approach to measuring quality of life**

Tom Keeley  
MRC Midlands Hub for Trials Methodology Research:  
Prof. Lucinda Billingham  
Health Economics Unit:  
Prof. Jo Coast  
Dr. Hareth Al-Janabi

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**Aims and objectives**

- Quality-of-life and trials  
- Possible limitations  
- Sen and Capability  
- The ICECAP measure  
- Discussion and questions

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**Quality of Life**

- Bodily integrity  
- Bodily health  
- Friendship  
- Sex  
- Love  
- Control  
- Emotions

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**Quality of Life**

- Affiliation  
- Achievement  
- Life  
- Senses  
- Play

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**The benefits of treatments/trials**

- An intervention to reduce alcohol intake in adult males  
  - Hepatic health  
  - Colorectal cancer  
  - Global health  
  - Social relationships  
  - Professional progression  
  - Criminal behaviour  
  - Independent living  
  - Enjoyment  
  - The lives of important others  
  - Obesity  
  - Cardiopulmonary health  
  - Diabetes  
  - Global health  
  - Mobility  
  - Social acceptance  
  - Body image/confidence  
  - Love, sex and relationships

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**Mobility**

- I have no problems walking about  
- I have some problems walking about  
- I am confined to bed  
- Self-care  
- I have no problems with dressing  
- I have some problems washing and dressing myself  
- I cannot wash or dress myself

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**Physical Functioning Mobility**

- Your health does not limit you in vigorous activities  
- Your health limits you a lot in vigorous activities  
- Your health limits you a lot in moderate activities  
- Your health limits you a lot in moderate activities  
- Your health limits you a little in bathing and dressing

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**Adaptation**

*People often remark about how quickly the extraordinary becomes commonplace....... We are highly adaptive creatures. The predictable becomes, by definition, background, leaving the attention uncluttered, the better to deal with the random or unexpected.*

Enduring Love, McEwan, 1997

In situations of persistent adversity do victims go on grieving and grumbling or do they come to terms with the adversity?

In health, adaptation is often considered a laudable attempt by the patient to "continue" and make the most of what they have; a form of bravery.

There are those who are 'too subdued or broken to have the courage to desire much'
Adaptation

Life-expectancy

Reported morbidity

• Sackett and Torrance (1978) showed considerable differences in how dialysis patients and the general public valued health related quality of life of requiring dialysis.

• Brickman et al. (1978) showed that paraplegics were only marginally less happy than non-paraplegic controls.

• Oswald (2008) has recently presented longitudinal evidence that the degree of adaptation of ‘life satisfaction’ is in the order of 30% to 50% in those who suffered “quite serious” levels of impairment.

Limitations for trials

Current measures may underestimate the effects of a trial on quality-of-life.

1. A narrow evaluative space

   Health-related quality-of-life measure

2. Through adaptation to existing conditions

Sen & Capability

Amartya Sen
Nobel Laureate, Economist, Philosopher
Poverty and Famine

Agency versus Well-being

Maximisation versus equality

Capability and functioning

Capability: What a person is able to do

Functioning: What a person does

The capability approach advocates the evaluation of programmes on the basis of what people are able to do, rather than what they choose to do.

Starving Fasting

Blood shortage Religious objection

Agency versus Well-being

People have goals and pursuits other than ones own well-being.

Agency:
• goals and values that one has reason to pursue
• may not be the same as well-being
• but may affect wellbeing
The ICECAP measure

- A measure of capability for the adult population
- Includes dimensions other than health alone
- Allows comparisons across interventions
- Can be used for economic evaluation
- A single page measure – 5 items/questions

Person focused development

- In depth interviews to define conceptual attributes of quality of life for the adult population
- Semi-structured interviews to develop relevant terminology
- “Think aloud” qualitative work
- Validation work

BEEP

Keele University

An investigation to assess whether helping people with knee pain to find the right exercise routine results in better outcomes

PastBP

Primary Care Department, The University of Birmingham

An intensive BP reduction trial for people with stroke or TIA.

Cardiovascular fitness in RA patients

The Department of Sport and Exercise Science, The University of Birmingham

An intervention fostering autonomous motivation, physical activity and cardiovascular fitness in rheumatoid arthritis

Quality of Life

- Emotions
- Bodily integrity
- Affiliation
- Bodily health
- Achievement
- Life
- Friendship
- Senses
- Sex
- Love
- Control
- Play

Conclusions

- Quality of Life is a broad area
- Capability is a new approach to measuring Quality of Life
- It aims to address weaknesses in current measures
- It has been “operationalised” in the form of the ICECAP measure
- ICECAP is currently being used worldwide in trials
Contact details

http://www.icecap.bham.ac.uk/index.shtml

tjk962@bham.ac.uk
0121 414 6575
07779 587 641

Thank you
Questions? Discussion?
Analysing and Reporting Quality of Life Data

Professor Lucinda Billingham
Director, MRC Midland Hub for Trials Methodology Research
Biostatistics Lead, Cancer Research UK Clinical Trials Unit
University of Birmingham

Quality of Life Assessment in Cancer Research Training Day
University of Birmingham, February 17th 2011

Agenda

• Design issues → data for analysis
• Difficulties with analysis
  – Nature of quality of life data: multivariate and longitudinal
  – Missing data particular due to patient dropout
• Simple analytical approaches to deal with multivariate and longitudinal
• Using Quality-Adjusted Life Years (QALYs) to deal with problem of dropout

Deborah Stocken: illustrative examples in pancreatic cancer

Design: Is QoL Assessment Appropriate in All Phases of Clinical Trial?

Phase I
What is a safe dose to give for the NEW treatment and with what toxicities?

Phase II
Is the efficacy of the NEW treatment worthy of direct comparison to STANDARD treatment in phase III setting?

Phase III
How does the NEW treatment compare to the STANDARD treatment of the day in terms of efficacy?

Dose Toxicities
Response rate
(surrogate for survival)
Survival time

Design: Who to Include in QoL Assessment

• Ideally all trial patients
• All trial patients in selected centres
  – Treatment comparison will still be unbiased if randomisation stratified by centre
  – Inferences may relate to different population
• Subgroup of patients
  – E.g. just consenting patients
  – Could be a problem in terms of providing unbiased treatment comparison
• All patients should be followed-up for full duration of study

Design: When to Measure QoL

• Increasing options of frequency
  – Once
  – Pre treatment and post treatment
  – Several occasions during treatment
  – Throughout treatment and regularly until fixed follow-up time or death
  – Daily diary cards
• Greater frequency of assessments may provide more accurate analysis
• Need to be consider burden on patients and practicalities
  – Balance between how much you ask and how often

Typical Data from a Quality of Life Study

Example: BTOG2 Trial in Advanced Non-Small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Number of Questions</th>
<th>Number of QoL Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC QLQ-C30</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>EORTC LC13</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td>27</td>
</tr>
</tbody>
</table>

Weeks
0 3 6 9 12 16 20 24
Baseline Cycle 2 Cycle 3 Cycle 4 End of treatment Follow-up 1 Follow-up 2 Follow-up 3
How Do We Create QoL Measures from Responses on a Questionnaire?

Example: Emotional Functioning Score from EORTC QLQ-C30

Q21: Did you feel tense? A little = 2
Q22: Did you worry? A little = 2
Q23: Did you feel irritable? Not at all = 1
Q24: Did you feel depressed? Quite a bit = 3

Raw score = (Q21+Q22+Q23+Q24)/4
= (2+2+1+3) / 4 = 2

EF score = {1 – [(Raw score – 1)/3]} x 100 = 67

If all responses were ‘Very much’ then score=0
If all responses were ‘Not at all’ then score =100

Example: Data for Patient 10 in BTOG2

Survival Data       Quality of Life Data

216 measures of QoL
213,079 measures of QoL (1363 patients, 8136 forms)

Problematical Nature of QoL Data

- Large quantities of data generated which need to be interpreted sensibly
  - Multivariate: many items measuring a variety of conceptual dimensions
  - Longitudinal: repeated measurements over time
Dealing With Multivariate Data

- Problem: Hypothesis testing for multiple variables increases the chance of making an erroneous conclusion
- Possible solutions
  - Focus on one global measure for full analysis and descriptive analysis for remainder
  - Repeat analysis for all dimensions and adjust for multiple testing
  - Use more complex multivariate methods
  - (Generally not possible to calculate a mean across all QoL measures)

Dealing with Longitudinal Data

- Repeated measures over time reduced to a single summary measure
  - mean value over all time points
  - change between two time points
  - maximum
  - time to QoL event
  - area under curve (AUC)
- Compare treatments using standard statistical methods
- Simple, flexible, easily interpretable results
- Does not fully capture dynamic nature of QoL data

Area Under the Curve (AUC) as a Summary Measure

- Survival time = 9 months
- AUC = 5.4 months

Problem of Missing QoL Data

- Planned completion: complete complete complete complete
- Single missing items: complete incomplete complete complete
- Intermittent missing whole questionnaire: complete complete complete
- Missing data resulting from patient dropout: complete complete
Problems of Interpretation of Summary QoL Measures with Dropout

Decision Making Using QoL Data

What do clinicians/patients want to know?
• Is the new treatment the best choice compared to the existing standard treatment?

<table>
<thead>
<tr>
<th>Survival</th>
<th>Quality of Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality-adjusted life years (QALY)</td>
<td></td>
</tr>
</tbody>
</table>

What do NICE want to know?
• Cost per QALY

Need QoL as utility for proper QALY calculation

Rationale for Quality-Adjusted Survival Analysis

• Optimal method for incorporating quality of life into decision-making
• Solves analytical problems of quality of life analysis
  – Multiple measures over time i.e. longitudinal data
  – Missing data resulting from dropout due to death
  – Differential follow-up (some methods)
• Does not solve other analytical problems
  – Multiple measures of quality of life
  – Missing data for reasons other than death

Four Different Approaches to Quality-Adjusted Survival Analysis

<table>
<thead>
<tr>
<th></th>
<th>Subject-based approaches (i)</th>
<th>Group-based approaches (j)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using health states</td>
<td>$Q_{ALY_i} = \sum_j q_j f_{ij}$</td>
<td>$Q_{ALY_j} = \sum_i q_i f_{ij}$</td>
</tr>
<tr>
<td>Q-TWIST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Using actual values</td>
<td>$Q_{ALY_i} = \int q_i \text{d}t$</td>
<td>$Q_{ALY_j} = \int q_i S_j(t) \text{d}t$</td>
</tr>
</tbody>
</table>

Requires full follow-up in terms of survival for analysis period
Deals with censored survival times during analysis period

Calculating QALYs at the Patient Level

Calculating QALYs at the Group Level: Integrated Quality Survival Product


• Simple methodology that directly combines longitudinal quality of life data with survival data at the group level

• Need the quality of life measure to be a utility to enable ‘proper’ calculation of quality-adjusted survival time
Simple Example of Calculating QALYs at the Group Level in a Clinical Trial

\[ \text{Mean survival time} = 100\% \times 1 + 80\% \times 1 + 60\% \times 1 + 50\% \times 1 + 20\% \times 1 = 3.1 \text{ years} \]

\[ \text{Mean QALY} = 100\% \times 0.2 \times 1 + 80\% \times 0.8 \times 1 + 60\% \times 0.7 \times 1 + 50\% \times 0.6 \times 1 + 20\% \times 0.2 \times 1 = 1.6 \text{ years} \]

Take Home Messages

- Analysis of QoL data is problematic due to the multivariate and longitudinal nature of the data
- Standard longitudinal methods will generally be invalid due to dropout due to death
- Quality-adjusted survival analysis accounts for problems of dropout and provides a useful outcome measure on which to compare treatments
QUALITY OF LIFE ASSESSMENT IN CLINICAL RESEARCH ANALYSING AND REPORTING

Deborah Stocken PhD CStat
Biostatistics Lead
Cancer Research UK Clinical Trials Unit
d.d.stocken@bham.ac.uk

The Pancreas

- is a solid gland
- 20-25cm in length, 4-6cm in width and 3-4cm in depth
- divided into 5 parts: head, uncinate process, neck, body and tail
- Attached in the back of the abdominal cavity behind the stomach
- Makes enzymes necessary to digest food in the intestines
- Produces insulin to enable the body to use glucose
- Digestive enzymes and insulin made by different parts of the pancreas

ESPAC-1: Pragmatic Trial Design

QoL sub-study

ESPAC-1: Overall Survival by Chemotherapy

Survival rates 2-year 5-year
No CT: 30.0% 8.4%
CT: 39.7% 21.1%
HR=0.71 (0.55, 0.92), p=0.009

Figure 2. Kaplan–Meier Estimates of Survival According to Whether or Not Patients Received Chemoradiotherapy (Panel A) or Chemotherapy (Panel B).
**ESPAC-1: Overall Survival by Chemotherapy**

<table>
<thead>
<tr>
<th></th>
<th>No CT</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-year</td>
<td>28.7%</td>
<td>43.3%</td>
</tr>
<tr>
<td>5-year</td>
<td>9.9%</td>
<td>23.3%</td>
</tr>
</tbody>
</table>

Survival rates 2-year 5-year
No CT: 28.7% 9.9%
CT: 43.3% 23.3%
HR=0.64 (0.52, 0.78), p<0.001

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**ESPAC-1: Conclusions**

We conclude that standard care for patients with resectable pancreatic cancer should consist of curative surgery followed by adjuvant systemic chemotherapy.

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**ESPAC-1: Quality of Life**

- Balance observed survival advantage vs. potential effects of toxicity on patients' perception of their QoL.
- QoL secondary outcome measure in ESPAC-1.
- Longitudinal data collected 3-monthly for 2-years.
- EORTC QLQ-C30 measuring multiple outcomes:
  - 5 Functional: Physical, Role, Emotional, Cognitive, Social
  - 3 Symptom: Fatigue, Nausea/Vomit, Pain
  - 1 Global health status
  - 6 Single items: Dyspnoea, Sleep, Appetite, Constipation, Diarrhoea, Financial
- Primary comparison of scores by treatment group.

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**EORTC-QLQ-C30 Questionnaire**

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Do you have any trouble aching a bag with?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Do you have any trouble rising a flag without the help of the hands?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Do you feel you are being a clear choice the day?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Do you have a help with eating, dressing, washing yourself or using the toilet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

- Multiple questionnaires at same time-point?
- Multiple answers to a specific question?
- Pre-defined 'rules' - unbiased

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**EORTC-QLQ-C30 Domain Scores**

Individual questions combined to 'domain' scores
Missing component when creating domain score?
E.g. Emotional Functioning

- Q21: Did you feel tense? A little = 2
- Q22: Did you worry? A little = 2
- Q23: Did you feel irritable? Not at all = 1
- Q24: Did you feel depressed? Quite a bit = 1

Raw score = (Q21+Q22+Q23+Q24)/4 = (2+2+1+3)/4 = 2
EF score = \(1 - \left(\frac{\text{Raw score} - 1}{3}\right)\) \times 100 = 67

If all responses were 'Very much' then score=0
If all responses were 'Not at all' then score=100

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**ESPAC-1: EORTC-QLQ-C30 Data**

- One patient 135 'pieces' of information!
- Multiple domains (max 15)
- Multiple time-points: for each (max 9)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Rand 3</th>
<th>Rand 6</th>
<th>Rand 9</th>
<th>Rand 12</th>
<th>Rand 15</th>
<th>Rand 18</th>
<th>Rand 21</th>
<th>Rand 24-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
</tr>
<tr>
<td>Role</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
</tr>
<tr>
<td>Emotional</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
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<tr>
<td>Cognitive</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
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<tr>
<td>Social</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
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<tr>
<td>Fatigue</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
</tr>
<tr>
<td>Nausea/Vom</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
</tr>
<tr>
<td>Pain</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
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</tr>
<tr>
<td>Sleep</td>
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<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
</tr>
<tr>
<td>Appetite</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
</tr>
<tr>
<td>Constipation</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
</tr>
<tr>
<td>Financial</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
</tr>
</tbody>
</table>

- How to summarise?
- Drop-out over time including drop-out for death?
ESPACEP-1: Quality of Life Results

Longitudinal quality of life data can provide insights on the impact of adjuvant treatment for pancreatic cancer—Subset analysis of the ESPAC-1 data

Inst. Centrol1, [name redacted], P. Ducreux2, [name redacted], [name redacted], D. Hofland3, [name redacted], J. Demaray3, [name redacted], M. Taillibert4, [name redacted], [name redacted], [name redacted], and [name redacted], for the European Study Group for Pancreatic Cancer (ESPAC-1).

**Change Between 2 Time-Points**
- **Summary measure:** 0-3 month change in score
- **Change = (score at 3-mo Form) – (score at Baseline)**

**Table 1: Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Main study</th>
<th>REF study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence grade</td>
<td>438 80 255 81</td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>111 20 63 19</td>
<td></td>
</tr>
<tr>
<td>Tumor grade</td>
<td>110 21 67 20</td>
<td></td>
</tr>
<tr>
<td>Metastasis</td>
<td>300 79 187 65</td>
<td></td>
</tr>
<tr>
<td>Histological type</td>
<td>912 20 53 17</td>
<td></td>
</tr>
<tr>
<td>Neat trait</td>
<td>106 47 154 49</td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>273 73 159 51</td>
<td></td>
</tr>
<tr>
<td>Male, female</td>
<td>497 249</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>7.0 54.0</td>
<td></td>
</tr>
<tr>
<td>IQR</td>
<td>2.5-10 2.5-10</td>
<td></td>
</tr>
<tr>
<td>Survival status</td>
<td>115 21 59 19</td>
<td></td>
</tr>
<tr>
<td>Survival estimates</td>
<td>439 79 237 61</td>
<td></td>
</tr>
<tr>
<td>Median survival</td>
<td>16.6 (95% CI: 15.4, 17.7)</td>
<td></td>
</tr>
<tr>
<td>12 and 24 months</td>
<td>65 and 35% 66 and 35%</td>
<td></td>
</tr>
</tbody>
</table>

**Availability of Questionnaires**

- Missing data not missing at random

**Is this a problem?**
- Representative Sample?
  - BUT France not involved

**Change Between 2 Time-Points**
- **Summary measure:** 0-3 month change in score
- **Change = (score at 3-mo Form) – (score at Baseline)**
Change Between 2 Time-Points

- What time-point?
- Number completing Baseline and 3-month forms?
  - Drop-out including death
- Multiple testing over different time-points?

Standardised Area Under the Curve (12)

E.g. Emotional Functioning
If all responses were ‘Very much’ then score=0
If all responses were ‘Not at all’ then score =100

<table>
<thead>
<tr>
<th>TNO</th>
<th>CTGP</th>
<th>SURV</th>
<th>DEAD</th>
<th>q1</th>
<th>q2</th>
<th>q3</th>
<th>q4</th>
<th>q5</th>
<th>q6</th>
<th>q7</th>
<th>qalm12</th>
<th>sauc12</th>
</tr>
</thead>
<tbody>
<tr>
<td>1067</td>
<td>No CT</td>
<td>63.9</td>
<td>145</td>
<td>33.3</td>
<td>33.3</td>
<td>0</td>
<td>33.3</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>188.59</td>
<td>14.93</td>
</tr>
<tr>
<td>1069</td>
<td>CT</td>
<td>76.9</td>
<td>40.8</td>
<td>66.7</td>
<td>66.7</td>
<td>66.7</td>
<td>33.3</td>
<td>66.7</td>
<td>33.3</td>
<td>-</td>
<td>603.77</td>
<td>52.56</td>
</tr>
</tbody>
</table>

Summary statistic:
Mean (95%CI) SAUC by TRT group

Average over time observed

SAUC(12) Assumptions

- Patients with baseline form only
  - Died < 12 months – join baseline score to QoL=0 at death
  - Died >12 months – Delete (too far to carry last QoL value)
  - Alive < 12 months – Delete (lost to FU)
  - Alive > 12 months – Delete (too far to carry forward)
- Patients with baseline form + forms > 12 months
  - Delete - too far to carry forward
Minimises multiple testing
Conditional on survival

SAUC(12) Analysis

- Method to directly combine QoL with survival data
- Accounts for longitudinal data
- Accounts for dropout due to death and censoring

1. Define survivor function for group $S(t)$
   - Proportion of patients who survive to time $t$
2. Define quality of life function for the group
3. Product of $S(t)$ and QoL function

ESPA-C1: SURVIVAL FUNCTION IN QOL PATIENTS

- Linear interpolation to calculate QoL scores at each death time
- Mean QoL connected at death times by step function

ESPAC-1: QUALITY OF LIFE FUNCTION

- Linear interpolation to calculate QoL scores at each death time
- Mean QoL connected at death times by step function

ESPAC-1: QUALITY-SURVIVAL PRODUCT

- Within 2 years of surgery:
  - CT provides on average an extra 2.4 LM
  - CT provides on average 1.0 extra QALM

ESPA-C1: Quality of Life

The previously reported survival advantage supporting the use of adjuvant chemotherapy is maintained when adjusted using quality adjusted survival methodology. Chemotherapy provided on average an additional 1.0 quality-adjusted life months within a restricted 2-year time period from the time of resection.

Carter, Stocken, Ghanem et al. 2009
Summary

- Important to balance any survival advantage against patient reported QoL.
- QoL data are problematic:
  - Sub-populations → biased
  - Multivariate nature → multiple testing
  - Longitudinal nature → drop-out
  - Missing data → q’re and domain level
- Aim to minimise missing data
  - Timely completion (feasible study design)
  - Responses elicited where possible (nurse)
  - Unambiguous questions (q’re design)

References

Practicalities of collecting quality of life data in clinical trials

In an ideal world…

“Patients should complete the questionnaires prior to treatment [or consultation] whilst waiting to be seen in clinic, ideally in a quiet area and without conferring with friends or relatives.”

How many people here think this accurately reflects what happens at most centres, most of the time?

How many people here think this accurately reflects what happens in their centre?

…With “ideal” patients

An ideal patient would presumably one who:
• Understands, speaks and thinks similarly to the form designer/distributor
  – Language (the average reading age in the UK is variously quoted as being between 9 and 14)
  – Culture (certain questions may put off particular groups from answering ALL questions, not just specific ones)
  – “Accommodation”. The patient may want to accommodate the views of the researcher or have an agenda about their answers

Real Patients

May not be able to read the questionnaire – may have simply left their glasses behind etc
May have questions “translated” by relatives or staff into paraphrases with subtly different meaning or bias
Even verbatim reading may still impart bias depending on inflection and body language

Real Researchers

Some questionnaires allow for the collection of qualitative data (and even those that don’t may have it added by the patient).
What do you do in research terms?
Supposedly just see if the form has been completed
What do you do as a duty of care?
A patient may give a harrowing narrative description which does not match their comments to the healthcare professional at any other time.
How do you react?

BTOG2 Trial Design

Max four cycles given 21 days 21 days 21 days 21 days

Day 1 Day 2

A Gem 30 Gem Gem

B Gem Cis 50 Gem

C Gem Carbo AUC6 Gem

N = 1363
Quality of Life within BTOG2

“Quality of life is an important outcome measure in this study and therefore all patients are required to participate in this aspect of the trial.”

Questionnaires used:
- EORTC QLQ-C30
- LC13
- EuroQol EQ-5D

Combined in a single booklet, provided as a pdf

Protocol Visits

Baseline (pre-randomisation)

<table>
<thead>
<tr>
<th>Treatment centre</th>
<th>Cycle 1</th>
<th>No QoL!</th>
<th>Cycle 2</th>
<th>QoL Form</th>
<th>Cycle 3</th>
<th>QoL Form</th>
<th>Cycle 4</th>
<th>QoL Form</th>
<th>End of Treatment</th>
<th>QoL Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up centre</td>
<td>1 month</td>
<td>QoL Form</td>
<td>2 months</td>
<td>QoL Form</td>
<td>3 months</td>
<td>QoL Form</td>
<td>4 months</td>
<td>QoL Form</td>
<td>5 months</td>
<td>QoL Form</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>QoL Form</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Procedural Issues

QoL problems are general data problems BUT QoLs are time-sensitive - once a QoL has been missed it cannot be retrieved

- Communication with the Study Office
  “A named person at each participating centre must be nominated to take responsibility for the administration, collection and checking of quality of life questionnaires” Study Office is not always informed of staff changes and if we don’t know, we can’t chase effectively

- Communication at the participating centre
  Multiple staff collecting and sending forms. It is not always clear which forms have been completed and which sent. Comprehensive records of what has been done, by whom, are essential for complete data

The Dating Game

“Blind” Dates There is no date at all on the form

Embarrassing Dates

- A patient’s date of birth has been entered instead of the date on which the form was given. The date on which the form was supposedly completed is AFTER the patient’s death!

Dates with a “significant other”

- Sometimes 2 forms with different data are received which are both said to relate to the same cycle

Dates with unfortunate consequences

- Eg. FU form 5 ticked yet the date the form date hints at is relating to a different visit

Data cannot be used

Neither form can be used

All subsequent forms out of sequence

Appointments and Sequences

Missed appointments

A missed appointment is usually genuinely missing data.

Clarification: In BTOG2, if a patient misses FU3, this does NOT mean that the next FU becomes FU3. FU3 is missing and the subsequent visit is FU4. Check the protocol or with the Study Office to see what rule applies to your trial

BUT why was the appointment missed? The answer to this question may itself reflect the patient’s quality of life. Ie felt depressed and DNA’d. In this example, FU3 QoL should be returned with the reason for the appointment being missed.

Admin. problems

Photocopying errors!

- The original QoL booklet is sent through a photocopier as a double-sided document, on single-sided copy mode. Half the data is irretrievably lost

Missed pages and responses

- The respondent doesn’t realise there is information on the back of the page or misses particular questions. Deliberately, or in error? Data lost

“Questionnaires will be collected before the patient leaves at which time they will be checked for any missing responses and patients will be asked to complete any missing items.”
Non-protocol visits

A specific problem:
At the end of the scheduled follow-up phase the patient reverts to the schedule of visits as per your standard practice.

This data is particularly sensitive to date errors and mismatches because the Study Office will not know when patients are scheduled to return.

Eg Centre 001 routinely has a 3 monthly schedule, Centre 002 has a 2 monthly schedule
Is FU9, 6 or 9 months after FU6? Only an accurate date can answer this.

End of Treatment/Withdrawal

Specific problem:
Treatment occurs in cycles. An end of treatment or withdrawal visit should coincide with the end of the last cycle in order to catch all the data from that cycle. The first FU is thus a month (or whichever protocol defined period) after the EoT/Withdrawal

Summary

• QoL questionnaires are imperfect tools for an imperfect world
• Understand the protocol – be clear about precisely when forms are required
• Keep the Study Office informed
• Keep your colleagues informed
• Check the forms before taking them off the patient
• Don’t be afraid to ask the Study Office

Happily Ever After
NICE Perspective on Quality of Life

How can QoL data change clinical practice, why interventions that appear to give clinical benefit might not be supported by NICE?

Andrew Stevens
Professor of Public Health U of B
Chair – NICE Appraisals Committee

NICE’s Dilemma
(at every appraisal)

1. What is the value of the (new) technology to patients?
   – comparative clinical effectiveness

2. What is the consequence of adoption of the technology for all patients?
   – cost effectiveness

3. Is our consequent decision fair and reasonable?

Decision Options

1. Yes
2. Restricted Yes
3. No
4. Only in Research

Breakdown of recommendations

Breakdown of individual decisions (TA 1-130)

Yes Optimised OIR No

Total to 2010

Comparison of all Technologies vs Cancer Drugs

NICE Recommendations 2000-2010
NICE’s Methods

(1) Limited Budget and opportunity costs necessitate economic analysis
(2) Requirement to compare across quite different methods means calculating cost-utilities

<table>
<thead>
<tr>
<th>Costs</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>£</td>
<td>E</td>
</tr>
</tbody>
</table>

(3) A QALY is a QALY regardless of who gets it.

Current NICE method cont.

(4) Patient derived generic preference-based measures of health
   (EQ-5D*: Mobility, Self-care, Usual Activities, Pain/Discomfort, Anxiety/Depression)
   - Valued by a sample of the public
   - Using a choice based (either time trade-off or standard gamble) method
(5) Patient evidence on QoL

*Where EQ-5D is not appropriate, then it ‘does not exclude other methods meeting it underlying criteria’ (the implies SF-6D and HUI2).
Additional analyses allowed using disease specific instruments or patient preferences.

Two Crucial Numbers

1) The Threshold

2) The ICER

Costs

Benefits

The Cost-effectiveness Threshold

Threshold

ICER

Less effective & more costly

More effective & more costly

Less effective & less costly

More effective & less costly

=£30,000 exceptional unless it’s an “End of Life Treatment”
£20-30,000 case needs further rationale
£20,000 generally acceptable

Technology B

Technology A

Cost

QALYs
The QALY

QALYs - patients on treatment 1

QALYs - patients on treatment 2

Time -years

QALY gains

QALYs - patients on treatment 1

QALYs - patients on treatment 2

Time -years

Economic modelling and Utilities

simple 3-stage Markov models:

Progression-Free (PF)  
Progressed (PD)

Requires 3 valuations
Death = 0
Progression
Progression-free

Cancer Utility Values

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>Progressive Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCC 1st line</td>
<td>0.78</td>
<td>0.70</td>
</tr>
<tr>
<td>RCC poor prog</td>
<td>0.66</td>
<td>0.45</td>
</tr>
<tr>
<td>Head &amp; neck</td>
<td>0.80</td>
<td>0.60</td>
</tr>
<tr>
<td>Adv Gastric Ca</td>
<td>0.95</td>
<td>0.575</td>
</tr>
<tr>
<td>Colo-Rectal</td>
<td>0.73</td>
<td>0.24 (relapse)</td>
</tr>
</tbody>
</table>

Why not just use life years?

Quality Of Life 1.0

Time -years
Pemetrexed in Mesothelioma

<table>
<thead>
<tr>
<th>Cisplatin</th>
<th>Cis + pem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS Months</td>
<td>12.1 (n=226)</td>
</tr>
<tr>
<td>Median OS in FS pts</td>
<td>13.3 (n=168)</td>
</tr>
</tbody>
</table>

- Utility c0.65 in Advanced Disease
- ICER c £50,000 per QALY
- c £35,000 per LY
- Slightly less in AD
- And Good performance status

The Comments – ways to bring the ICER nearer the threshold

Real
1. Pemetrexed stopping rule (non responders at 12 weeks)
2. Fewer cycles per patient
3. Limit to staged (advanced) disease

Ruses
1. Use median, not mean, survival
2. Use LYGs not QALYs
3. Threshold – change it for this special case

Mesothelioma

Breathlessness, other respiratory symptoms and fatigue plus

Treatment toxicity - Grade 3 and 4 toxicities

<table>
<thead>
<tr>
<th></th>
<th>Cis %</th>
<th>Cis+pem %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>All</td>
<td>7</td>
<td>23</td>
</tr>
</tbody>
</table>

Informal Reporting on Quality of Life due to AEs – CML

CML
1996 – Alfa Interferon – Side Effects minor (manage with simultaneous analgesia)
2006 – Alfa Interferon – Intolerable
Imatinib – Side Effect Free

CRF
2008/9 – Sunitinib - Side Effects tolerable
sunitinib/PFS = 0.77; IFN-α/PFS = 0.79;
2010/11 – Sunitinib – Toxicity requires 2 wk periods of discontinuation
Pazopanib – Better A/E profile

Why not just use life years?

Relative Importance of Life-years and Quality of Life in Appraisal

Cancers (typically fatal) | Chronic eg Musculo-Skeletal

- Qol
- Lol

- Qol
- Lol
Temzolomide in newly diagnosed Glioma

<table>
<thead>
<tr>
<th></th>
<th>QALYs</th>
<th>£s</th>
<th>Inc Cost</th>
<th>Inc QALYs</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>0.889</td>
<td>17,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT + TMZ</td>
<td>1.106</td>
<td>24,800</td>
<td>7,800</td>
<td>0.217</td>
<td>35,900</td>
</tr>
</tbody>
</table>

Glioma Utilities

1) Based on EORTC QLQ-30 + BC20 in 105 patients
2) Scenarios valued by a panel of 36 non-patients
   - Stable disease: -0.887
   - SMG treated with RT: -0.824
   - SMG treated with RT + TMZ: -0.743
   - Progressive Disease: -0.731 declining 0.5% pwk
Sample of Non-Cancer Utility Values

<table>
<thead>
<tr>
<th>Condition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>0.8</td>
</tr>
<tr>
<td>Mild Depression</td>
<td>0.59-0.73</td>
</tr>
<tr>
<td>Influenza</td>
<td>0.52</td>
</tr>
<tr>
<td>Terminal MND</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Stein et al 2005

Tocilizumab: Mapping HAQ → EQ-5D

- Linear and non-linear regression models
  - Non-linear model used as base case
  - ERG note that non-linear model predicts lower EQ-5D at high HAQ scores versus linear model

Critical Issues in Cancer Appraisals

- Extrapolation of short-term trial data
- Compensating Cross-over
- Comparator selection
- Indirect Comparison
- Case Series without comparators
- Sub-Group selection

But we usually say yes in Cancer anyway

Pragmatic Use of the Threshold

1) CANCER (Legion)
2) Severity (PAH, Riluzole)
3) Children (HGH, CSR)
4) Advance over alternatives / Innovation (Imatinib, Bortezomib)
5) Disadvantage (Cetuximab, Pemetrexed, AChEIs)
6) Small numbers (Rule of rescue, Budget Impact) (PAH, HGH, GIST)
7) Avoiding exclusions (Secondary Osteo, AMD)
8) End of life timespan (Temozolomide)
9) Time limited problem (Pemetrexed)
10) Corporate responsibility (Pemetrexed)