Quality of life Assessment In Clinical Trials

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Abstract

- The assessment of patient reported outcomes (PRO) is increasingly incorporated in clinical trials. Statisticians collaborate in design, conduct, analysis, and reporting of clinical trials including the PRO part. Quality of life (QoL) is a subjective construct which varies with the population studied. It is generally conceptualized as a multi-dimensional construct made up of a number of independent domains including, physical health, psychological well-being, functional roles, social relationship, and subjective sense of life satisfaction. Each QoL domain can be assessed from the point of view of the clinician, client or caregiver, and the relative weighting of the importance of each domain can also vary from one observer to another.

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Overview

- **What is Quality of Life?**
- Measurement and Characteristics
- Selection of instrument
- Design, analysis, and reporting
- Example
- Advantages, concerns and general issues

Quality of Life (QoL)?

- An individual's perception of their position on life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, and their relationships, and their salient features of their environment.

WHO

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HRQoL is about:

- Functioning (what the person can do)
  - Self care
  - Role
  - Social

- Well-Being (how the person feels)
  - Emotional well-being
  - Pain
  - Energy

Quality of life is not

- Quality of environment
- Type of housing
- Level of income
- Social support

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HRQoL measures how is the patient doing

- Physiological:
  - Vital signs (PB, Pulse, temperature, respiration)
  - Hematocrit
  - Abumin

- Physician observation
  - Physical performance

- Self-reported indicators
  - Functioning and well-being

Wilson IB, Cleary PD. JAMA 1995

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Measures of HRQoL: Approaches

- Health Status Measures:
  - Rating scales, varying ranges (0-100)
  - Psychometric approach
  - Produces relative ranking and shows change in health status overtime

- Utility Measures:
  - Econometric approach, scale 0 (death) to 1 (perfect health)
  - Produces trade-offs of time (quantity) and quality.

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"Universal Quality of Life Scale"

1	2	3	4	5
I'd rather not be in my body	I'm a reluctant participant in my daily life	I'm an active spectator in my daily life	I accompany myself whenever I get a chance	I just can't get enough of myself!

Measures of HRQoL: Instruments

- Generic Instruments
  - Focus on broad aspects of QoL and health status
  - Intended for use in general populations or a wide range of disease conditions
  - Appropriate for comparing data from different clinical trials
  - Required for health-economic assessment using utilities, preference methods
  - Designed to assess HRQoL in individuals with and without active disease (MOS SF-36)

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Examples of Generic instruments

- Sickness Impact profile (SIP)
- Nottingham Health profile
- Health Survey (SF-36)
- EuroRol (EQ-5D), self report questionnaire
- Patient Generated Index of Qol (PGI)
- Assessment of Motor and Process Skills (AMPS)
- Computer-adaptive testing (CAT)
- Health Utilities Index (HUI)
- McGill Pain Questionnaire (MPQ)
- Functional activity Questionnaire (FAQ)
- Profile of Mood Scale (POMS)
- Multidimensional Fatigue Inventory 20 (MFI-20)

Measures of HRQoL: Instruments

- Disease Specific Instruments
  - Narrower scope to address in details the impact of:
    - Disease specific
    - Function specific
    - Condition or problem
    - Population specific
  - Designed to detect subtle disease and treatment effects
  - Contains items of issues important to the patient and may provide information of clinical relevance to the management for future patients.

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Disease specific Instru. by pathology/disease

1. Bacterial infections and mycoses

2. Cardiovascular diseases

3. Congenital, hereditary, and neonatal diseases and abnormalities

4. Digestive system diseases

5. Disorders of environmental origin

6. Endocrine system diseases

7. Eye diseases

8. Female genital diseases and pregnancy complications

9. Hemic and lymphatic diseases

10. Immune system

11. Male genital diseases

12. Musculoskeletal diseases

13. Neoplasms

14. Nervous system diseases

15. Nutritional and metabolic diseases

16. Otorhinolaryngologic diseases

17. Pathological conditions signs and symptoms

18. Psychiatry/psychology

19. Respiratory tract diseases

20. Skin and connective tissue diseases

21. Stomatognathic diseases

22. Surgical Procedures, Operative

23. Urologic diseases

24. Virus diseases

Important Properties: Validity

- Content validity:
  - The extent to which the items are sensible and reflect the intended domain of interest
  - Face validity: Items cover the intended topics clearly and unambiguously.
- Criterion validity:
  - Examines the instrument against accepted standard indicating the true values for the instrument? Gold standard do not exist in QoL.
  - Concurrent validity: Comparing new one with well-established instrument
  - Predictive validity: ability to predict future health status
- Construct validity:
  - Measure the construct that it was designed to measure, checking dimensionality, homogeneity, overlap between latent variables
  - Convergent (correlation between related dimensions)
  - Discriminant/divergent validity (recognition of unrelated dimensions)

Important Properties: Reliability

- Reliability: reproducible and consistent results
  - Is it consistent under similar conditions?- subjects will give same answers at different times if experience same HRQoL?
  - Internally consistent? All items should measure same thing?
  - Stable? Repeatability
    - Test-retest (correlation over time)
    - Inter-observer (correlation between raters)
    - Equivalent-forms (correlation between similar forms measuring same attribute)

Factors influencing QOL

- Interventions/Treatment
- Disease Processes
- Labeling: diagnosis brings on 'change'
- Concomitant Care
- Non-related life events (e.g. death in the family)

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Selecting Instruments: Initial decisions

- There are many instruments available
- Books and articles providing reviews in addition to websites.

- Adult vs. Children
  - Different set of challenges and age specific priorities

- Generic vs. Disease specific
- How do you choose among a short list once you decide on a list

Selecting Instruments: Checklist

- Development
- Documentations
- Validation
- Scoring
- Feasibility
- Population
- Interpretation
- Cultures
- Resources

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Selecting Instruments: Checklist

- Development
  - Aims clearly defined?
  - Clear concept basis for dimensions? Assessed?
  - Development results published (item selection, field testing, issues identification)?

- Documentations
  - Formal written documentations
  - User manual
  - Peer-review publications supporting the claims?

Selecting Instruments: Checklist

- Validation
  - Documented evidence of adequate validity?
  - Evidence of adequate reliability/reproducibility of results?
  - Evidence of sensitivity, affect on sample size
  - How comprehensive the validation process? Sample size used?

- Scoring
  - Is it well defined?
  - Global questions and/or score about QoL?

Selecting Instruments: Checklist

- Feasibility
  - Feasible method of administration?
  - Patient burden (completion time)
  - Embarrassing or difficult items?
  - Ease of coding
  - Easy to understand items?
  - Compatibility and order of multiple instruments

- Population
  - Suitable for target population?
  - If your population differ, need additional testing to confirm?
  - Tested on wide range of subjects from your population?
  - Young children? Impaired adults for whom instrument is not appropriate?

Selecting Instruments: Checklist

- Interpretation
  - Guidelines for interpretation of scores?
  - Sample size estimation guidelines for designing a trial?
  - Need to provide open-ended question about factors affecting your trial?
  - Global question/measure of overall QoL?

- Cultures
  - Valid for patients of relevant cultural, ethnic, eduacational background?
  - Validated translation?
  - Tested language version ?

Instrument Resources

Many sites like QoLID (QoL instruments database), MAPI
Research Institute and others

- Provide an overview of existing PRO instruments
- Provide relevant and updated information on PRO instruments
- Facilitate access to the instruments and their developers
- Facilitate the choice of an appropriate PRO instruments
- Translated instruments

Harmonization?

- *In 1999, four organizations/societies produced supporting guidance documents on the use of HRQL evaluation in drug development:*

1. European Regulatory Issues on Quality of Life Assessment (**ERIQA**) Group
2. International Society for Quality of Life Research (**ISOQOL**),
3. International Society for Pharmacoeconomics and Outcomes Research (**ISPOR**),
4. Health Outcomes Committee of PhRMA (**PhRMA HOC)**

With support of :

a. DDMAC (FDA Division of Drug Advertising and Marketing Communication,
b. Mapi Research Institute.

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Purposes of Harmonization

The main objectives of the PRO Harmonization program are:

- To clarify areas of concern or confusion about PRO evaluation;
- To explain the added value of PRO outcomes among all key players, i.e., academics, regulators, industry researchers, and prescribers;
- To open and maintain communication between key players; and
- To disseminate meeting outcomes
- Website: www.pro-harmonization-group.com

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Study Design: Analysis Plan

- Primary analysis
  - Power and sample size
  - Procedure for handling multiplicity and adjustment procedures
  - Statistical modeling of repeated measures/Longitudinal data
  - Missing data assumptions, rate, effect on the analysis

- Sensitivity analysis
  - Plan for sensitivity analysis
  - Models considered and justification
  - Clear implementation instruction

Analysis Plan: cont.

- Secondary analysis
  - Excluded scales? What exactly will be reported about them?
  - Justification for including these assessments if not part of the primary analysis
  - Planned exploratory analyses?
    - Relationship between clinical outcomes and HRQoL
    - Treatment effect in specific subgroups
    - Psychometric analysis of HRQoL instrunment
- Endpoints
  - Specific objectives
  - Superiority vs. equivalence
  - Summary measures
  - Primary and secondary endpoints

Analysis plan: Sample size

- Longitudinal study
  - $H_o : \theta = C\beta = 0$ vs. $H_a : \theta = \delta_\theta$
  - Assume N=Nc/min(p), where min(p) is the minimum proportion expected to overtime, and Nc = complete cases
  - MLE estimate assuming MAR

$$N = \left(z_{\alpha/2} + z\beta \right)^2 \sigma_\theta^2 / \delta_\theta^2$$

$$\sigma_\theta^2 = N . \mathrm{var}(\hat{\theta}) = N_c . \mathrm{var}(\hat{\beta}) C'$$

$$= C \left| \sum_{k=1}^{K} p_k X_k' \,{}_{\Sigma_k^{-1}} X_k \right|^{-1} C'$$

where p_k is the proportion of sample with design X_k
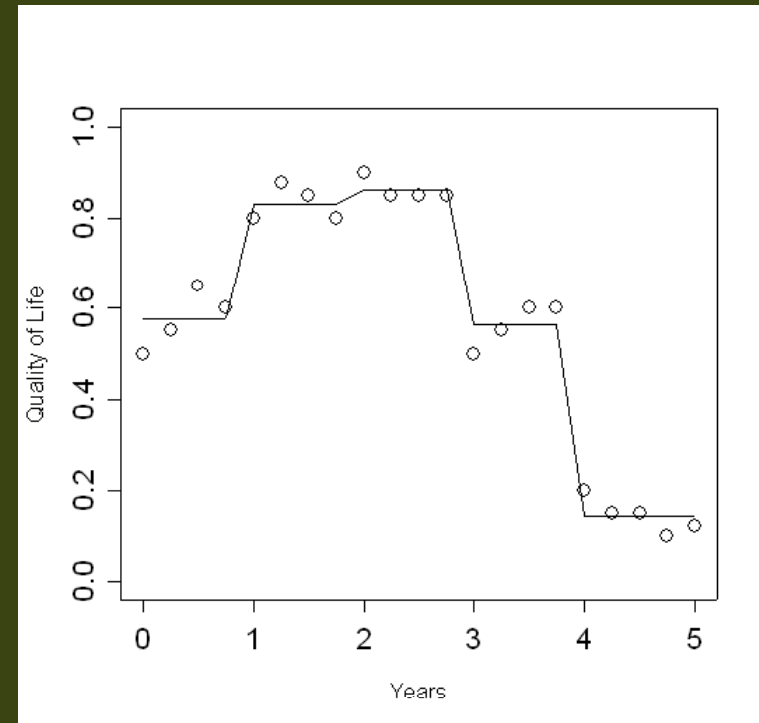
Analytical considerations: Models

- Repeated measure models
  - Covariance structure
  - Mean structure

- Growth curve models
  - Mean structure (Polynomial models, piecewise linear regression)
  - Covariance structure (random effects, residual errors)

Analytical considerations: Missing data

- Handling missing data
  - Pattern of missing data: MCAR, MAR, MNAR
  - Ignorable and non-ignorable
  - Imputations methods: single and multiple imputations

- Approaches to Incomplete Longitudinal data
  - Repeated measures mixed-effects analysis of variance
  - Mixed –effects model after imputation
  - Pattern mixture model
  - Kaplan-Meier analysis of time to definitive deterioration of QoL from baseline

Quality Adjusted Survival (QTWST)

- QTWIST: Quality-Adjusted Time Without Symptoms of disease and Toxicity.
- Evaluate therapies based on both quantity and quality of life through survival analysis
- Based on QALYs.
  - Define QOL health states, including one with good health (minimal symptoms).
  - Patients progress through health states and never back-track.
  - Partition the area under the Kaplan-Meier Curve and calculate the average time spent in each clinical health state.
  - Compare treatment regimens using weighted sums durations, weights are utility based.
- Example: 5 year survival

$$0.6 \times 1 + 0.8 \times 2 + 0.6 \times 1 + 0.2 \times 1 = 3$$

3 adjusted years of life

Compare the average QTWIST in two treatment groups.
Could be that on treatment A, people live longer, but QOL is worse.

Analytical considerations: Endpoints

- Handling Multiple endpoint
  - Primary and secondary
  - Within the same instruments
  - More than one instruments

- Multi dimensions
  - QOL measured by multiple indicators
  - Need validated overall/composite 'score'
  - Or use multivariate methods

- What to measure?
  - Improved survival? Quality adjusted survival?
  - Improved symptoms? Disability measurement or Disease specific symptoms?
  - Global perception of function?

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Reporting HRQoL trials

- Rational
- Objective and hypotheses
- Methods
  - Justification of selection of instruments
    - Validation and references
    - Modifications of questions/formats
    - Copy of questionnaire
    - Psychometric properties
  - Cross cultural validation if relevant
  - Method of administration (self-report, face-to-face, etc.)
  - Method of scoring and interpretation of scores
  - Methods of analysis (a priori vs exploratory)
  - Summary measures

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Reporting HRQoL trials

- Results
  - Timing of assessments and follow-ups
  - Missing data (Proportion missing, drop-outs, dead)
  - Summary of all dimensions/domains
  - If no change were observed, then report
    - Evidence of responsiveness to measures in related settings
    - Lack of floor and ceiling effects in current study
  - Analyses and interpretations
  - Recommendations
  - Drawbacks

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Adolescents with Sickle Cell Disease

- Goal: association between pain, psychological adjustment, and family functioning with HRQoL
- Population: adolescents with Sickle Cell Disease (SCD), 42 patients ages 12-18
- Method:
  - Varni Pediatric Pain Questionnaire (PPQ)
    - patient & parents reporting pain rating scale
  - The Behavioral Assessment System for Children (BASC)
    - Teacher and parents reporting adaptive and clinical functioning
  - Pediatric Inventory for Parents (PIP)
    - 42-items completed by primary care giver re. stress associated with caring for a child with chronic illness
  - Child Health Questionnaire (CHQ)-50
    - Primary care giver and teen assess physical, health and social well-being

Case study: Descriptive Stat

Variable	Mean	SD	Range
Parents			
PPQ pain frequency	2.56	2.07	0.00-7.0
BASC Anxiety	50.05	11.18	33.00-79.0
BASC Depression	48.51	9.92	35.00-75.0
PIP Difficulty	97.87	33.19	47.00-175.0
CHQ Physical Functioning	56.91	32.51	0.00-100.0
CHQ self Esteem	70.04	23.86	16.67-100.0
Child			
PPQ pain frequency	2.41	1.99	0.00-7.0
BASC Anxiety	49.98	8.67	34.00-70.0
BASC Depression	50.71	9.57	43.00-74.0
CHQ Physical Functioning	73.98	24.69	14.81-100.0
CHQ self Esteem	73.61	17.54	33.93-100.0

Case study: Results

- Identified concomitant pain variables of internalizing symptoms and family variables as mediators

- A number of diseases factors have been found to affect HRQoL in pediatric SCD

- Only one significant difference on physical functioning on the CHQ as teens reported higher physical functioning {t(80)—2.68, p=0.009}

- Notice use more than one instrument

- Details are in the referenced py by Barakat et.el.

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Advantages of QoL

- Focus on illness rather than disease
    - patient centered, not laboratory based

- Potential for standardized assessment method

- Potential to assess relative impact of events
    - Traditional clinical end-points may be mixtures of events
    - The events in the mixtures do not have the same impact

- Potential to integrate risks and benefits
    - Traditional approach considers efficacy and adverse experiences separately

Role in Therapeutic Development

- Primary endpoint ?

- Secondary measure to support primary finding ?

- Basis for comparative claim for equally effective drugs ?
  (which implies measuring adverse experiences)

- Advertising claim ?

- Economic aspect

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Concerns

- Global Measures may be Less Sensitive

- Lack of Standardized Instruments
  - Many clinical trials have "custom" instruments that might be tailored to favor the sponsor's treatment
  - Lack of interpretability by clinicians and patients
  - Lack of comparative experience across trials
- Potential to integrate risks and benefits (Conceptual)
  - Is the integration meaningful to the patient ?
    - wearing corrective lenses and death on the same scale
    - considering social functioning & symptoms together rather than separately
- Potential to integrate risks and benefits (Temporal)
  - Adverse experiences mostly occur early clinical benefits mostly occur late
  - Methods may not adequately distinguish reversible from irreversible AE
  - Results may be sensitive to duration of follow-up
  - Study drop out after adverse experiences is common & creates analysis problems

Data Collection

- Mode: self-administered vs. interview
  - Self-admin: Reading ability, fine-motor skills
  - Interview: Hearing problems, age/gender/ethnicity sensitivity, training of interviewer
  - Either: Language

- Content
  - Instrument validity, sensitivity, specificity
  - Sensitivity of questions
  - Frame of reference (cognitive skills, privacy, cultural background)

- Source(s)
  - Patient vs family vs health care provider

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Other QOL issues

- Often interested in whether or not survival with poor quality of life is better than death without suffering.
- "QALY"= Quality Adjusted Life Years
- Example:
  - Cancer: many patients would rather not get toxic therapies and have more enjoyable end of life
- The general idea is to down-weight time spent in periods of poor quality of life.
- Methodologically challenging:
  - How to determine the weights?
  - Different settings might need different weights.

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