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To cite this version:

Annalisa Trama, Massimiliano Dieci. Quality of life in clinical trials for children. European Journal of Clinical Pharmacology, 2010, 67 (S1), pp.41-47. 10.1007/s00228-010-0924-0 . hal-00643026

HAL Id: hal-00643026

https://hal.science/hal-00643026v1

Submitted on 21 Nov 2011

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Journal:	*European Journal of Clinical Pharmacology*
Manuscript ID:	EJCP-2010-0287
Type of submission:	TEDDY Supplement: Review
Date Submitted by the Author:	04-Aug-2010
Complete List of Authors:	Trama, Annalisa; Fondazione IRCCS Istituto Nazionale dei Tumori, Epidemiology Dieci, Massimiliano; Free Consultant, psychiatrist

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Manuscripts

Quality of life in clinical trials for children[1]

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ABSTRACT

Purpose

This review aims at: 1) discussing the importance of measuring Quality of Life (QoL) in children, 2) describing the measures actually available for measuring QoL in children, and 3) listing methodological issues related to the inclusion of QoL outcomes in clinical trials.

Methods

Literature review. Searches were conducted in Pubmed. All articles with the objectives of assessing and reviewing use and issues related to QoL instruments in children were reviewed during the last twenty years.

Results

Despite the numerous arguments for assessing QoL, these data are not typically collected in paediatric clinical trials and research protocols. Because adult measures may fail to address the specific aspects of QoL that are important to the child, many different measures, both generic and diseases specific, have been developed to assess QoL in children however their quality in terms of psychometric properties seems often questionable. Methodological recommendations are provided for designing a study including QoL outcome.

Conclusions

This review confirms the importance of measuring QoL in children because of increased survival rates of children with chronic health conditions and because children account for the highest prevalence of disabling conditions. However, measuring QoL in children is still a challenge mainly because of the limitations of the currently available measures. Further research is needed to reach a consensus on the most appropriate formats for child-centered instruments.

DEFINITION

Definitions of Quality of Life (QoL) vary widely however, there are two central aspects of this construct that are common in most definitions: it is a subjective and multidimensional construct [16].

After much discussion, an international panel of experts agreed upon the concept of QoL. It was defined as "individuals' perception of their position in life in the context of culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad concept affected by the persons' physical health, psychological state, level of independence, social relationships and their relationship to salient features of their environment" [19].

This concept confirms and emphasizes the essentially subjective nature of this entity and it also accepts QoL as a multidimensional concept. Hence, assessment of a number of domains is necessary to derive a comprehensive view of a person's QoL [19].

Although this general definition also applies to QoL of children, the specific aspects of a child's life that comprise the domains of functioning are different. Thus, when designing a paediatric Health Related Quality of Life instrument (HRQL), it is important to ensure that items correspond to experiences, activities, and contexts that are directly relevant to the age of the sample [16].

WHY MEASURING QUALITY-OF-LIFE?

A number of reasons contribute to explain the emergence of QoL as an important outcome measure in Health Services work including: increased survival rates, recognition that treatment should increase life expectancy as well as improve QoL; limited correlation between morbidity and patient satisfaction; and demands for more engagement of patients in decision-making and self-care [9].

[1] Part of TEDDY Supplement

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With regards to children, measuring QoL is important because: 1) advances in medical care are contributing to increase survival also of children with chronic health conditions; 2) children account for the highest prevalence of disabling conditions [13].

In addition, self-report measures can help pediatricians and parents make decisions about the care and treatment of sick children by providing information about the quality of children's life alongside survival time. In chronic non life threatening conditions requiring long term treatments, when the two drugs have similar efficacy and safety, the information on HRQL might be important for the choice of one medicinal product over the other in the current clinical practice [8].

Finally, it is worth mentioning that, although medical intervention often results in the improved health status of pediatric patients, frequent hospitalizations, intrusive medical procedures, and uncertainty of survival, negatively impact childhood development and adjustment. Hence, there is growing interest in the inclusion of *QoL outcome measures in clinical trials to evaluate differential changes in morbidity and the relative efficacy of medical interventions* [20].

The inclusion of *QoL measure in a clinical trial can be helpful to distinguish between drugs with apparently equal efficacy and safety or between treatment programs with similar physical health effects.* In addition, self-reports on subjective states from patients themselves can provide information on consequences of treatment plans (behavioral or psychological problems) that may not be captured by traditional outcome indices [6].

However, planning to include QoL assessment in clinical trials it should be kept in mind that QoL measurement is more relevant in clinical trials with a longer time frame and in disorders affecting patients' multifarious functioning. QoL assess the subject's perception of life over a period of time, thus it is not expected to show rapid changes over hours or days. Clinical trials aiming at demonstrating quick changes are therefore unlikely to benefit by the use of a QoL instrument [19].

In summary, QoL measures can be potentially useful in a variety of contexts including:

- comparing outcomes in clinical trials
- evaluating interventions
- assessing the outcomes of treatment in the long term and palliative care
- allocating scarce resources
- estimating the health care needs of a population

HOW TO ASSESS QOL IN PEDIATRIC PATIENTS?

Adult vs children specific QoL measures

In general, adult QoL measures are inappropriate for use with children because of the level of abstract decision making that may be required, the advanced reading levels, the lack of developmental considerations, and the inclusion of content areas (such as financial concerns) that may be irrelevant [20].

Domain and content

Children's daily activities and experiences differ substantially from those of adults thus, the traditional domains, including physical QoL may not have the same meaning for children as adults. In addition, the impact of compromised health status on income, employment and sexuality may not apply to young children [5]. For children, also a domain such as independence in daily life (e.g. toilet use, dressing and tying one's own shoelaces) may be inappropriate [21].

Developmental Stage

There are differences in the cognitive capabilities and linguistic skills of children under and over 8. Children's cognitive and emotional development affects the overall reliability of self-reported health outcomes. Because children are always changing and developing a successful paediatric HRQL instrument must adjust for age and take into account the pattern of change that children experience over time [5].

Format and scale

Response scales, wording and format of adult measures may require modification to account for children's cognitive and language skills [9].

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In summary, adult measures may fail to address the specific aspects of QoL that are important to the child.

Many different measures, both generic and diseases specific, have been developed to assess HRQL in children [6, 9-10, 17].

Eiser and Morse's [9-10] reviewed 19 generic measures and 24 disease specific measures concluding that only three (Child Health Questionnaire; Pediatric Quality of Life Questionnaire; Health Utilities Index Mark 2) generic measures and two disease specific measures (Pediatric Asthma Quality of Life Questionnaire; The Pediatric Cancer Quality of Life Inventory) fulfilled very basic psychometric criteria.

Rajmil [17] reviewed 10 of the most common QoL instruments to examine the extent to which the content of existing HRQL questionnaires for children and adolescents reflected a coherent concept related to the existing definitions of HRQL. The review concluded that reasonably coherent notion of HRQL underlies instruments currently available to measure HRQL in children and adolescents. However, there is a need for more information on which items and dimensions function best in terms of classic psychometric properties of reliability, validity, and sensitivity to change.

The review of Cremeens [6] confirms the questions raised on the quality of the QoL instruments actually available. Cremeens looked at the different measures of QoL including also self-esteem, self-concept and mental health to make recommendations about the format and quality of health-related self-report measures for children aged 3–8 years. The review revealed shortcomings of the currently available instruments specifically in relation to internal reliability, validity and responsiveness.

Although many measures are available for measuring QoL in children and adolescent, their quality in terms of psychometric properties seems often questionable. A comprehensive conceptual framework of QoL has not yet emerged to guide the development and selection of QoL measures for children and adolescents. However, consensus has been reached on a number of points:

1. QoL is a subjective and multidimensional construct thus instruments should include at least the four core QoL domains (disease state, physical, psychological and social functioning)
2. profile scoring systems that provide a score for each QoL domain are preferable to index or total scores in studies where the richness and multidimensional nature of QoL data are needed for outcome comparisons
3. QoL measures should be reliable and valid, and discriminate between stages of disease and level of dysfunction.

For work evaluating clinical trials, Eiser [9-10] recommended that QoL measures should:

- be brief in order to be completed during a regular clinic visit
- be simple to administer with minimal training or expertise in order to recruit a large sample of patients
- *include those aspects of functioning that are most likely to be compromised by the treatment protocol.*

Rajmil [17] suggested that considering the wide range of QoL instruments available, researchers should look for an instrument that fits their age group and the content of the questionnaire.

Everybody agrees that despite the limitations with current measures and the difficulties in developing new instruments, ***it is important that children have the opportunity to describe their own subjective experience and that specific instruments for children are used in assessing QoL in paediatric population*** [6].

In this context, it is evident that there is a need for a set of minimum standards for child self-report measures, and further research is needed to reach a consensus as to the most appropriate formats for child-centered instruments.

The proxy problem

Assessing QoL in children, the question of who is going to give an evaluation of the child's HRQL has to be addressed: the child him/herself or some proxy such as a parent, a nurse, a doctor or a teacher?

Parents differ considerably from their child in their judgement about the child's HRQL i.e that the level of parent–child agreement about children's lives and functioning is quite poor. This is a common finding that has been described extensively in the literature on proxy ratings.

Matza [16], in her review suggests three options for addressing the proxy issue:

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1. if a child is able to provide reliable and valid data, the child's self report should be used.
   It has been suggested in the literature that children as young as 5 years of age can provide empirically reliable reports on concrete concepts such as pain and over-the-counter medication use, whereas an estimate of 9 or 10 years of age is recommended for subjective concepts such as behaviour or self-esteem [5]
2. if complex constructs have to be assessed, it may be necessary to use a proxy respondent such as adults since they provide more reliable information on more complex, abstract, psychologically oriented concepts. Evidence suggests that parent reports are more accurate than those given by physicians or nurses [1]
3. if a child is very young or severely disabled, parents reports should be used

Because no golden standard exists and both parents' and children's opinions may be valuable in evaluating treatment effects researchers [6, 9-10, 1] have suggested obtaining both parents' and children's evaluations whenever possible.

This approach may provide the most complete information however, it raises several methodological questions (pool data for the analysis? How to interpret findings when parents and children's reports diverge?) [16].

Since there is not a solution to the proxy question it is recommended that researchers carefully examine the costs and benefits of each possible approach. The decision of whether to use child-report, parent-report, or both requires consideration of numerous factors including the child's age, the domains of HRQL that may be addressed, the disease area, the study design, and the intended use of the data.

Generic vs diseases specific measures?

A major advantage of generic measures is that results can be compared across studies and illnesses. Generic measures are suitable to assess QoL regardless of the child's specific condition thus, such measures are preferable for decision on allocation of resources. The disadvantages of generic measures are that they may lack precision and sensitivity.

Disease-specific measures include disease-specific questions thus, these questionnaires are more sensitive to disease-related changes in a patient's health status and are more likely to provide information that is clinically relevant. To determine which type of measure is most appropriate for a given situation depends on the type of study. A descriptive study comparing the self-reported HRQOL for children with constipation with their healthy peers would require a generic questionnaire. However, a clinical trial comparing the effect upon HRQOL for two medical antireflux therapies would require a more disease-specific questionnaire [14].
Modi and colleagues, assessing the changes in pediatric health-related quality of life in cystic fibrosis after intravenous antibiotic treatment for pulmonary exacerbations supported the importance of measuring disease-specific HRQOL when evaluating the impact/effectiveness of medical interventions in children and adolescents with chronic illnesses [15]. Gulvin and colleagues demonstrating that the Food Allergy Quality of Life Questionnaire – Parent Form is responsive to change, and has excellent longitudinal reliability and validity, confirmed, again, that diseases specific measure have to be used to assess the effectiveness of interventions. These studies support further also the application of the minimal clinically important difference (MCID) value for each of the HRQOL measures. MCID scores, go beyond tests of statistical significance and facilitate interpretation of the amount of change patients perceive to be beneficial (Modi). These values can be used as cut-points to classify patients into improved and deteriorated HRQOL categories which can be used to determine the numbers of patients whose scores have changed more than the cut-point and, hence the proportions of patients who do, or do not, report improvement after an intervention. This result is more easily interpreted, in clinical terms, than are mean change scores [7]. In addition, use of the MCID value may allow studies to be adequately powered with fewer patients.

However, HRQOL measures for children are not currently available in may pediatric specialties. The development of a questionnaire is a time-consuming process that should be performed in methodologically sound ways. Sufficient time spent in development is important so as to provide a reliable and valid product [Loonen, 2001]. So far, for children with many other conditions it is only possible to rate QoL using a generic measure while the low incidence of some conditions can preclude development of disease specific measures [9].

Furthermore, disease specific measures are inappropriate where a child has more than one conditions, however the main objection to using disease-specific measures is that they are not comprehensive and do not allow for comparisons of dysfunction across illness groups. Hence, there are trade-offs to consider when choosing between a generic and disease-specific measure [20].

Anyway, the FDA is currently encouraging the use of well-validated patient-reported outcomes, such as HRQOL, in clinical trials [15].

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Common practices

Despite the numerous arguments for assessing QoL data, such data are not typically collected in paediatric clinical trials and research protocols.

Between 1972 and 1992 only 5% of all Phase III Cooperative Group paediatric oncology clinical trials included QoL outcomes [3].

The more recent review of Clarke and Eiser [4] confirms limited use of QoL measures in paediatric clinical trials: only 18 trials including assessment of QoL between 1994 and 2003, 14 different QoL measures used with only 2 fulfilling minimal defined criteria for quality.

Challenges for including QoL measures in trials involve anticipated increased costs, extra time needed to gain patient and parent consent, and lack of sophistication of currently available measures. A major restriction to inclusion of QoL assessment in clinical trials remains limitations in currently available measures, especially for less prevalent chronic conditions. A second problem is that, as already reported, disease specific measures may simply not be available for rare conditions.

Other possible explanation accounting for the limited interest in using QoL measures may include the concern with psychometric properties and the perceptions that QoL measurement imposes an additional and unnecessary burden on families.

MEANINGFUL EXAMPLES

Eiser and Moore in the health technology assessment report [10] provide interesting examples of the use of QoL measure in different context. Some of these meaningful examples follow:

QoL assessment for comparing outcomes in clinical trials

Barr and colleagues [2] used the Health Utility Index (HUI) to assess HRQL in children with acute lymphoblastic leukaemia in remission during post-induction chemotherapy. The data suggest that the burden of morbidity is cyclical in nature, mirroring the schedule of chemotherapy: the impact on QoL was least at the beginning of the treatment cycle and greatest at the beginning of the second week (following use of steroids). Pain was the most frequently reported indicator of morbidity, followed by emotion and mobility. This study providing direct evidence of the morbidity associated with maintenance chemotherapy (relationship between QoL and steroid therapy), and evidence for the sensitivity of the HUI measures, support the feasibility and importance of assessing QoL outcomes in clinical trials.

Harper [11] compared multiple short courses of cyclosporin (12 weeks) with continuous therapy for a year with respect to efficacy, safety, tolerability and QoL. Although there were no differences in QoL at 12 weeks, it was better for both child and family in the continuous treatment group at 12 months.
This information reflects the perceptions patients have on the improvement of their condition and it is important because of the consequences that such perceptions can have on the adherence to the therapy: if patients themselves do not notice an improvement they are unlikely to adhere to protocols.

QoL assessment for evaluating interventions

Jelalian [12] reported an intervention to increase food intake and weight gain in children with cystic fibrosis. The intervention was successful (with regards to the gain of weight) but what is interesting is that families rated the accompanying improvements in the child's energy levels and ability to participate in sports as equally important. Demonstrating that perceived improvements in QoL may be more important to child and family than changes in clinical function noted by paediatricians, the study support the recommendations of assessing QoL in evaluating treatment interventions.

QoL in the assessment of long term treatment outcome

QoL assessments have been reported for survivors of neonatal intensive care by Saigal and colleagues [18]. The HUI measures was used: 78 survivors of neonatal intensive care reported a greater burden of morbidity and rate their QoL to

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be lower than the healthy controls. It is worth mentioning that most survivors were anyway relatively satisfied with their QoL. These kind of findings confirm the importance of QoL measures in assessing outcomes.

METHODOLOGICAL ISSUES TO CONSIDER IN DESIGNING THE STUDY INCLUDING QOL OUTCOMES

Formatting and design [16]

1. Design the response options to help children understand the task.
2. Tie the recall period to a concrete event that children would remember to help younger children understand this task
3. Design instrument appropriate to the children's ability to maintain attention to tasks
4. Adjust administration procedures for different ages: younger children may require interviewers to assist them, older children can be expected to be more independent.
5. When designing child-report measures, it is particularly important to attend to details of formatting, such as maintaining a clear layout of items and using larger print for younger children.

Developmental differences [16]

1. Create multiple forms of a child report instrument, each designed for a different age group. An example of an instrument that uses this multiple form approach is the Childhood Asthma Questionnaire (CAQ)

Because the forms contain different items and domains, data cannot be pooled across age groups. If analyses are conducted separately for the different age groups, it will be necessary to collect a sample that is large enough to ensure sufficient statistical power for each age group.

Statistical analysis

The analysis of multivariate QoL data (including the inevitable missing data) poses different problem compared with analyses based on univariate outcomes such as survival. Strategies to manage missing data are important, as is the need for hypothesis driven trials [10].

Where the aim of the trial includes QoL assessment, power calculations must be performed and are an essential element of clinical trial design. In cases where measurement of QoL is a secondary endpoint, sample size calculations are rare and difficult to establish. However attempts should be made to hypothesise expected changes in QoL scores in relation to the agreed sample size prior to the trial [10].

In addition, because of the greater variability is expected with younger children due to measurement error, a larger sample size will be required to detect treatment effects [16].

Cross-cultural considerations

Measures developed for a specific purpose in one culture may be inappropriate elsewhere:

- specific items may differ in meaning between cultures
- norms developed in one culture may not translate well to others

Cultural differences exists in the meaning of illness, relationships between parents and children, and organisation of health care services.

Because cultural differences do exists, when translating a QoL instrument for use in different countries considerable work has to be dedicated to establish true comparability.

CONCLUSIONS

This review confirms the importance of measuring QoL in children because of increased survival rates of children with chronic health conditions and because children account for the highest prevalence of disabling conditions [13].

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However, measuring QoL in children is not an easy task. Adult QoL instruments seems inappropriate for use in children [20] and although many measures are available for measuring QoL in children and adolescent, these have shortcomings in relation to internal reliability, validity and responsiveness [6, 9-10, 17]. Despite the limitations with current measures and the difficulties in developing new instruments, there is a global consensus on the importance that children have the opportunity to describe their own subjective experience and that specific instruments for children are used in assessing QoL in paediatric population.

Children's cognitive and emotional development affects the overall reliability of self-reported health outcomes. Because children are always changing a successful paediatric HRQL instrument must adjust for age and take into account the pattern of change that children experience over time [5].

Despite the growing interest in the inclusion of QoL outcome measures in clinical trials to evaluate differential changes in morbidity and the relative efficacy of medical interventions the actual use of QoL measures in paediatric clinical trials is limited. In addition to anticipated increased costs, extra time needed to gain patient and parent consent, a major restriction to inclusion of QoL assessment in clinical trials remains limitations in currently available measures, especially for less prevalent chronic conditions [3-4].

In this context, it is evident that there is a need for a set of minimum standards for child self-report measures, and further research is needed to reach a consensus as to the most appropriate formats for child-centered instruments.

ACKNOWLEGMENT

This contribution is part of the Task-force in Europe for Drug Development for the Young (TEDDY) Network of Excellence supported by the European Commission's Sixth Framework Program (Contract n. 0005216 LSHBCT- 2005-005126)

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