Paediatric health related quality of life : a European perspective : instrument development, validation, and use in clinical practice

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General introduction and outline of the thesis

> The goal of all medical interventions should be to promote the patient's health, and thus, to increase their health related quality of life (H.I. Brunner, 2003).

Introduction and outline of the thesis

The DISABKIDS project is a European collaboration of clinicians and investigators that received funding from the European Commission in 2001. Over the last four years the DISABKIDS project's aim was to cross-nationally develop a new European health related quality of life (HRQoL) instrument for children and adolescents with a chronic medical condition [1](Box 1). Some of the steps taken during the developmental process of the European DISABKIDS HRQoL instrument for children and adolescents with a chronic medical condition are described in this thesis. Data from the asthma population is a recurring theme in most chapters as the Dutch DISABKIDS centre operated as asthma consultant.

Four criteria must be met:

- If it occurs in children aged 0 to 18 years inclusively
- If its diagnosis is based on medical scientific knowledge and it can be diagnosed using reproducible and valid methods or instruments according to the professionals
- If it is not (yet) curable
- If it has been present longer than three months or if it will very probably last longer than three months, or if it has occurred three times or more during the past year

Box 1. Criteria used to define when a disease or condition is considered chronic in childhood [2].

This introduction will first supply the readers with an informative background on HRQoL research. The general HRQoL principles will be explained together with the impact of paediatric asthma on the life of a child or adolescent. The development of HRQoL instruments is also explained and the aim and developmental steps of the European DISABKIDS project are described.

Health related quality of life

In 1948 the World Health Organization (WHO) defined health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"[3]. This realisation has initiated the discussion on how to improve and measure health. At the same time the shift in mortality and morbidity rates of some chronic medical conditions (e.g. cystic fibrosis, cancer and metabolic disorders) have encouraged the discussion on how to improve quality of life (QoL) in patients. The first hit on QoL in PubMed* dates back to 1966 and although QoL has become a general concept in research and daily life since then, it is still an elusive concept.

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* The National Library of Medicine's search service that provides access to an electronic database of over 15 million citations in biomedical literature dating back to the 1950's.

Definitions of QoL often include aspects as: "the perceptions of physical, psychological, social, cognitive, functional and behavioural dimensions of well-being and function as perceived by the person concerned" [1]. The World Health Organisation QoL (WHOQoL) group defines QoL as: "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad-ranging concept, incorporating in a complex way individuals' physical health, psychological state, level of independence, social relationships, personal beliefs and their relationships to salient features of the environment" [4]. When assessing the impact of health and illness on a person's life one hopes to measure the subjective perspective called health related quality of life (HRQoL) [5]. HRQoL can be defined as: "a psychological construct which describes the physical, mental, social, psychological and functional aspects of well-being and function from a patient perspective" [6]. HRQoL assesses the patient's functioning from a broader scope than clinical measures alone to help understand the effects of a medical condition on a patient's well-being. Not only the objective aspects related to illness and treatment are assessed, but also the more subjective concepts surrounding a condition, for example the patient's perception of their emotional and social situation [7,8].

Over the last decades there has been an increase in publications on HRQoL assessment in children and adolescents, healthy or with a chronic medical condition [9,10]. In general one can distinguish two main areas in which HRQoL assessment can be used: research and clinical practice. Most publications on paediatric HRQoL have psychometrically described the development and validation of questionnaires [11-17]. Numerous evaluative studies of children and adolescents with chronic conditions have been published [18-25]. There is also an increased interest in implementing HRQoL assessment in paediatric clinical trials, for instance when choosing between medications or comparing benefits or impact of a certain treatment regime [26-31].

The latest challenge is to implement HRQoL questionnaires in paediatric clinical practice for individual assessment [32-34]. There is an awareness of the importance of not only treating a child's physical condition, but also incorporating the psychological and social aspects, acknowledging that the child's total well-being is affected by a medical condition [35]. One reason for this awareness may be that objective measures of disease severity (e.g. pulmonary function) have shown modest correlations with how a patient feels and are thus seen as insufficient determinants of health status. The HRQoL of one patient can also differ extensively with another, even when their objective clinical parameters are similar [36-40].

There is evidence that HRQoL assessment can aid patient management in adults. Benefits include monitoring changes in patients, improving the clinician-patient relationship and communication, and potential screening for problems [41-48]. While HRQoL assessment is on the rise in adult clinical practice this is not being imitated in the paediatric setting. Although investigators have suggested to assess HRQoL in paediatric clinical practice, proven relevance of HRQoL implementation in paediatric clinical practice is unavailable and there are few indications that routine HRQoL assessment is being included in paediatric clinical practice [30,33,34,49-51]. Thus it is only assumed that, as in adults, individual HRQoL assessment in paediatric clinical practice can improve the clinician-patient relationship, facilitate communication, provide a complete impression of the child or adolescents health status, identify existing problem areas and initiate necessary intervention. Why HRQoL assessment is not widely included in paediatric clinical practice may depend on several factors. Some of these issues include the lack of valid and reliable questionnaires, minimal evidence of the benefit to patient care, the limited availability of disease specific measures, limited self-completion questionnaires for children and adolescents adapted to their age group, insufficient information on interpretation and use of questionnaires, and cultural barriers [9,30,52].

The clinician can add to these barriers through insufficient knowledge of HRQoL, constraints on financial and human resources, the belief that HRQoL assessment is unimportant, unawareness of available questionnaires or inexperience with questionnaires [32,42,47,53,54]. Encouraging is the confirmation that clinicians do consider their patient's HRQoL to be important and are interested in implementing HRQoL assessment in clinical practice [32,53-56]. This is reason enough to further develop and improve HRQoL assessment and eliminate any obstacles that stand in the way of implementation in clinical practice. Moreover, the use of HRQoL questionnaires is likely to improve if clinicians have access to valid and easy to use questionnaires with clinical value in areas they find important.

HRQoL and asthma

The most common chronic medical condition among children is asthma. Its prevalence varies greatly between countries, with a high prevalence in Australia, New Zealand and Ireland (20-28%) and a low prevalence (mostly under 5%) in countries in South-East Asia and Northern and Eastern Europe [57]. The majority of children develop their asthma before five years of age [58,59]. Asthma is a chronic inflammatory disease of the airways. A diagnosis of asthma is mainly based upon clinical observations [60]. In susceptible individuals inflammation and airway narrowing can cause recurrent episodes of wheezing, chest tightness, coughing (typically nocturnal or exercise related) and shortness of breath [60,61]. These episodes are usually reversible either spontaneously or with treatment [60] and can arise spontaneously or can be triggered by factors such as pollen, cigarette smoke, house dust mite, viral infections, exercise or weather changes [61-63]. In cases of acute asthma exacerbations symptoms can be more severe and in some cases even life threatening [58,60]. Asthma is linked to family atopy, and children with asthma are prone to allergies [61,62]. Asthma management consists of monitoring the course of the disease, avoiding or eliminating triggers (allergens, respiratory infections, irritants, chemicals, physical activity and emotional stress) that influence asthma symptoms or exacerbations, educating patients and pharmacological therapy [60,63]. Pharmacological treatment is focussed on suppressing inflammation and reversing bronchoconstriction. Initial treatment usually includes inhaled bronchodilators as reliever and, if this is insufficient, inhaled anti-inflammatory agents as protector in daily doses [61,63].

Asthma can impact a child or adolescent's life in several areas [64]. Children need to cope with taking their daily medication and some may be concerned about possible adverse effects. The symptoms they experience can lead to physical limitations, for example during sport or play. Nocturnal symptoms may disturb their sleep [60]. Children might miss school days or experience poor school performance [60,65]. Some may experience fear or panic due to the often sudden, life-threatening nature of the attacks [66,67]. Their social activities may be limited due to the necessity of avoiding potential trigger factors (e.g. cigarette smoke, house dust mite) or as a result of physical limitations [14]. The above factors can also add to the fear of being rejected by peers because of feeling "different" [68]. Children can be troubled because they cannot integrate fully with their peers, making them feel isolated and left out. Any of these experienced limitations in physical, social and emotional functioning can cause feelings of anger, depression, anxiety, embarrassment or frustration [69-72]. A study by Forrest et al. (1997) has also shown that teenagers with asthma experience more physical and emotional problems, lower perceived well-being, more activity restrictions and more negative behaviours that threaten social development than teenagers with no asthma [73]. A meta-analysis by McQuaid et al (2001) shows that children with asthma have more adjustment difficulties and more internalising and externalising problems related to the severity of their asthma than healthy children [74]. Asthma can disrupt the family routines and cause an increase in family stress [75] but can also be affected by family factors [76]. Parents may overprotect a child with asthma, creating the possibility of restricting them in their normal daily activities [65,77].

Overall, there are many factors that can cause extra stress and influence a child's or adolescent's mental and physical behaviour. These factors make it important for clinicians to become aware of the impact of asthma on a child or adolescent and their family. HRQoL questionnaires for children and adolescents are therefore likely to become increasingly important for the future of paediatric clinical practice and research.

Developing HRQoL instruments

An increasing number of paediatric generic and condition-specific HRQoL questionnaires have been developed since the first publications on paediatric HRQoL in the 1970's [5,9,78]. Some of the more well-known generic questionnaires include the Pediatric Quality of Life Inventory™ (PedsQL™4.0)[79], the Child Health Questionnaire (CHQ)[80] and the Child Health and Illness Profile (CHIP)[81]. Frequently used measures of HRQoL in children or adolescents with asthma are the Paediatric Asthma Quality of Life Questionnaire (PAQLQ)[36] and the Childhood Asthma Questionnaire (CAQ)[13,82].

In general the development of each new HRQoL questionnaire follows similar phases [83]. First, one should determine if there is a need for a new questionnaire [32]. Secondly a basic consensus within the research group should be reached on the content and structure of the questionnaire [84]. Choices include what one wants to measure, which group to test, their age range, their specific situation, and how long the questionnaire should be. Subsequently one should consider if a questionnaire is to be used for instance for individual assessment, group comparison or national screening surveys [85,86]. Nowadays there is a preference for cross-national questionnaires for use in multi-national clinical trials or to enable comparisons between different cultures or social groups [87]. Decisions need to be taken on whether to develop the instrument in one country and translate it for use in other countries (sequential), or develop it cross-nationally (simultaneously)[88].

The next phase is to generate questionnaire items through a top-down or bottom-up developmental process. Items can be collected in an expert consensus meeting (top-down development) and include clinical experience, literature or available questionnaires [11,15,18]. While the clinician's and even parent's opinion on HRQoL was regarded as sufficient, it is now known that their opinion can be different to that of the child or adolescent's [33,89-92]. For this reason the bottom-up (patient-derived) process is often applied in which the group of interest (e.g. children with asthma) provide the aspects they find important. Patient-derived methods can include interviews, focus group discussions or surveys [14,93,94]. The statistical data on selected items, collected in a pilot test, can then help to reduce the items and test the domain structure for the final instrument.

As mentioned before, there have always been restrictions to the use and availability of paediatric HRQoL questionnaires. So, although there are several HRQoL questionnaires for children and adolescents, new questionnaires are still being developed or improved, either for new chronic conditions or for use in new situations. Another reason for the ongoing development of new questionnaires is the growing need for (translated) HRQoL instruments in cross-national multi-centre studies. The aim of the DISABKIDS project was to take existing limitations into account and cross-nationally develop a new European instrument through a bottom-up process, consisting of a chronic generic and several condition-specific modules, for use in children and adolescents with a chronic medical condition and their parents.

DISABKIDS

The DISABKIDS project is a collaboration of investigators from seven European countries (Figure 1) that set out to develop a new European HRQoL instrument for children and adolescents with a chronic medical condition [1]. Included in the project were children and adolescents in three age groups (4-7, 8-12, 13-16) with one of the following chronic medical conditions: asthma, juvenile idiopathic arthritis (JIA), atopic dermatitis, cerebral palsy (CP), cystic fibrosis (CF), diabetes or epilepsy. Each country had a consulting role in one of the chronic medical conditions. The project was funded through the Fifth Frame work Research Programme 'Quality of life and management of living resources' of the European Community and was oriented towards three tasks:

1. Developing modules for assessing HRQoL in children and adolescents with chronic medical conditions.
2. Psychometrically testing the instruments in different countries.
3. Assessing the value of the DISABKIDS instrument by implementing and evaluating it in paediatric clinical practice.

Figure 1. Participating countries in the DISABKIDS project

The DISABKIDS project is unique due to the simultaneous cross-national development, the patient-derived bottom-up procedure, the modular design, the inclusion of seven chronic medical conditions, the wide age range (4-16 years) and the availability of a self-assessment and a proxy version. The instrument will be available in paper-pencil and as computer version in several languages.

The DISABKIDS project runs parallel to the KIDSCREEN project, which is an epidemiological research project that aims to develop and test a generic HRQoL questionnaire in primarily healthy children and adolescents [84,95].

The DISABKIDS and KIDSCREEN projects have defined and developed a three level modular instrument (Figure 2) by combining the following modules:

1. The KIDSCREEN generic module
2. The DISABKIDS chronic generic module
3. The DISABKIDS condition-specific module

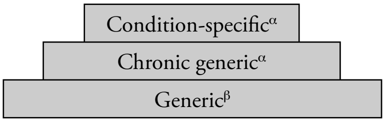

Figure 2. Modular design of the DISABKIDS$^{\alpha}$ and KIDSCREEN$^{\beta}$ instrument.

The generic module consists of items that are applicable to all children and adolescents, healthy or ill. This module is capable of measuring HRQoL across patient populations and can compare the outcome to a healthy population. The chronic generic module, as defined bij the DISABKIDS group, is applicable to any child or adolescent with a chronic medical condition (Box 1). Items relate to areas of life that are affected by chronic medical conditions. This module can be useful in situations where it is important to be able to measure HRQoL across different conditions and take into account common areas affected by chronic conditions. The condition-specific module assesses those aspects that are specific to patients with a certain chronic medical condition, often referred to as disease-specific. It can only compare between groups of patients with the same chronic condition but has the potential to identify smaller changes important to research or clinical practice [5,34,96,97]. This three modular design is unique to the DISABKIDS and KIDSCREEN projects and can supply the investigator or clinician with the opportunity to assess HRQoL at different levels.

International consensus was reached on the methodology of the questionnaire development. The procedure was derived from earlier experience of investigators in (international) instrument development [15,98-101] and consists of several work packages that reflect a stepwise instrument development procedure (Box 2).

WP 1: Literature review
WP 2: Focus groups
WP 3: Item development
WP 4: Translations
WP 5: Pilot study
WP 6: Analysis pilot study
WP 7: Field study
WP 8: Analysis field study
WP 9: Implementation and final results

Box 2. Work packages (WP) within the DISABKIDS project

DISABKIDS work packages

Literature Review (WP 1)

A literature search in Medline (1985-2000) was done for the identification of abstracts concerning HRQoL assessment in children and adolescents with a chronic medical condition. Available assessment instruments and known HRQoL dimensions were reviewed for their use in the project.

Focus Groups (WP 2)

Children and adolescents with asthma, juvenile idiopathic arthritis, atopic dermatitis, cerebral palsy, cystic fibrosis, diabetes mellitus and epilepsy participated in focus groups or interviews. Statements were collected from the literal transcripts for the item generation. A guideline manual insured that the groups were conducted in a similar method in all participating countries.

Item Development (WP 3)
The collected statements were used for the construction of the DISABKIDS instrument. The statements were divided into separate modules; a generic module, a chronic generic module and seven condition-specific modules. The statements underwent a reduction process to limit the amount of items for the pilot instrument.

Translations (WP 4)
Guidelines were established to harmonise the translations across countries. Two translators independently conducted a forward translation of the English pilot items into the target language. The translations were reviewed for conceptual equivalence and a single forward translation was decided upon. A backward translation was then performed, which was compared to the original item for the final translation. This process was performed in all the participating countries and compared across languages.

Pilot Study (WP 5)
Data were collected for the psychometric analysis. Each condition was tested in at least two countries, while asthma was tested in all countries. Children and adolescents participated in a cognitive interview to determine the comprehensiveness, clarity and acceptance of the questions.

Analysis pilot study (WP 6)
Data were collected in an international SPSS[†] data file. The analysis was carried out at an international level using classical multi-scaling as well as modern psychometric methods. The final domains were determined and item numbers reduced through quantitative psychometric analysis and the qualitative cognitive interview.

Field study (WP 7)
Data were collected to test the psychometric performance of the pilot instrument in populations of children and adolescents with selected chronic conditions. Asthma was again tested in all countries.

Analysis field study (WP 8)
The final scale structure of the DISABKIDS instrument was tested, including the reliability, validity, retest-reliability and the construct validity.

Implementation (WP 9)
The DISABKIDS instrument was implemented and tested in several settings. Analyses are still in progress. A paper and computer version was made available in several languages.

[†] Statistical Package for the Social Sciences: software package used for conducting statistical analyses.

Outline of this thesis

In this first chapter we set out to explain some general principles related to HRQoL, asthma, developing a questionnaire and the DISABKIDS project (**Chapter 1**). The second chapter describes a survey done under the members of the Dutch Paediatric Association. The objective was to learn more about the perspectives of the paediatricians on HRQoL assessment in clinical practice. Knowing what the opinion of a future user group is helps to implement a new HRQoL questionnaire, like the DISABKIDS instrument (**Chapter 2**). The third chapter describes the applied patient-derived methodology. Focus groups and interviews were used to identify the relevant aspects of HRQoL from children and adolescents with chronic medical conditions. Statements for the chronic generic and condition-specific modules were generated through this patient-derived method. Focus groups have proven to give a good indication of what the patient finds important and therefore emphasises the importance of the DISABKIDS bottom-up procedure (**Chapter 3**). The results of the asthma focus groups and interviews, conducted in four European countries, are described in chapter four. Recurring themes are discussed and aspects related to living with asthma are described in a quantitative manner (**Chapter 4**). Qualitative data was collected from the cross-national DISABKIDS focus groups and interviews. The sequential reduction steps necessary to cut down the vast amount of collected statements for use in the pilot study are set out in chapter five (**Chapter 5**). The development of the seven condition-specific modules is described in chapter six. A stepwise analysis was applied including the statistical results from the pilot and field study, the cognitive interview and expert opinions (**Chapter 6**). The validation study of the asthma population is presented in chapter seven. The relationship between HRQoL, disease severity and existing questionnaires is evaluated (**Chapter 7**). The discussion is laid out in chapter eight in which limitations of questionnaire development and future suggestions for research are presented. Concepts regarding the implementation of individual HRQoL assessment in clinical practice are discussed, including limitations, necessary requirements and clinical value (**Chapter 8**).

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