Electronic patient and parent reported outcomes in pediatric clinical practice
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Chapter 1

General Introduction
Introduction

As a result of the improvements in medical care, the prevalence of chronic illness in children has increased worldwide. In the Netherlands, at least 14% (500,000 children) of children grow up with a chronic illness. The term ‘chronic illness’ refers to illnesses that require at least 6 months of continuous medical care, permanent lifestyle changes and continuous behavioral adaptation to the unpredictable course of the illness. Chronic illnesses have no known cures but can be managed medically. The medical treatment forces these children to face several problems such as frequent hospitalizations, painful medical procedures, pharmacological interventions, school absenteeism, and restriction of activities. Based on extensive pediatric research, we know that these children have negative outcomes on different aspects of their lives. They often suffer from a multitude of short and long-term cognitive, behavioral and emotional problems (e.g. anxiety, attention problems, and lower self-esteem), social maladjustment and a lower Health Related Quality of Life (HRQOL).

In addition, the impact of chronic illness in childhood on the “Course of Life” (CoL) of a child is inescapable. It is difficult for chronically ill children to meet their age-related developmental tasks (such as making contacts outside the family, participate in social or sport activities, or to gain independency). So, their CoL is at risk to be delayed. However, going through these experiences is tremendously important to the adjustment needed later in adult life. For example, parents of a chronically ill child are in general more involved in daily activities of the child, as a result of the chronic illness. This parental involvement and the treatment regimens that restrict the child’s physical activities may limit the child’s opportunities for unsupervised time with peers, which may affect the achievement of developmental milestones. In addition, a hampered CoL can lead to decreased HRQOL later in life.

As a result of the improvements in medical care, the number of families living with a chronically ill child has also increased. A chronic illness has an impact on the whole family, especially on the parents caring for the ill child. Although much research is done on children with chronic illnesses, relatively little is known about the (psychosocial) functioning of their parents. Living with a chronic illness requests from the child and the family to manage various stressors related to uncertainty and uncontrollability of the disease. Therefore, it is important to investigate the unfavorable outcomes in both children with a chronic illness and their parents, and to develop and implement interventions to support them.

In this thesis we focus on children, adolescents and young adults with Juvenile Idiopathic Arthritis (JIA), their parents, parents of children with different chronic illnesses and a new intervention for monitoring HRQOL. This thesis comprises three main topics; 1) Patient Reported Outcomes, 2) Parent Reported Outcomes and
3) Feedback of electronic Patient Reported Outcomes (ePROs) in pediatric clinical practice.

**Patient Reported Outcomes**

One way to get insight in the functioning and HRQOL of children is with the use of Patient Reported Outcomes (PROs). PROs include the self-assessment of functional status, symptoms or other concerns, such as patient’s needs and satisfaction with care. Questionnaires retrieve information directly from the patient without the intervention of an observer and are therefore a form of PROs 18.

**Juvenile Idiopathic Arthritis (JIA)**

This thesis focuses on children, adolescents and young adults with JIA. JIA is arthritis of unknown etiology that starts before the age of 16 years. It is one of the most common rheumatic diseases in childhood and a major cause of childhood disability. Worldwide, 0.07-4.01 per 1,000 children is affected 19,20. Children with JIA experience functional impairment due to joint manifestations of the disease, morning stiffness, and fatigue 21, but the degree to which patients are affected differs. The course of the illness is related to the subtype. The mildest form of JIA is in general persistent oligoarthritis. Systemic JIA is the most severe form. When the disease is not completely controlled, long term complications can occur, including flexion deformities, damage of bones, and bony overgrowth that may result in different length of limbs 19,22,23. In addition, chronic uveitis (inflammation of the middle layer of the eye), which occurs as a complication in 5-20% of patients, can lead to cataracts and blindness 24.

**Treatment of Juvenile Idiopathic Arthritis (JIA)**

There is no definite cure for JIA; treatment is aimed at controlling pain and achieving inactive disease or remission by means of medication, which might have side effects 19.

During diagnosis, while other causes of arthritis are being excluded, most patients are given NSAIDs. These drugs relieve pain and stiffness usually within a few days and do not, as more aggressive treatments can, interfere with the disease course in case of misdiagnosis. Children with oligoarticular disease are often given NSAID monotherapy, intra-articular corticosteroids alone, or a combination of both. Patients with a definite diagnosis of polyarticular disease or oligoarticular disease refractory to intra-articular steroids are candidates for treatments with second line agents, including DMARDs (sulfasalazine, methotrexate, prednison and biologicals, depending on the course of the disease).

Depending on the JIA subtype and severity of disease, recommendations for treatment are coordinated by regular checks by a pediatric rheumatologist and ophthalmologist. Occupational and physical therapy are integral in the management
of JIA to improve mobility and help to manage pain. Psychosocial support for the patient and family by a psychologist and social worker is often recommended to improve self-management and coping with the challenge of the impact of the disease in daily life. The idea is that a well chosen multidisciplinary team will enable the best possible care 20,28.

Even with the improvements in treatment in the last decades, a large proportion of children with JIA still has active disease throughout childhood into adulthood 25-27.

Health Related Quality of Life (HRQOL)
One of the main topics of this thesis is to measure HRQOL, and to feed back HRQOL to the pediatrician. We know that physical measures alone are not sufficient to assess the impact of JIA on a child’s life. Different PROs are possible to include in outcome studies, such as functional ability, anxiety and depression and behavioral problems. However, the evaluation of HRQOL is essential for a full assessment of the influence of the illness on a child’s life. Quality of Life (QOL) is defined by the World Health Organization as “individuals’ perceptions 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” 29. Health Related QOL (HRQOL) is a concept that incorporates measures of physical symptoms, functional status, and disease impact on psychological and social functioning 30,31.

JIA and HRQOL
Some studies suggest that JIA does not negatively affect HRQOL or psychosocial functioning during childhood 3,32-34, whereas other studies report that children with JIA have a lower HRQOL compared to healthy children 35-40 and compared to children with other chronic illnesses 41,42. Although a large number of studies have assessed HRQOL in children with JIA, only few studies focused on predictors of HRQOL in children with JIA. So far, risk factors identified for impaired HRQOL are polyarticular arthritis or extended oligoarthritis 43, short disease duration 40, pain 37,44, disabilities and increased disease severity 45.

HRQOL studies in Europe are scarce 39,40,46 and they often include heterogeneous groups of patients based on different age cohorts and with different national health care systems 43,47. Many studies use proxy reporting 39,48,49, whereas other studies have shown that self-reporting appears to be more reliable for evaluating HRQOL44,50. Different HRQOL questionnaires have been used, both generic and disease-specific. Because of all these aspects, it is difficult to compare the various studies and to generalize the results to the JIA patients in the Netherlands. In addition, to develop tailored interventions for children with JIA, it is important to gain more insight in the predictors of HRQOL.
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Growing up with JIA
Children with JIA have a major risk of having active inflammatory disease entering adulthood 51,52. Besides, pediatric rheumatic disorders are typically more severe than the same disorders in adults and may have substantial psychological and medical consequences 53. In addition, children and adolescents with JIA have more problems compared to healthy peers, such as internalizing problems including depression and anxiety 35,54.

For all these children, transition into adulthood is a critical phase. Children and adolescents with JIA are expected to pass similar developmental stages as their non-disabled peers; to leave home, develop psychosocially, and define a role for themselves in the community through employment or other activities. However, young adults with JIA face many challenges to obtain normative developmental milestones. The achievement of psychosocial milestones while growing up (psychosocial developmental trajectory) is related to participation in society, for example labor participation. Based on former studies, up to 60% of all patients with rheumatic disorders continue to have limitations in their daily life 32,55-58 and also work disability is much higher in patients with Rheumatoid Arthritis compared to the general population 59,60. Insight into early determinants of adjustment in adult life may help to develop interventions in pediatric healthcare to create conditions for better participation in society, including labor participation. Therefore, and because little is known on this topic, it is important to assess the psychosocial developmental trajectory of young adults with JIA.

Parent Reported Outcomes
As described earlier, chronic illness during childhood has an impact on the whole family, especially on parents taking care of their ill child 16. Daily care involves management of the illness; parents spend on average 3-5 hours a day on medical care management 61,62. Daily care also includes instructing others, incorporating care in daily family life, managing the consequences on siblings and finding the balance between caring and their personal needs 63.

Parents of a chronically ill child frequently report mood problems, anxiety, physical problems, cognitive problems and a feeling of lack of control over daily events because of the unpredictable nature of their child’s illness 64. They are also more likely to report higher levels of parental distress and lower levels of HRQOL than parents of healthy children 65,66. Parenting a child with a chronic illness affects the roles of parents, such as being a partner, employee or family member 67-70, ultimately resulting in increased burden for parents 61,71. They are therefore at risk of suffering from a burn-out 72. Anxiety and depression in fathers and mothers of a chronically ill child has been documented only to a limited extent, and studies often focus on a
single diagnosis or report only small sample sizes\textsuperscript{73-76}. However, the previous studies all point in the same direction: parents of a chronically ill child are more vulnerable to have higher levels of anxiety and depression. Therefore, it is necessary to investigate this in a large sample of parents with a chronically ill child.

Parents of children with JIA
Like other chronic illnesses, caring for child with JIA places enormous demands upon the entire family and may have many adverse social and emotional consequences\textsuperscript{77}. The psychosocial impact of JIA on parents has been documented only to a limited extend. Results suggested that mothers of a child with JIA experience more feelings of depression\textsuperscript{78,79}, show more mental health problems\textsuperscript{80} and more psychological distress\textsuperscript{81}. However, another study did not find any differences between parents of a child with JIA and a comparison group on parental distress\textsuperscript{82}, on HRQOL and anxiety and depression\textsuperscript{83}.

It is important to gain more insight in the psychosocial functioning of these parents, because their well-being affects the well-being of the child. For example, increased parental distress is associated with more depressive symptoms in children with JIA\textsuperscript{84}. Furthermore, a parent’s belief that a child is vulnerable can potentially have an adverse effect on the child’s development\textsuperscript{85}. Children with a chronic illness tend to be more socially anxious when their parents perceived them as more vulnerable\textsuperscript{86}. In addition, perceived vulnerability can lead to overprotective behavior in parents and psychological problems in children, such as psychosomatic complaints and school underachievement\textsuperscript{87}.

In conclusion, more insight is needed in the functioning of parents with JIA, their HRQOL and if they perceive their child as vulnerable, to be able to support these parents, increase their psychosocial functioning and as a result positively influence the well-being of the child.

Screening and monitoring for parental distress
High levels of distress in parents are associated with the child’s maladjustment to the illness\textsuperscript{88-91} and it is therefore important to gain insight in the emotional functioning of parents in order to be able to develop strategies to support them. In pediatric clinical settings, parental support is often integrated in pediatric care, for example with a medical social worker as part of the multidisciplinary team. However, identifying parents with a chronically ill child who are experiencing psychological distress or who are at risk for distress can be difficult and time consuming. Parent reported outcomes are usually general instruments which do not focus on the impact of caring for a chronically ill child. A short non-invasive screening-tool that detects the level of parental distress, indicates a starting point for targeted interventions
and can monitor the functioning of parents over time, would be useful. However, currently no appropriate short questionnaire is available to identify parents in need of additional support.

Feedback of HRQOL Patient Reported Outcomes (PROs) in Pediatric Clinical Practice

The use of PROs in daily clinical practice is receiving increased attention. HRQOL questionnaires are commonly used to collect information about a specific group of patients. These questionnaires retrieve information directly from the patient and are, as described above, a form of PROs. Today, HRQOL questionnaires are increasingly used in daily clinical practice. The PROs are provided to the physician to facilitate communication with patients during a consultation. The majority of HRQOL studies focuses on adults and oncology practice. Routine assessment of HRQOL in a clinical setting improves communication between physicians and patients and facilitates early recognition of lowered HRQOL in adult patients. Although solving problems in social and emotional functioning is not the main scope of a physician, the discussion of HRQOL topics itself can lead to a decrease in negative feelings or feelings of insecurity. Physicians generally consider the use of PROs as a valuable addition to daily health care. Nevertheless, finding an improvement in patient satisfaction with care or detection of an increase in HRQOL scores is still difficult. This is due to methodological challenges, such as high baseline scores on patient satisfaction (ceiling effect) or the nature of the study design.

Especially in pediatrics, there is a need to address HRQOL and psychosocial issues in daily clinical practice. In the developmental context PROs can be valuable, because children with a chronic illness are at a greater risk for psychological problems than their healthy peers. In addition, children have more difficulties expressing themselves verbally than adults. The use of PROs may therefore help to monitor, identify and discuss HRQOL issues in children with chronic illnesses. However, studies on the use of (HRQOL) PROs in pediatric clinical practice are scarce compared to adult practice. Only two studies on the feedback of PROs are conducted in pediatrics. The first is the study of de Wit et al. She showed that systematic monitoring and discussing HRQOL in adolescents with diabetes improved their psychosocial well-being and their satisfaction with care. After one year, de Wit showed that the beneficial effect of discussing and monitoring HRQOL during pediatric clinical practice did not sustain when the feedback was discontinued. This underlines the need to incorporate the continuous HRQOL feedback in clinical practice. The other study is the Quality of Life in Child Oncology (QLIC-ON) project, which was conducted in our children’s hospital.
The QLIC-ON study was conducted by our research group between 2005 and 2009. This study was aimed at pediatric cancer patients in the period shortly after the end of successful treatment. The results of the QLIC-ON study were encouraging, as they demonstrated that the feedback of HRQOL increased discussion of emotional and psychosocial functioning. Additionally, it improved the identification of emotional problems. Furthermore, the intervention did not lengthen consultation duration.

In this study, the HRQOL questionnaires were completed at the outpatient clinic immediately before the actual doctor’s visit, with patients using stand-alone or touch screen computers. A printed version of this PRO was handed to the physician to be discussed during the consultation. This method was very time consuming and often had logistical problems such as lack of privacy and room at the clinic. The use of a web-based program could overcome these problems and could contribute to an improved use of PROs in clinical practice.

Therefore, we started a new multicenter study, the KLIK (Dutch: Kwaliteit van Leven in Kaart) study and we developed a website (http://www.hetklikt.nu). The KLIK study was developed based on the experiences of the QLIC-ON study. Children or their parents (depending on the age of the child) could now complete the HRQOL questionnaires at home and pediatricians could retrieve these PROs directly from the website during the visit. This multicenter KLIK study, presented in this thesis, aimed at using these electronic PROs (ePROs) in daily pediatric rheumatology clinical practice.

The intervention: The KLIK ePROfile
The intervention consisted of providing HRQOL scores of the patient (ePROfile, figure 1) and scores on functional ability (ePROfile, figure 2) to the Pediatric Rheumatologist (PR) during consultation, focusing on identifying, monitoring and discussing HRQOL problems. The answers on the online questionnaires were automatically converted into an ePROfile and keyed to colors, with red (“often” and “almost always”) indicating that a child experienced problems with an issue, orange (“sometimes”) representing mild problems, or green (“never” and “almost never”) indicating no reported problems. The items and sum cores were shown on the computer screen and provided the opportunity to discuss the results directly with the child and parents. To optimize the effectiveness, all PRs were trained in the use of the PROfile.
Chapter 1

Figure 1. The ePROfile - Generic HRQOL scores
Chapter 1

Study design
A sequential cohort design was used (figure 3)\(^{104,105}\). Patients took part in either the control or intervention group, depending on the date of consultation; if a patient participated in the control group, that patient was not eligible anymore for participation in the intervention group. All PRs first participated in the control group (control period: February to April 2009; online questionnaires completed by the patient but the ePROfile not provided to the PR) and thereafter in the intervention group (intervention period: May 2009 to February 2010; online questionnaires completed by the patient and the ePROfile provided to the PR). Randomization was not desirable, because it could result in the provision of extra attention to HRQOL issues in the control group (contamination)\(^{99,110}\). To assess the effectiveness of the intervention, shortly after the consultation the parents and the PR completed an online questionnaire about the HRQOL topics discussed, referrals, and their satisfaction with the consultation, again using the website. In addition, the ePROfile was evaluated by the parents and PRs in the intervention period.
Chapter 1

Aims of the thesis

This thesis adds to the current literature by focusing on three aspects of pediatric PROs research:

1. Patient Reported Outcomes

   Aims:
   - To assess the HRQOL and the predictors in a group of children and adolescents with JIA.
   - To assess the HRQOL and the psychosocial developmental trajectory of young female beneficiaries with JIA.

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Figure 3. KLIK study: sequential cohort design
2. Parent Reported Outcomes

Aims:
- To assess the HRQOL, parental perceived child vulnerability and the associated variables of parents of a child with JIA.
- To determine the levels of anxiety and depression and the associated variables in parents of a child with a chronic illness.
- To develop and validate the Distress Thermometer for Parents (DT-P) and to determine a cut-off score for clinical parental distress.

3. Development, effectiveness and implementation of PROs in pediatric clinical practice

Aims:
- To describe the development of the QLIC-ON and KLIK ePROfile and intervention.
- To investigate the effectiveness of the KLIK ePROfile.
- To describe the implementation of the KLIK ePROfile in pediatric clinical practice.

Outline of the thesis

The general introduction of this thesis is covered in Chapter 1. The chapters include the identification of problems in children, adolescents and young adults with a chronic illness (Patient Reported Outcomes) and their parents (Parents Reported Outcomes). In addition, the chapters describe the development, the evaluation of the effectiveness and the implementation of the KLIK intervention (the use of PROs in pediatric clinical practice). It therefore encompasses the model of knowledge.

Part one of this thesis, covering Patient Reported Outcomes (PROs), describes the identification of problems of the children, adolescents and young adults with JIA and is presented in chapter 2 and 3. In Chapter 2 we aimed to examine the HRQOL of all children and adolescents with JIA attending one of the pediatric rheumatology centers in Amsterdam, the Netherlands. We investigated the HRQOL of children with JIA of a broad range of ages (6–18 years) using generic HRQOL questionnaires, we used self-report (ages 8–18 years) or proxy report (ages 6–7 years). We compared the HRQOL of children with JIA to a healthy Dutch youth norm population and to children with other chronic health conditions. In addition, we assessed the proportion of children with JIA and an impaired HRQOL and the predictors of HRQOL. Chapter 3 describes the psychosocial developmental trajectory and HRQOL of young females with JIA who claim the Wajong benefit compared to a norm group of peers from the Dutch general population.

The second part of this thesis covers Parent Reported Outcomes and is presented in chapter 4, 5 and 6. In Chapter 4 the HRQOL and perceived vulnerability of parents of children with JIA is described, as well as the variables associated with
the perceived vulnerability. In addition, no large-sample studies have examined the prevalence of anxiety and depression in fathers and mothers of a chronically ill child. Therefore, we wanted to determine the levels of anxiety and depression in fathers and mothers of a chronically ill child and to assess the degree to which parental and child characteristics are associated with anxiety and/or depressive symptoms. This is described in Chapter 5. It is important to gain insight in the emotional functioning of these parents in order to be able to develop interventions to support them. A short screening tool that detects the level of parental distress would be useful. For this reason, we developed a questionnaire for parents of a chronically ill child, the Distress Thermometer for Parents (DT-P). Chapter 6 describes the examination of the psychometric properties (internal consistency and validity) of the DT-P in a sample of parents of a chronically ill child, and the determination of a cut-off score to identify distressed parents.

In the third part of this thesis, the use of Patient Reported Outcomes in pediatric clinical practice is described (chapter 7, 8, 9 and 10). The focus is on the different phases of our KLIK intervention: development, effectiveness and implementation. The development of the KLIK intervention is described in two steps in Chapter 7 and Chapter 8. We first provide a detailed description of the development and design of the QLIC-ON study and a training program for pediatricians to improve effectiveness in the use of PROs about HRQOL in pediatric practice. The development of the KLIK website was an important step in the use of PROs in daily pediatric clinical practice, because it was now possible to change from a stand-alone laptop to collect the PROs to a web based program, the PROs were converted to electronic PROs (ePROs). In Chapter 8, we describe the ongoing process of the KLIK ePROfile development using the KLIK website and how to make the use of HRQOL data more efficiently. In Chapter 9, the results of the study on the effectiveness of the KLIK ePROfile are presented in terms of communication, referrals, satisfaction and evaluation of the KLIK ePROfile. As a result of the positive findings of the QLIC-ON and KLIK study and the readiness of our hospital to incorporate systematic attention for HRQOL in clinical practice, we started the implementation of the use of the KLIK ePROfile in daily clinical practice for children with various chronic illnesses. The implementation of the use of ePROs in daily clinical practice creates new challenges and opportunities for care, as is extensively described in the International Society for Quality of Life Research (ISOQOL) guidelines 111,112. Chapter 10 elaborates a thorough description of the implementation of KLIK ePROs in daily pediatric clinical practice following the methodological recommendations and decisions using the guidelines provided by the ISOQOL 111,112. This thesis ends with Chapter 11; a general discussion including a summary of the results, main findings, limitations, future perspectives and the key messages.
Reference List


