Changing pediatric cancer care: development and implementation of electronic patient and parent reported outcomes

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Citation for published version (APA):
Chapter 1
General Introduction
PEDIATRIC CANCER

In the Netherlands, an estimated 550 new cases of children will be diagnosed with cancer yearly. Although pediatric cancer survival rates have increased to almost 80 percent in the past four decades, cancer still remains the second leading cause of death among children. The major types of cancer in children are acute lymphoblastic leukemia, brain and other central nervous system tumors, and solid tumors such as neuroblastoma. Cancer in children is different than in adults and therefore treatment and side effects can also differ. For example, children in general are treated with higher doses of chemotherapy than adults. That is because children can be given higher doses of treatment over a shorter period of time than adults before serious side effects occur. Relating to radiation therapy, children are more vulnerable than adolescents and (young) adults to the development of tissues as a result of ionizing radiation. With regard to surgery, this is more readily applied to adults than to children, but children are more likely to recover from the deficits and disabilities caused by the removal of large tumors and their attached tissues or structures. Survival rates for children are generally higher than in adults. Yet, because children are still in development, side effects of treatment can cause more long term harm to children than to adults, because cancer and its treatment (i.e., chemotherapy and radiation) are more likely to affect developing organs. The side effects of treatment can occur immediately (short-term effects) or weeks or even years later (long-term or late effects). These effects may include physical (e.g., pain, nausea, fatigue, fertility) and psychosocial (e.g., distress, anxiety, depression) issues.

PSYCHOSOCIAL IMPACT OF PEDIATRIC CANCER

Since pediatric cancer survival rates have improved tremendously in the past four decades, family adjustment to a pediatric cancer diagnosis changed from an almost certain loss of the child, towards an uncertain and unpredictable situation regarding the outcome of the disease in the child. Children have to deal with the often lengthy and demanding treatment regimens and the burden of daily care has an impact on the whole family. Thus, being diagnosed with childhood cancer remains an obvious stressful and potentially traumatic event for the entire family. Children and parents may experience pediatric medical traumatic stress (PMTS) reactions to pain, injury, serious illness, medical procedures, and invasive or frightening treatment experiences. PMTS symptoms can include arousal, re-experiencing and avoidance, just like a post-traumatic stress disorder (PTSD). However, children or parents that experience PMTS as a result of cancer, do not necessarily have to meet the criteria for a PTSD. Children and parents may have other kinds of reactions to illness and injury as well, including behavioral changes or symptoms of depression or anxiety. In a recent review on PMTS, it was described that 40-83% of parents of children with cancer experience PMTS within the first month post-diagnosis, while this ranges from 18-30% at 6 months post-diagnosis, and from 7 to 22% after 10 months post-diagnosis. Studies on childhood cancer survivors show that child PMTS rates range from 8 to 75%, while for parents this ranges from 20 to 22%.

Even though it is widely acknowledged that families experience significant distress, especially at diagnosis and during treatment; a substantial amount of research has shown that in the
long-term, adaptive psychosocial adjustment is common for the majority of affected families. Still, a considerable part of the families develops psychosocial problems and are therefore at risk for ongoing distress. Risk and protective factors that are known to be associated with mental, social and physical adjustment include illness and treatment characteristics (e.g. severity, treatment intensity, length of hospital admission); pre-existing child characteristics (e.g. age, temperament, behavior); family structure and resources (e.g. being a single or teenage parent); financial problems; psychopathology of family members; a background of family dysfunction and lack of social support; and parental cognitions about and stress reactions to the course and outcomes of treatment.

The conceptual Pediatric Psychosocial Preventative Health Model (PPPHM; see Figure 1) is based on the prior empirical literature and guides systematic assessment of family psychosocial adaptation by distinguishing families with different levels of risk. Following this model, the majority of families of children with cancer experience initial distress but have minimal risk factors (or many protective factors) present for developing psychosocial problems (universal level). Those families are helped with basic psychosocial interventions to prevent pediatric medical traumatic stress (e.g., appropriate psycho-education and assistance with treatment demands). A smaller group of families (targeted level) have some identified areas of risk and moderate resources available. They could benefit from increased psychosocial support and focused guidance to help them anticipate challenges and to strengthen their coping skills (e.g., interventions for procedural pain and anxiety, such as relaxation). A minority of the families experiences more severe problems with many risk factors (and few resources) present and they can be classified at the top of the pyramid (clinical level). They need more extensive psychosocial support and evaluation or treatment by a mental health professional. The PPPHM suggests that the healthcare team provides basic support and information to every ill child and its family and that they regularly screen for acute distress and risk factors to determine which children and families might need more support.

Early monitoring of and screening for psychosocial distress and pre-existing problems is an important first step to identify families at risk for problems and to provide psychosocial care according to the specific needs of the families. The internationally established pediatric oncology psychosocial standards of care endorse routine and systematic psychosocial assessment in pediatric cancer care. However, to be able to monitor and screen for problems in a reliable and valid way and to allocate care according to the specific needs of children with cancer and their families, psychometrically sound questionnaires are crucial. Validated standardized questionnaires are currently not always available in the Netherlands, or representative reference data is missing.

PATIENT AND PARENT REPORTED OUTCOME MEASURES

Patient-reported outcomes (PROs) are defined as any report of the status of a patient's health condition that comes directly from the patient (or parent), without interference of the patient’s (or parent’s) response by a clinician or other third party. PRO measures usually take the form of standardized questionnaires. PRO measures can be divided into generic (to measure broad and general constructs in healthy as well as disease populations) or disease-specific (e.g., to measure the impact of a disease or treatment on a patient’s health-related quality of life). They
can provide a way to get insight in the psychosocial functioning and health-related quality of life (HRQoL) of children with cancer and their families and they can serve several purposes. For instance, PROs can be used at the group level to study differences between disease populations, to describe the effects of treatment in clinical trials or to assess quality of care. In clinical practice, PROs can be used as an objective measurement of the patient’s subjective view of their health status, as a supplement to other clinical measures. Examples of clinical applications for the use of PROs are: monitoring (e.g., HRQoL, or response to treatment/management) or screening (e.g. psychosocial problems) to promote patient-centered care and guide clinical decision-making; and facilitating communication (e.g., between patients and healthcare professionals, or within teams and between professionals)31,32.

**Patient HRQoL PRO measures**

Compared to their healthy peers, children with cancer have an increased risk to experience HRQoL issues both during and after treatment12,33-36. HRQoL is a multidimensional construct and is defined to cover “the subjective perceptions of the positive and negative aspects of patients’ symptoms, including physical, emotional, social, and cognitive functions and, importantly, disease symptoms and side effects of treatment”37. Several determinants of poor HRQoL in children with various forms of cancer have been identified, such as the type of cancer (i.e., children with brain and central nervous system tumors)38, intensity and duration of the treatment given34,39, children that experience a relapse38, child female gender34,39,40, child older age at diagnosis34, low household income39-42, parental health and well-being (i.e., anxiety, depression, parental distress, parental quality of life, parenting stress and parents with a chronic condition)38,42, and poor family functioning and coping7,41,42. The evaluation of HRQoL is essential for a full understanding of the influence of a health condition on a given individual43. HRQoL as reported by the patient is a type of PRO, as it implies the perceived impact of the disease on a person’s life. Consequently, one health condition may have very different impacts on the HRQoL of different individuals. According to the pediatric cancer PRO literature, relevant HRQoL measures should cover the three major domains of physical, psychological and social health44.

Several aspects have to be taken into account when measuring children’s PROs compared to adult PROs. That is, relevant PRO dimensions and the item content of pediatric PRO measures may differ substantively from those of adult measures, and can vary with developmental age30. This implies that PRO measures for children should be age-specific or covering a broad age range. Also, it should be realized that the age of the child may influence the PRO and it is therefore important to compare children’s outcomes to age-matched reference data. Relating to the informant of PROs, self-report is usually preferred, because the patient’s report is the best source of information about what he or she is experiencing45,46. In general, children as young as 8 years are cognitively capable to complete self-reported PROs47,48. However, when children are too young, too cognitively impaired, too ill or too fatigued to complete a PRO instrument, parent proxy-report is recommended49.

To date, several psychometrically sound generic and disease-specific HRQoL PRO measures have been developed for children up to 18 years old. Examples are the TNO AZL Preschool
Chapter 1

Children Quality of Life (TAPQOL)\textsuperscript{50}, the Child Health Questionnaire (CHQ)\textsuperscript{51}, the Pediatric Quality of Life Inventory (PedsQL)\textsuperscript{52} and the PedsQL Cancer Module 3.0\textsuperscript{33}. The most commonly used instruments to measure HRQoL in children with cancer are the generic PedsQL 4.0 and the disease-specific PedsQL Cancer Module\textsuperscript{44,53}. The PedsQL has the advantage that it has age-specific versions that cover a very broad age range, such that children from different age groups can be compared cross-sectional, or children can be followed longitudinally in their developmental trajectory.

To be able to reliably measure the impact of cancer on children compared to their healthy peers, it is important to have reliable reference data available. Yet very often, such reference data is missing for the Dutch population, sample sizes for specific age groups are small, or the collected sample is biased. This is particularly the case for current HRQoL instruments for young children (aged 0-7 years). For example, for the PedsQL version for children aged 2 to 4 years, no Dutch reference data is currently available and age-specific samples with normative data for 0-1 year-old children (TAPQOL)\textsuperscript{50} and 5-7 year-old children (PedsQL)\textsuperscript{54} are relatively small.

**Parent and family psychological distress PRO measures**

Of course, children are surrounded by a broader socio-ecological system, and as described above, the functioning of their family can influence their HRQoL and wellbeing. It is therefore important to monitor children within the broader context of their family (e.g. parents, siblings) and subsystems (e.g. grandparents, healthcare providers, teachers, friends)\textsuperscript{7}. A growing body of research has investigated the psychosocial outcomes for parents of children with cancer\textsuperscript{55}. Parents of children with cancer more often report a lower HRQoL\textsuperscript{56} and higher distress\textsuperscript{13,57} than parents of healthy children. However, identifying those parents who are experiencing psychological distress or who are at risk for distress can be difficult and time-consuming. According to current screening approaches, psychosocial screening should be brief, with minimal burden for children and their families, and identifying families at risk for ongoing distress, such that they can be efficiently directed towards evidence-based treatments\textsuperscript{58}.

The Distress Thermometer for Parents (DT-P) is a non-invasive screening tool to detect parental distress in parents of children with a chronic health condition. The DT-P appears to be an internal consistent and valid instrument for identifying parental distress\textsuperscript{59}. However, within the general population, the reliability (internal consistency), known-groups validity (the extent to which a measurement is sensitive to differences in various groups) and normative data are currently lacking. To be able to compare the distress of parents of children with cancer, compared to parents from the healthy population, it is important that Dutch normative data is collected for this generic instrument on parental distress.

Furthermore, families of children with cancer can experience a different impact of the disease than families of children with a chronic illness. In order to provide timely and cost-effective care, it is therefore of utmost importance to develop evidence-based family reported outcome measures that are adapted towards and target the specific needs of children with cancer and their families. The Psychosocial Assessment Tool (PAT)\textsuperscript{60} is a brief and well-validated screener for psychosocial risk, designed specifically for families of children with cancer\textsuperscript{60-64}. The PAT maps on to the conceptual
model of the PPPHM and distinguishes among families that are at low or high risk for psychosocial problems. Studies on the effect of using the PAT showed it to be an efficient screener in the United States, Canada and Australia. For instance, several studies showed that by screening with the PAT at diagnosis, families could be identified as universal, targeted or high risk for psychosocial problems\textsuperscript{60,61,63,64}. Furthermore, PAT risk scores were shown to predict intensity of social work services\textsuperscript{63,65} for the US pediatric cancer population, but not for the Australian population\textsuperscript{66}. Finally, a Canadian study found that screening with the PAT resulted in reduced levels of family risk and an improved child HRQoL\textsuperscript{67}. To conclude, these findings address the importance of systematic and evidence-based screening in pediatric cancer care. However, disease-specific brief evidence-based psychosocial screening tools are currently not available in the Netherlands.

**Figure 1. Pediatric Psychosocial Preventative Health Model**

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EVIDENCE FOR USING PROS IN CLINICAL PRACTICE

Medical healthcare professionals (HCPs, e.g., pediatric oncologists or nurse specialists) are not always aware of the psychosocial and HRQoL problems that children with cancer experience\(^{37,68,69}\). Therefore, these problems are not always sufficiently addressed. Systematic feedback and discussion of PROs in clinical practice helps to manage acute issues, prevent or reduce late psychosocial and physical effects and improve care in adults with cancer\(^{70-72}\).

In pediatrics, four studies have been conducted with regard to the effectiveness of systematic HRQoL PRO monitoring in clinical practice. In a study with adolescent diabetes patients, discussing HRQoL had positive effects on psychosocial well-being and satisfaction with care\(^{73}\). HRQoL and satisfaction with care decreased to baseline values, when systematic attention for HRQoL was no longer part of standard care\(^{74}\). In a randomized controlled trial conducted by Wolfe et al.\(^{75}\) in children with advanced cancer, it was shown that PRO feedback did not directly influence the child’s symptoms or HRQoL, but it led to the initial consultation of a psychologist by physicians in 56% of the cases. Also, exploratory subgroup analyses showed improvements in HRQoL for children \(\geq 8\) years of age and children who survived beyond 20 weeks.

The other two studies that were performed in pediatrics are the precursors of the present study. The quality of life in childhood oncology (QLIC-ON) study provided a HRQoL PROfile during consultations after successful treatment for childhood cancer. This led to an increased and more detailed discussion of emotional and psychosocial functioning and an improved identification of emotional and cognitive problems compared to consultations without HRQoL PRO feedback provided to pediatric oncologists. Importantly, it did not lengthen the consultation duration\(^{76,77}\). The KLIK study (In Dutch: Kwaliteit van Leven in Kaart; in English: Quality of Life in Clinical Practice) assessed the effectiveness of the use of electronic PROs (ePROs) in children with juvenile idiopathic arthritis. The use of HRQoL ePROs increased the discussion of psychosocial functioning and resulted in a higher HCP-reported satisfaction with provided care\(^{78}\). These pediatric studies provide evidence for more systematic assessment of HRQoL ePROs and underline the need to incorporate the continuous feedback of HRQoL ePROs in clinical practice.

TRANSLATING SCIENCE INTO PRACTICE: REAL-WORLD IMPLEMENTATION OF PROS

Even though studies show the positive effects of the use of PROs, making the transfer to real-world clinical practice remains a challenge. In general, it is estimated that two-third of any developed interventions fail to successfully implement change in organizations\(^{79}\). As such, it is important to understand and measure implementation fidelity (the degree to which an intervention is used as intended) and implementation determinants (predictors of successful or unsuccessful implementation processes). This enables researchers and practitioners to gain better knowledge on how and why an intervention works and the extent to which outcomes can be improved\(^{80}\). The conceptual model of Fleuren et al.\(^{81}\) describes the dynamic interplay between characteristics of the intervention, the user, the organization and the socio-political context in relation to the process of implementation. In general, implementation outcomes are influenced by barriers and facilitators.
in different domains, such as the intervention itself (e.g., simplicity and adaptability to the context); the user (e.g., individual user knowledge and outcome expectations); and the organization (e.g., organizational commitment, such as policies). It is crucial to identify determinants of a particular intervention to be able to develop an appropriate and effective innovation strategy that targets these determinants. Porter et al. have identified 5 key issues that need to be considered for successful implementation of PROs in clinical practice: “the purpose of using the measure, the characteristics of the PRO itself, the setting, the feedback system, and the additional support to the implementation”.

So far, no studies have been conducted on the barriers and facilitators to the implementation of PROs in pediatric cancer care. HCP-reported barriers described in adult oncology practice include time constraints (e.g., concern that there may not be enough time to address issues that derive from PROs); a lack of training on the use and interpretation of PROs; and doubt about the added value of PROs (e.g., sufficient clinical relevance for their patients). Key facilitating factors that are reported in adult oncology practice are when PROs are integrated in clinical practice guidelines; automatic flagging of clinically important scores; appointing a coordinator and providing sufficient training of staff.

THE KLIK METHOD

The KLIK method is an online system (www.hetklikt.nu) to enable routine monitoring and discussion of ePROs for children with a chronic disease or cancer. With the KLIK method, validated age-appropriate HRQoL or psychosocial screening questionnaires are completed by children and/or their parents a week before an outpatient visit. Their answers are being schematically converted into a so-called KLIK ePROfile. HCPs can directly retrieve the ePROfiles from the website and discuss the answers with the patient and/or their family members. As a result of the positive outcomes in the effectiveness studies that were described earlier in this introduction, the KLIK method is currently being implemented in 70 patient groups in 16 different hospitals in the Netherlands.

Within the pediatric oncology setting, only experience with systematic feedback of PROs after the end of treatment was available, and this study was performed within a highly controlled clinical research setting. Implementing a new intervention to become part of standard care in a complex setting such as pediatric oncology during early stages of treatment, has specific challenges for the implementation fidelity. That is, the main focus of the family and HCP lies on the survival of the child, children are hospitalized for a long period of time, too sick to complete questionnaires, or consultations are cancelled at the last minute. Adult oncology clinical trial studies have also described multiple challenges on integrating PRO data in daily care because of the complexity of the disease (e.g., high attrition rates during treatment). It is therefore important to assess which factors might influence the implementation process, such that tailored implementation strategies can be developed. Considering PRO monitoring and screening is being internationally conveyed as a standard of care in pediatric cancer, little is known about barriers and facilitators for the use of PROs in pediatric oncology practice.
AIM, DESIGN AND OUTLINE OF THE THESIS

The general objectives of this study were to (1) develop reliable and valid ePRO measures for children with cancer and their families and (2) implement ePROs in pediatric cancer care and assess factors that determine the implementation process.

Specific aims of the thesis were:

(1) Development of electronic patient and parent reported outcome questionnaires
   • To assess health-related quality of life in Dutch infants, toddlers and young children and establish appropriate norm data for infants, toddlers and young children with cancer
   • To determine the psychometric properties of and provide Dutch norm data for the Distress Thermometer for Parents (DT-P)
   • To assess the reliability, validity and usability of the Dutch electronic Psychosocial Assessment Tool (ePAT)
   • To assess parental distress at 6 months post-diagnosis in relation to family psychosocial risk at diagnosis

(2) Implementing electronic patient and parent reported outcomes in pediatric cancer care
   • To describe the development and implementation of the KLIK method in real-world pediatric practice
   • To assess parents' and healthcare professionals' preferences for the implementation of the KLIK method in Dutch pediatric cancer care
   • To evaluate how well the KLIK method is implemented (fidelity) and to assess implementation barriers and facilitators (determinants) during treatment for childhood cancer
   • To describe the feasibility and usability of the electronic Dutch Psychosocial Assessment Tool (ePAT) in pediatric cancer care
   • To determine healthcare professional-reported international preferences and perceived barriers for routine assessment of PROs in pediatric cancer care

Study design

To establish Dutch reference data for the pediatric cancer population, Dutch normative data were collected for generic HRQoL questionnaires in infants, toddlers and young children (TAPQOL 0-1 years, and PedsQL 2-7 years) and for the Distress Thermometer for parents (DT-P) between November and December 2014.

The development and implementation of ePROs for children with cancer and their families was collaboration between the Academic Medical Center/Emma Children’s Hospital in Amsterdam and the Radboud University Medical Center/Amalia Children’s Hospital in Nijmegen, the Netherlands. All patients with a new diagnosis of cancer (0-18 years) in the Academic Medical Center/Emma Children’s Hospital in Amsterdam, the Radboud University Medical Center/Amalia Children’s
Figure 2. Study design IMPROVE:
(1) implementation of a HRQoL ePROfile as part of standard pediatric cancer care and (2) Screening for family distress without (ePAT psychometric properties phase) and with (ePAT feasibility/usability phase) sending the PAT ePROfile to the psychosocial team.
Hospital in Nijmegen, the VU University Medical Center in Amsterdam, and the Erasmus Medical Center/Sophia Children's Hospital in Rotterdam, the Netherlands, were invited to participate (see Figure 2). For children under the age of 8, parents provided information about their child. The evaluation of the implementation of patient-reported HRQoL outcomes by the medical HCPs (i.e., pediatric oncologist, nurse specialist) took place between June 2012 and March 2014. Evaluation of the use of the HRQoL ePROfile took place within 1 month (T1), 3 months (T2), and 6 months (T3) after diagnosis. Fidelity of the use of HRQoL ePROfiles was assessed in terms of uptake rate (percentage of registrations on the KLIK website, percentage of HRQoL-questionnaires that were completed by the children and parents before an outpatient consultation and percentage of ePROfiles discussed by HCPs during outpatient consultations. Barriers and facilitators for the use of the HRQoL ePROfile reported by medical HCPs were determined with the measurement instrument for determinants of innovations (MIDI)82.

Simultaneously to the implementation of patient-reported HRQoL as part of standard care, parents could also choose to participate in a study that screened for family psychosocial risk. Data collection took place between June 2012 and January 2015. Parents participated either in period 1 (psychometric properties of the Dutch ePAT) or period 2 (feasibility and usability of the ePAT by the psychosocial team in clinical practice). The psychometric properties of the Dutch ePAT were studied between January 2012 and December 2013, when no feedback of results was provided to the psychosocial team. Families completed the ePAT and several validation questionnaires at one month post-diagnosis (T1) and the DT-P at 6 months post-diagnosis (T3). In the second study period (January 2014-January 2015), ePAT answers were transformed into an electronic PROfile (ePROfile) and results were fed back to the psychosocial team. Psychosocial team members interpreted the PAT ePROfiles of the families and completed a Staff ePAT evaluation questionnaire. Feasibility was determined by: percentage of website registrations, completed ePATs, and PAT ePROfiles reviewed and discussed by the psychosocial team. Usability was evaluated on a 10-point scale measuring perceived match with the team's own risk estimation, perceived added value and by percentage of actions undertaken as a result of the ePAT.

**Outline of the thesis**

The general introduction of the thesis is covered in **Chapter 1. Part one** of the thesis (chapters 2, 3, 4, and 5), describes the development, validation, and evaluation of ePRO measures. **Chapter 2** starts with the assessment of health-related quality of life of Dutch infants, toddlers and young children (0-7 years) and provides norm data for the TNO-AZL Preschool Children Quality of Life (TAPQOL) and the Pediatric Quality of Life Inventory (PedsQL). **Chapter 3** reports on Dutch normative data of the Distress Thermometer for parents (DT-P) and assesses the reliability and validity of the DT-P in the general Dutch population. **Chapter 4** determines the reliability, validity and usability of the Dutch electronic Psychosocial Assessment Tool (ePAT) for families of a child with cancer. In **Chapter 5**, we describe the association between parental distress (DT-P) at 6 months post-diagnosis and family psychosocial risk (ePAT) at the moment of a pediatric cancer diagnosis.
The second part of this thesis focusses on the implementation of ePROs in pediatric cancer care. The development of, rationale behind, and overall implementation of the KLIK method in pediatric practice is described in Chapter 6 to provide a thorough outline of the background. In Chapter 7, we report on parents’ and healthcare professionals’ recommendations for the implementation of the KLIK method in pediatric cancer care. Chapter 8 describes the real-world implementation of the KLIK method in pediatric cancer care. Actual use of ePROs in clinical practice (implementation fidelity) and barriers and facilitators for the implementation process (implementation determinants) are addressed. First experiences with feedback of the ePAT to the psychosocial team are reported in Chapter 9. Finally, Chapter 10 addresses healthcare professionals’ international preferences and perceived barriers for the routine assessment of PROs in pediatric cancer care. Chapter 11 provides an English summary and the general discussion of this thesis. This thesis ends with a Dutch summary in Chapter 12.
Chapter 1

Reference list


