Chapter 11
Summary and General Discussion
The general objectives of this thesis were to (1) develop reliable and valid electronic patient and parent reported outcome (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. This final concluding chapter gives a summary of the main findings and considers limitations of the studies included in this thesis. Further, it gives directions for future research and implications for the use of PROs in clinical practice. An overview of the studies presented in this thesis is provided in Table I.

**SUMMARY OF MAIN FINDINGS**

**Aim 1: Development of electronic patient and parent reported outcome questionnaires**

In light of studying patient and parent PROs through different developmental stages, there was a need for representative Dutch reference data for several PRO questionnaires. Although many well-researched PRO questionnaires are available, for some questionnaires there was a lack of different age versions (i.e. Pediatric Quality of Life Inventory (PedsQL) for toddlers) or (sufficiently reliable) normative reference data (i.e. the TNO AZL Preschool Children Quality of Life questionnaire (TAPQOL) for infants and the acute version of the PedsQL for toddlers and young children, the Distress Thermometer for parents (DT-P), and validation of the electronic Psychosocial Assessment Tool (ePAT) for families of children with cancer).

Chapter 2 showed that the TAPQOL and the PedsQL, with the exception of one TAPQOL scale (i.e., stomach scale; $\alpha=.39$), are reliable questionnaires to assess HRQoL in children aged 0-7 years. However, it remains unclear whether these HRQoL instruments can distinguish between healthy children and children with a chronic health condition under the age of five, because a difference was only clearly shown for the children aged 5-7 years. Despite the fact that average HRQoL scores may not always differentiate between children with and without a chronic health condition, poor HRQoL scores may still provide clinically meaningful information.

In chapter 3, psychometric properties and Dutch normative data of the DT-P were presented. It showed that the DT-P subscales have moderate to good reliability. Also, the DT-P distinguished in elevated levels of distress between parents of healthy children and parents of children with a chronic health condition.

In chapter 4, we described the reliability, validity and usability of the Dutch ePAT at the moment of a pediatric cancer diagnosis. Acceptable reliability was obtained for the ePAT total score ($\alpha=.72$) and for the majority of subscales ($\alpha=.50-.82$). Two subscales showed inadequate internal consistency (Social Support $\alpha=.19$; Family Beliefs $\alpha=.20$). With respect to content validity, the total ePAT scale significantly correlated with the validation measures (Inventory Social Reliance (ISR, $r=-.38$), Strengths and Difficulties Questionnaire (SDQ-patient, $r=.61$; SDQ-sibling version, $r=.49$), Hospital Anxiety and Depression Scale (HADS, $r=.46$), Parenting Stress Index (PSI, $r=.56$), and the Illness Cognition Questionnaire for parents (ICQ-P, subscale helplessness $r=.23$, subscale acceptation $r=-.35$). No significant association was found between the ePAT total scale and the ICQ-P perceived benefits subscale. The Pediatric Psychosocial Preventative Health
Model (PPPHM) classifies families into different levels of risk (universal, targeted, clinical) for developing psychosocial problems. In agreement with the PPPHM, the majority of families were identified by the ePAT as universal, a smaller part as targeted, and only a minority was classified as being at clinical risk for developing psychosocial problems. Parents indicated the ePAT to be comprehensible, clear, appropriate, not too long and not unpleasant to complete. We conclude that the ePAT is a reliable, valid and usable questionnaire to apply in Dutch pediatric cancer care.

In chapter 5, we took a closer look at parental distress at 6 months, as assessed with the DT-P, and we determined the relationship of the DT-P at 6 months with family psychosocial risk at diagnosis as measured with the ePAT. Results revealed that at 6 months post-diagnosis, parents of children with cancer showed higher levels of distress, and a higher percentage of clinical distress than parents of healthy children. The ePAT score appeared to be related to parental distress 5 months later. That is, parents that had many risk factors present at the 1 month post-diagnosis (i.e., targeted and clinical ePAT risk scores), experienced higher levels of distress at 6 months post diagnosis, than parents that had few risk factors present (i.e., universal ePAT risk score). This supports the predictive validity of the ePAT and further supports the discriminative validity of the DT-P.

**Aim 2: Implementing electronic patient and parent reported outcomes in pediatric cancer care**

More and more studies have shown the positive effects of monitoring and discussing PROs in clinical practice. Yet, the actual translation of research results into practice remains a major challenge. The second part of this thesis described the implementation of an electronic system for the routine monitoring of patient and parent reported outcomes in clinical practice (KLIK method). In chapters 6 and 7, we described the considerations behind the development and implementation of the KLIK method. Chapter 8 presented the results on the real-world implementation of discussing PROs during the consultation with the medical healthcare professional in pediatric cancer care. In chapter 9, the first experiences with electronic feedback of the PAT in Dutch pediatric cancer care were evaluated with the psychosocial team. Chapter 10 determined medical healthcare professionals’ international preferences and perceived barriers for the routine assessment of PROs in pediatric cancer care.

**Chapter 6** provides an overview of the historical background and the 10-year steps and strategies that were undertaken in the development and implementation of the KLIK method. These steps were described according to the 8 methodological recommendations of the International Society of Quality Of Life research.

In **chapter 7**, we assessed parents' and medical healthcare professionals’ specific preferences for the implementation of the KLIK method in Dutch pediatric cancer care. Both parents and healthcare professionals indicated that they wanted the discussion of PROs to become part of standard pediatric cancer care, starting during the treatment phase and with an assessment frequency of every 3 months. Findings from this study formed the theoretical rationale for the actual implementation of the KLIK method in pediatric cancer care (chapter 8).
Chapter 11

Chapter 8 focused on (1) how well the KLIK method was being implemented at 1, 3, and 6 months post-diagnosis (implementation fidelity) and (2) the influencing factors for the outcome of the implementation process (implementation determinants). Results showed that during treatment, fidelity was acceptable for website registration and completion of health-related quality of life questionnaires. However, only half of the available ePROfiles were discussed by the medical healthcare professional during the consultation. Barriers turned out to be mainly related to the organizational context (e.g., other organizational changes going on) and less frequently to the user (e.g. experienced social support colleagues), or to the KLIK method (e.g., compatibility with current workflow). Facilitators were related to the user (e.g., positive outcome expectations about the use of the KLIK method), and to the KLIK method (e.g. not too complex to use), but not to the organization. We therefore stressed the importance of a flexible electronic system and concluded that organizations have to become conscious of their own role in the possible failure or success of a new to be adopted intervention. Nevertheless, also less distinct healthcare professional concerns about the implementation process that may not have been captured with our standardized MIDI questionnaire (e.g., doubt about added value during treatment, or difficult password), might have played a role.

In chapter 9, first experiences with the use of the Dutch ePAT by the psychosocial team were described. We aimed to determine the feasibility and usability of the use of the ePAT in clinical practice at one month post-diagnosis. The use of the ePAT was generally feasible for website registration and ePAT completion by parents, and also for reviewing of the PAT ePROfile results by the psychosocial team. Yet, the PAT ePROfile results were not always discussed between members of the psychosocial team. Relating to the experienced usability of PAT ePROfiles, psychosocial team members reported that the PAT ePROfile matched well with their own family risk estimation, and did not provide them with a lot of extra information. Notwithstanding, as indicated by the team, PAT ePROfiles that were reviewed or discussed at one month post-diagnosis still influenced 25% of psychosocial actions undertaken.

At last, to provide a more international perspective on experiences with the routine assessment of PROs in pediatric cancer care, we described the results of a worldwide study in chapter 10. Results showed that medical healthcare professionals working in pediatric oncology practice, preferred to have both information on physical (e.g., pain) and psychosocial (e.g., feeling sad or depressed) PRO topics available in the care for their patients with cancer. However, the actual integration of routine PRO assessments was limited. Barriers expressed by healthcare professionals were: time, insufficient staffing available, logistics, and financial resources. The barriers of insufficient staff, logistics and financial resources were shown to be more prevalent in the organizations from developing countries, than in the organizations from developed countries.
REFLECTION ON MAIN FINDINGS

Reliable and valid ePRO measures for children with cancer and their families

As shown in chapter 2, 3, 4, and 5, reliable measures were developed and relevant normative data were collected to measure HRQoL in children with cancer, to assess parental distress, and to identify families at risk for developing psychosocial problems. In the introduction of this thesis, it was described that a cancer diagnosis has an impact on the whole family and that there is a bidirectional relationship between family functioning and child adjustment. It therefore is important to initially screen the whole family for psychosocial risk factors, and to closely monitor parental distress during the cancer care trajectory. This importance becomes even more clear from Chapter 5, which shows that families with more psychosocial risk factors present at diagnosis, experience higher levels of parental distress 5 months later. This finding supports the predictive value of the PAT and asks for close monitoring of and applying targeted care to the whole family, already starting at diagnosis with the goal to prevent or reduce later problems.

Moreover, as borders are collapsing and cultures are growing closer and closer day by day, we should be conscious about the fact that PRO preferences, outcomes, and determinants for using PROs might differ between cultures and within individuals. As was shown from the majority of our studies, ethnic minority families, low-educated families, and single-parent families remain understudied populations. It appears to be difficult to include these families in our studies. Nevertheless, their perspectives on the assessment and implementation of PROs are evenly important and efforts should be made to stimulate participation rates in these study populations.

Regarding the priority for PRO topics, our international study (chapter 10) on the preferences of HCPs demonstrated that all of the proposed PRO domains and subcategories were considered relevant by at least 50% of the HCPs in our sample. Still, the most highly ranked topics by HCPs (pain, depression, overall physical issues, adherence, and emotional issues) could be used as a starting point for fundamental elements of PRO assessment in pediatric oncology practice. These results should be integrated with research on patients and parents preferences, such that a common set of relevant PRO topics can be identified.

Implementation of ePROs during treatment for childhood cancer: valued, but with substantial barriers present

Many steps have already been undertaken in the development the KLIK method (chapter 6) to make this implementation process as fluently as possible for children, parents, and healthcare professionals. Yet, this thesis shows that the full integration of the discussion of PROs in the flow of everyday pediatric cancer care still remains a big challenge. Most of the barriers that we found in our pediatric oncology studies (practical, organizational, system not fully compatible with clinical workflow) have also been demonstrated in adult PRO implementation research or in other pediatric disease groups.

The routine assessment of PROs in clinical practice is highly valued both by parents (chapter 7) and by medical healthcare professionals working in pediatric oncology practice (chapters 7 and...
Table I. Overview of studies presented in this thesis

**Aim 1: Development of patient and parent reported outcome questionnaires**

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Purpose</th>
<th>Sample characteristics</th>
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| **2**   | To assess health-related quality of life in Dutch infants, toddlers, and young children and establish appropriate norm data for young children with cancer | • N= 794 total sample  
• N= 744 parents of healthy children  
• N= 50 parents of children with a chronic condition (such as asthma, diabetes, ADHD) |
| **3**   | To determine the psychometric properties of and provide Dutch norm data for the Distress Thermometer for Parents (DT-P) | • N= 1421 parents representative for the Dutch population of children 0-18 years  
• N= 287 parents of a child with a chronic condition |
| **4**   | To assess reliability, validity and usability of the electronic Dutch Psychosocial Assessment Tool (ePAT) in pediatric cancer | N = 117 parents of children (0-18 years) with a new cancer diagnosis from four Dutch pediatric oncology centers |
| **5**   | To assess parental distress at 6 months post-diagnosis in relation to family psychosocial risk at one month post-diagnosis | • N=192 families of children (0-18 years) with cancer at 1 month post-diagnosis  
• N= 98 fathers and 119 mothers at 6 months post-diagnosis  
• N=1134 parents of healthy children |
### Table I. Overview of studies presented in this thesis

#### Chapter 1: Development of patient and parent reported outcome questionnaires

<table>
<thead>
<tr>
<th><strong>Aim 1</strong></th>
<th><strong>Main findings</strong></th>
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<tr>
<td>To assess health-related quality of life in Dutch infants, toddlers, and young children and establish appropriate norm data for young children with a chronic health condition.</td>
<td>(1) HRQoL can be reliably measured with the TAPQOL and PedsQL in 0-7 year-old children. (2) Under the age of 5, it remains unclear if HRQoL can be distinguished between healthy children and children with a chronic health condition. (3) In children aged 5-7, the PedsQL reliably differentiates between children with and without a chronic health condition.</td>
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<tr>
<th><strong>Measures/content</strong></th>
<th><strong>Main findings</strong></th>
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<tbody>
<tr>
<td>- Socio-demographic questionnaire</td>
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<td>- TAPQOL 0-1 years</td>
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<td>- PedsQL 2-4 years</td>
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<tr>
<td>- PedsQL 5-7 years</td>
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#### Chapter 2: Determining the psychometric properties of and providing Dutch norm data for the Distress Thermometer for Parents (DT-P)

<table>
<thead>
<tr>
<th><strong>Aim 2</strong></th>
<th><strong>Main findings</strong></th>
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<tr>
<td>To determine the psychometric properties of and provide Dutch norm data for the Distress Thermometer for Parents (DT-P)</td>
<td>(1) The DT-P showed acceptable internal consistency (Cronbach’s alphas=.52-.89). (2) Parents of a child with a chronic condition more often reported clinically elevated distress than parents of healthy children (53.0% versus 38.2%, p&lt;.001). (3) On all domains they reported more problems (p=.000-.022).</td>
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<td>- Socio-demographic questionnaire</td>
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<td>- DT-P thermometer (0-no distress to 10-extreme distress, ≥4 clinically elevated distress), and 6 problem domains (practical, social, emotional, physical, cognitive, and parenting)</td>
<td>(1) Acceptable reliability was obtained for the ePAT total score (a=.72) and majority of subscales (0.50–0.82). Inadequate internal consistency for Social Support (a=.19) and Family Beliefs (a=.20). (2) The total ePAT score was significantly related to all of the validation measures (r=.23–.61), with the exception of the ICQ-P perceived benefits (r=.07). Of the families, 66% scored low (Universal), 29% medium (Targeted), and 5% high (Clinical) risk. (3) Parents were positive about the comprehensibility, clarity, appropriateness and length of the ePAT and did not find it unpleasant to complete the ePAT around one month post-diagnosis.</td>
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<td>- Family risk and resilience (ePAT total score and 7 subscales: structure and resources, social support, family problems, parent stress reactions, family beliefs, child problems, sibling problems)</td>
<td>(1) Parents of a child with cancer more often reported clinically elevated distress than parents of healthy children (fathers: 59.2% versus 32.3%, mothers: 63% vs. 42.3%, p&lt;.001). (2) On almost all domains they reported more problems (p&lt;.001-.643). (3) Parents with targeted/clinical ePAT scores reported more problems than parents with universal scores on most of the DT-P domains (p&lt;.001-1.00)</td>
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<td>- Validation measures (SDQ, ISR, HADS, PSI, ICQ-P)</td>
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<td>- ePAT usability measure (comprehensibility, clarity, appropriateness, unpleasantness, length)</td>
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### Chapter 11

**Summary and General Discussion**
## Aim 2: Implementing patient and parent reported outcomes in pediatric cancer care

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<tr>
<th>Chapter</th>
<th>Aim</th>
<th>Sample characteristics</th>
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<tr>
<td>6</td>
<td>To describe the implementation of the KLIK method in pediatric practice</td>
<td>Development and implementation of the KLIK method was described for N=17 patient groups, N=160 professionals, and N=1450 registered patients (different pediatric diagnoses)</td>
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<td>7</td>
<td>To assess parents' and healthcare professionals' preferences for the implementation of the KLIK method in Dutch pediatric cancer care</td>
<td>N=74 parents of children who participated in the intervention group of the QLIC-ON study and successfully completed their cancer treatment, N=21 HCPs</td>
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<td>8</td>
<td>To evaluate how well the KLIK method is implemented (fidelity) and to assess implementation barriers and facilitators (determinants) during treatment for childhood cancer</td>
<td>N=205 children with newly-diagnosed cancer aged 0-18 years, At one (T1), three (T2) and six (T3) months post-diagnosis, patients (8–18 years) or parents (of patients 0–7 years) completed HRQoL questionnaires, which were transformed into an ePROfile and discussed by their HCP during consultations. N=31 HCPs completed the MIDI</td>
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<tr>
<td>9</td>
<td>To describe the feasibility and usability of the electronic Dutch Psychosocial Assessment Tool (ePAT) in pediatric cancer care</td>
<td>N=123 parents of children with a new cancer diagnosis, N=3 psychosocial teams from 3 Dutch pediatric oncology centers</td>
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<tr>
<td>10</td>
<td>To determine healthcare professional-reported international preferences and perceived barriers for routine assessment of PROs in pediatric cancer care</td>
<td>N=352 pediatric oncology HCPs from 52 countries</td>
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### Chapter Aim Sample characteristics

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<tr>
<th>Measures/content</th>
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<tr>
<td>• ISOQOL guidelines with 8 recommendations for using PROs in clinical practice.</td>
<td>(1) This chapter provides an overview of the historical background and the 10-year steps and strategies that were undertaken in the development and implementation of the KLIK method in pediatric clinical practice.</td>
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<td>• Sociodemographic questionnaire</td>
<td>(1) Parents and HCPs indicated that the KLIK ePROfile should become part of future standard care.</td>
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<td>• PRO preferences (self-constructed 3-item evaluation questionnaire)</td>
<td>(2) Parents and HCPs recommended future use during the treatment period</td>
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<td>• Fidelity (percentage of patients registered at <a href="http://www.hetklikt.nu">www.hetklikt.nu</a>, HRQoL-questions completed, and ePROfiles discussed)</td>
<td>(3) Parents and HCPs preferred an assessment frequency of every 3 months or more.</td>
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<td>• MIDI: Implementation determinants (assessed with HCPs after the final T3)</td>
<td>(1) Depending on time point (T1-T3), fidelity was 86-89% for website registration, 66-85% for completed HRQoL-questionnaires, and 56-62% for ePROfile discussion.</td>
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<td>• Family risk and resilience (ePAT total risk score)</td>
<td>(2) Barriers were mainly related to organizational issues (e.g. organizational change) and less frequently to users (e.g. motivation to comply) or the intervention (compatibility). Facilitators were related to the user (e.g. positive outcome expectations) and intervention (simplicity), but not to the organization.</td>
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<td>• Staff ePAT evaluation (Semi-structured 7-item questionnaire, with feasibility records (%) and usability questions (10-point scale)</td>
<td>(1) Feasibility was 70% for website registration, 87% for completed ePATs, 85% for ePROfile reviewing, and 67% for ePROfile discussion.</td>
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<td>• PRO preferences/barriers: semi-structured online 28-item questionnaire</td>
<td>(2) Team members reported that the ePROfile matched well with their own family risk estimation (M=7.92, SD=1.88), but it lacked additional information (M=2.18, SD=2.30).</td>
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<td>(3) For 25% of the families, the PAT ePROfile led to actions as indicated by the team.</td>
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(1) The five highest ranked PRO topics relevant in routine assessment by HCPs were: pain (98%), feeling sad or depressed (96%), overall physical symptoms (95%), problems with therapy adherence (94%), and overall emotional issues (93%). Five lowest ranked topics were: difficulties praying (50%), other spiritual concerns (55%, 56%, 60%), and feeling bored (60%).

(2) Barriers for assessing PROs were: time (58%), insufficient staff (49%), logistics (32%), and financial resources (26%). Providers from developing countries more often reported barriers concerning insufficient staff, logistics, and financial resources.
However, fully applying these views to clinical practice remains a challenge, as was shown from chapters 8, 9, and 10. Even though healthcare professionals’ attitude about the use of the KLIK method was mainly positive, it is still the question whether the majority really wanted to personally use it as part of their standard practice. The KLIK method was a tool introduced to clinical practice, but healthcare professionals did not specifically ask for this tool to become part of their daily clinical practice. Therefore, less distinct concerns about the implementation process and the use of the KLIK method could also have played a role. Vakola, Tsaousis, and Nikolaou\textsuperscript{15} stress that “unless the majority of staff perceives that the organization develops supportive organizational mechanisms to change such as top management commitment, allocation of resources, rewards, training, participation in the planning and implementation, successful change implementation will be at risk”. To gain a deeper understanding about the possible underlying aspects of possible reluctance to the implementation of PROs in pediatric cancer care, focus groups or individual interviews could be conducted, such that appropriate (individual) implementation strategies can be selected.

Future studies are needed within and outside the pediatric oncology setting that investigate factors that explain both successful and unsuccessful implementation of PROs in clinical practice. The NIH Healthcare Systems Research Collaborative describes 5 practical strategies for overcoming clinicians reluctance to change\textsuperscript{16}. The first is collaboration with clinicians to define the goals and expectations for PRO use. Second is the establishment of standard operating procedures around the collection of PROs. The third recommendation is to integrate the data that is generated from PROs into the clinical workflow. The fourth is to define clinical triggers and specific interventions that will improve outcomes. Lastly, they emphasize the importance of engaging a senior physician champion.

Fortunately, even though implementation research can be very challenging, it has become increasingly valued as is shown by the change in research focus of, for instance, the Dutch Cancer Society. To achieve more impact on their mission, the Dutch Cancer Society started a program ‘research and implementation’; with the aim to quickly translate research results into actual applications for the patient.

Currently, no actual guidelines for successful implementation of PROs in pediatric oncology practice are published yet. As was shown from this thesis, theory can be different from clinical practice and it is therefore important to evaluate the implementation process and look at factors that influence this process\textsuperscript{17-19}. Only then can targeted interventions be applied on barriers\textsuperscript{20}. A helpful and validated tool to determine the influencing factors on the implementation of a new PRO intervention is the Measurement Instrument for Determinants of Innovations (MIDI)\textsuperscript{21}, which we used. We recommend that, before starting to implement PROs in clinical practice, a change management theoretical framework (e.g., Fleuren et al.\textsuperscript{21}; see Figure 1) is used, such that starting points for implementation strategies can be determined.
METHODOLOGICAL CONSIDERATIONS

The findings of the studies described in this thesis must be considered in light of some overall limitations.

Representativeness of participants
First, caution is warranted regarding the generalizability of the results as the majority of the parents in our studies were born in the Netherlands, highly educated, and married or partnered. Families with a lower educational level may have had more issues (e.g. no access to the internet, difficulties with understanding) with completing an electronic questionnaire, which could have possibly led to non-response with a selection bias as a consequence. Future research could study if response rates go up (notably in lower-educated or ethnic minority families) if families have the choice for either online or paper-pencil versions of the questionnaires. Furthermore, on advice from the medical doctor, we did not include some families with psychosocial or medical complications. This could have led to underestimation of parental distress because the excluded families may be the families with the most problems and the fewest resources.

Timing and setting of assessment
Since we wanted to be able to reliably assess the fidelity and determinants for the implementation of ePROs in all participating hospitals (chapter 8), measurement points were fixed around outpatient consultations at 1, 3 and 6 months post-diagnosis. This set-up was also chosen because parents and HCPs recommended to use PROs throughout treatment with an assessment frequency of every 3 months (chapter 7) and PROs seem to be most effective when they are used in an outpatient setting. However, taking the number of outpatient consultations into account during

![Figure 1. Framework representing the innovation process and related categories of determinants (Fleuren et al.17).](image-url)
these time-points and number of times it was discussed, only a minority of patients profited from feedback. To increase the applicability and reduce the risk of failure of implementation, the assessment points should be adapted towards the individual treatment plan and course of disease.23-25.

Also, since the moment of a pediatric cancer diagnosis can be very burdensome for the family and the psychosocial team, we chose to assess the ePAT around one month post-diagnosis. Yet, even though the psychosocial team members thought that the PAT ePROfile matched well with their own perspective on the family, it did not give them a lot of new information. If the PAT ePROfile would have been available for the team at an earlier stage (e.g. within two weeks post-diagnosis) the team might have experienced more additional value by the availability of the PAT.26 Taking this into consideration, we think that the PAT is still of additional value at a later stage, since, according to the team, it influenced their actions undertaken for the families.

**One-dimensional perspective on healthcare professional**

Even though we provided a detailed insight in the major barriers and facilitators for PRO implementation in pediatric cancer care, a major limitation of the studies is that they mainly capture the perspective of the (medical or psychosocial) healthcare professional as an endpoint user. It should be noted that patient and parent perspectives are of inestimable value as well and it is known from the literature that the thoughts of HCPs and patients or parents on PRO themes can essentially differ from each other.23,27,28 For example, where medical HCPs mainly prefer to receive feedback on pain and other symptoms, patients generally indicate to be more helped by discussing overall HRQoL, treatment information, and care coordination needs.24,29 Future research could focus on the combination of perspectives from different end-point users of PROs (i.e., patients, parents, and healthcare professionals).

**Confounding factors**

As a possible confounding factor, it should be mentioned that during the data-collection, the participating hospitals were in a transition phase from moving from a paper to an electronic patient health record system. Furthermore, the participating pediatric oncology centers were preparing for a big change in Dutch pediatric cancer care: centralizing care to one Dutch pediatric oncology center. These circumstantial changes could have possibly influenced our findings in a negative way, especially the fidelity outcomes regarding the implementation of the KLIK method. On the contrary, this is exactly what can be expected to happen when conducting research in real-world pediatric cancer care, and it therefore gives helpful insights into how other organizational changes affect the fidelity outcomes of a new intervention. It is essential to create a balance between fidelity to evidence-based programs and adaptation to the local setting.

**CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES**

The pediatric oncology psychosocial standards of care endorse the systematic assessment of PROs in children with cancer and their families throughout the cancer care trajectory.30 According to Wiener and Pao "excellent psychosocial care begins at the time of diagnosis, incorporates
early assessment, continuing and consistent care, a range of therapeutic interventions, and utilizes interdisciplinary resources for all family members. Through the years, the increased risk for psychosocial problems in families of children with cancer has become evident, and the need for monitoring and screening has been addressed in the literature time after time. Yet, the actual application of monitoring and screening in clinical practice remains limited.

Because hospitals are under financial pressure, the biggest challenge remains in the provision of psychosocial resources. Screening seems a cost-effective and evidence-based way to identify high risk families or families that express significant distress. Psychosocial screening can be applied by the psychosocial team at important transition phases, such as at the time of diagnosis, at the end of treatment, and when transitioning to adult care or entering the phase of survivorship. Monitoring PROs has the goal to observe and discuss the impact of the disease on the patient and its family. Medical healthcare professionals have a gatekeeper function and should therefore systematically communicate on standardized PROs. As a result of PRO monitoring and screening, targeted evidence-based psychosocial interventions can be applied. In the long run, the quality of this care process should be evaluated with patient-reported experience measures (PREMs) and organizations could prioritize their objectives according to the needs of children with cancer and their families.

Within this thesis, several steps were conducted in implementing PROs in pediatric oncology practice and several challenges for successful PRO integration can be identified based on the results. Strategies to overcome barriers and future directions are described in the sections below and summarized in Table II.

Reliable and valid non-burdensome PRO measures

In addition to the PRO questionnaires that were normed or developed in this thesis, there are good initiatives to decrease the burden of completing long questionnaires. Using Computerized Adaptive Testing (CAT) to shorten the list of items and the short Patient reported outcomes measurement information system (PROMIS) pediatric forms could offer a solution for repeated assessment of the same questionnaire. PROMIS aims to provide clinicians and researchers access to efficient, precise, valid, and responsive adult– and child– reported measures of health and well-being. By using PROMIS item banks, patients or parents only need to answer 4 to 8 items per item bank, which decreases burden, but at the same time reliability remains the same as conventional PRO measures or is even increased. Therefore, PROMIS is now seen as the new ‘gold standard’ for measuring PROs. Our hospital currently takes part in the pediatric translation, validation and implementation of the Dutch and Flemish PROMIS item banks. Once sufficient reference data are collected in the healthy and pediatric cancer population, we aim to incorporate the PROMIS item banks into the KLlK system for children with cancer and for children with chronic health conditions. Different authorities should be working hand-in-hand to actually finalize the realization of the PROMIS item banks.
Sufficient PRO communication education and training

Levetown\textsuperscript{39} emphasizes that healthcare communication skills are crucial to provide safe and effective medical care in the everyday interactions with children and their families. Effective communication should be a cornerstone of care and is adaptive to the needs of the child and its family (i.e. patient- and family-centered). Even though communication is the most common procedure in pediatrics, the teaching of effective healthcare communication skills still form a minor part of most medical training\textsuperscript{39}. Medical healthcare communication is mainly learned by trial and error, and psychosocial and practical/family issues are often overlooked\textsuperscript{39}.

It is widely known from the literature that the use of PROs support the communication between children, parents, and healthcare professionals. Medical healthcare professionals that participated in our studies, indicated PRO information to be valuable (chapters 7, 8, and 10) and they thought it should become part of standard care (chapters 7 and 10). Yet, there can be a difference between intentions and actual behavioral change (e.g., when the user lacks control over the behavior, or when psychosocial support is not always readily available).\textsuperscript{40}

One important aspect to increase healthcare professionals' knowledge in effective PRO use is to provide an educational program or training in how to use PROs in routine clinical practice \textsuperscript{41-43}. The KLIK method uses a one-hour training program, to teach clinicians how to effectively use PROs in routine clinical care\textsuperscript{41}. Nevertheless, more research should be performed on the impact and effects of several aspects of training on the application of PROs in clinical practice. This includes studies on the effects of initial communication training (e.g., face-to-face, web based, or manual-based), ongoing supervision (e.g., live or indirect supervision, on a group or individual level, audio and video-based recording, attending conferences, and the effect of personal communication styles on patient and parent reported outcomes).

Efficient technology system

An important strength of the KLIK method is that it uses an online system to collect and transfer PRO data\textsuperscript{44}. This makes it possible for the system to be used and adapted according to the needs of any hospital in the world, as it is not tied to a specific electronic record system. Also, PRO results and clinical scores are automatically calculated by the system, which saves HCPs time in scoring as opposed to paper-and-pencil formats. The downside of a separate online system is that it is not integrated in the electronic medical record. In the KLIK system, PDF files of the ePROfiles can be printed and saved in the electronic medical record, but currently there is no direct link provided. HCPs frequently addressed this as a problem during our study. Entering a difficult password and opening a separate window during a busy outpatient clinic is sometimes too much to ask. We therefore adapted the system, such that users can now choose their own password (as long as it corresponds to the regulations of their organization). Additionally, we are currently discussing the possibilities with IT managers of the hospitals to link the KLIK ePROfile to their electronic medical record.

Efficient communication of different electronic information systems should also be a guiding principle if we want to link PRO outcomes (i.e., from population surveillance, clinical trials or research studies, individual patient-HCP interactions) with clinical outcomes (i.e., from the electronic medical record, patient registry files, clinical trials and research studies)\textsuperscript{29}. We should think of smart ways to reduce the burden for children, their families, and healthcare professionals.
In light of this, in 2012, our hospital started collaboration with the Dutch Childhood Oncology Group (DCOG) to decrease burden for children and their families in the assessment of HRQoL PRO data. An agreement was made, such that paper-based or electronic PRO data collected for clinical trials in the Netherlands, will be collected through the KLIK system. As a result of this collaboration, the KLIK system has undergone tremendous changes, which were accomplished in April 2016. New features of the system are: (1) more clear and appealing lay-out of the website, (2) patients being able to register under one account both for care and research purposes, (3) built-in questionnaires used for several DCOG treatment protocols (i.e., ALL11, PNET-5, and EWING2008), (4) possibility to plan multiple PRO completion dates in advance, (5) system recognizes when duplicate PRO questionnaires for care and research have overlapping assessment points, (6) PRO administrators will only have access to data of hospitals/patients that are assigned to them. To conclude, both for research and clinical practice it is crucial to develop an efficient technology system that integrates information derived from several sources.

**Importance of top-down support**

To further reduce reluctance to change and increase the motivation to comply—especially in the case of a psychosocially-oriented intervention—formal ratification by medical leaders and engaging senior physician champions who actively promote the implementation process remains of utmost importance. With regard to providing support, practical issues could be addressed and barriers overcome by providing ways to integrate PRO monitoring and screening in clinical routines (e.g. investing in efficient technology systems which can integrate PRO data into the electronic file, and appointing a coordinator/facilitator for the implementation process). Research-funded implementation should in the long run be replaced by organizational resources dedicated towards implementation of continuous operations. It is therefore important that professional societies recognize their influencing role in the failure or success of the integration of PROs in clinical practice. This may entail looking for ways to allocate funds for health systems change or incorporating the monitoring of PROs in the financial system of health insurance companies.

**Embedding ePROs in the pediatric cancer care trajectory**

In the future, organizations should look at pragmatic ways to provide cost-effective and evidence-based embedded PRO monitoring and screening. Multidisciplinary exchange can be stimulated by the use of patient and parent-reported outcomes. In the sections below, main recommendations for the monitoring and screening of PROs are provided for different stages in the pediatric cancer care trajectory. Figure 2 presents a procedural model to embed ePROs through the pediatric cancer care trajectory.

*At diagnosis & during treatment*

During the first month post-diagnosis, it is known that families experience elevated levels of distress and anxiety. It is therefore essential that understandable information is given to the child and family members and both the medical and psychosocial team should be available to offer support and guidance to the family. As some families are at risk for ongoing distress, early assessment of family risk and supportive factors should be applied, such that the team can provide efficient psychosocial care to the specific needs of families and prevent an escalation of problems. Families should preferably be screened for psychosocial risk with the ePAT within 2 weeks post-
Table II. Determinants for PRO implementation outcomes and applied strategies or future perspectives

<table>
<thead>
<tr>
<th>Level</th>
<th>Facilitating factors</th>
<th>Obstructing factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRO Questionnaires</td>
<td>• Short, non-burdensome</td>
<td>• No Dutch normative data was available for parent-reported HRQoL in young children</td>
</tr>
<tr>
<td></td>
<td>• Online format</td>
<td>and for parental distress</td>
</tr>
<tr>
<td></td>
<td>• Covering a broad age range, including age-matched reference data</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Generic and disease-specific versions available</td>
<td></td>
</tr>
<tr>
<td>KLIK ePROfile</td>
<td>• Gives clear and graphical overview of patient’s wellbeing over time</td>
<td>• Difficult password</td>
</tr>
<tr>
<td></td>
<td>• Helps to detect HRQoL problems with patient</td>
<td>• Not incorporated in electronic patient record</td>
</tr>
<tr>
<td></td>
<td>• Not tied to a specific hospital, discipline, age or illness type</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ePROs can be completed and reviewed prior to a patient’s visit</td>
<td></td>
</tr>
<tr>
<td>PRO training Healthcare professionals</td>
<td>• Supports self-efficacy of discussing PROs</td>
<td>• Time-consuming (one hour face-to-face)</td>
</tr>
<tr>
<td></td>
<td>• Increases healthcare professionals’ knowledge on how to effectively utilize PROs data in clinical practice</td>
<td></td>
</tr>
<tr>
<td>User</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completing PROs- Patient/Parent</td>
<td>• Supporting patients/parents in website registration (e.g. PRO coordinator provides information) and completing PROs (e.g. sending reminders)</td>
<td>• Registration at website</td>
</tr>
<tr>
<td></td>
<td>• Website available in English, generic PRO questionnaires in 8 different languages</td>
<td>• Patient/Parents do not always complete questionnaires (e.g. because they do not always see or experience the added value, repetition of the same questionnaires over time, think it is research instead of care)</td>
</tr>
<tr>
<td></td>
<td>• ePROfile is discussed by medical HCP during consultation</td>
<td>• Language, cognitive or cultural barrier</td>
</tr>
<tr>
<td></td>
<td>• Experienced usefulness of discussing PROs</td>
<td></td>
</tr>
<tr>
<td>Discussing PROs-medical healthcare professional</td>
<td>• Evidence of PROs in shown</td>
<td>• Motivation: insufficient perceived personal benefit of using PROs?</td>
</tr>
<tr>
<td></td>
<td>• Sufficiently trained in knowledge about PROs</td>
<td>• Insufficient skills to discuss psychosocial PROs?</td>
</tr>
<tr>
<td></td>
<td>• KLIK does not result in a longer consultation duration</td>
<td>• Insufficient time</td>
</tr>
<tr>
<td></td>
<td>• Local champion that supports PRO discussion</td>
<td>• Not sufficiently compatible with clinical workflow</td>
</tr>
<tr>
<td>PRO screening-psychosocial healthcare professional</td>
<td>• Parents think the ePAT at diagnosis is a clear, non-burdensome and usable questionnaire</td>
<td>• Not a lot of new information from the PAT at one month post-diagnosis</td>
</tr>
<tr>
<td></td>
<td>• Psychosocial risk at diagnosis (ePAT) is related to psychosocial distress (DTF) at 6 months post-diagnosis</td>
<td>• No clear guidelines on what actions to take as a result of a concerning score on the PAT or DTF</td>
</tr>
<tr>
<td></td>
<td>• PAT risk ePROfile matches with psychosocial team risk estimation of the family and influences 25% of actions as indicated by the team</td>
<td>• No integration of PRO monitoring and screening by medical and psychosocial team</td>
</tr>
<tr>
<td></td>
<td>• The DT-P differentiates between distress in parents of children with cancer and parents of healthy children</td>
<td></td>
</tr>
<tr>
<td>Organization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustainable integration of PROs in pediatric cancer care</td>
<td>• Negative implementation climate (i.e. other changes going on)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No policy plans about using PROs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No financial or practical investment</td>
<td></td>
</tr>
</tbody>
</table>
Strategies/future perspectives

- Sufficiently reliable Dutch normative data for infants, toddlers and young children, and normative data for parental distress were collected
- Normative reference data should be built into the KLIK portal
- Dutch PROMIS® item banks should be validated

- Let HCPs choose their own password as long as it corresponds to the password rules of their organization
- Provide link with electronic record
- Set up good communication with IT from different organizations, such that electronic system can be adapted according to specific requests of the organization

- Develop online training for healthcare professionals
- Develop online training for patients/their parents in how to actively participate during consultation?

- Campaign: further inform patients/parents about existence and value of intervention
  Incorporate website registration in core of hospital registration (i.e. secretary or research nurse)
- Adapt system such that patients can independently plan or change their future outpatient consultation date
- Add PRO topics (e.g. overall HRQoL, treatment information, and care coordination needs) that are experienced as relevant by patient and parent

- Add PRO topics (e.g. acute symptom information) experienced as clinically relevant by healthcare professional
- Local champignon provides training?
- Adapt PRO assessment and feedback according to the flow of medical care

- Develop psychosocial guidelines for screening and integrate with medical protocol guidelines
- Discuss with psychosocial team of the hospital how screening can best inform their care provided to the families of children with cancer

- Ratification management: use of KLIK as a tool to accomplish the mission of achieving better HRQoL
- Provide users with sufficient resources (e.g. repeated training sessions, reminders, PRO coordinator, integration in electronic record) to integrate PRO results in clinical workflow
diagnosis. During treatment, PRO assessment should include measures that next to a general perspective, also capture treatment-related concerns, for instance the PedsQL Cancer Module.49

Furthermore, patients who are in transition from pediatric to adult care face some challenges: they have to leave the safe hospital environment, are suddenly placed in a room with adult patients and have to apply to adult rules and regulations. The generic On Your Own Feet Self-Efficacy Scale50 measures coping, disease-knowledge and skills for independent hospital visits of adolescents with various chronic diseases. This instrument informs clinical practice in how well adolescents are capable of the self-management of their disease, such that appropriate educational programs or targeted interventions can be applied.

After end of treatment

After the end of treatment, families have to deal with issues such as going back to school or work, reactions from their environment, and the fear of a possible relapse. Possible consequences of the cancer treatment (e.g. attention problems and fatigue) should be regularly monitored (e.g., once in every 3 months), for example with the generic PedsQL and the PedsQL fatigue.49

Parents and siblings

As earlier described in this thesis, a diagnosis of childhood cancer and its accompanying treatment has an impact on the whole family.8,48,51 Parents can experience pediatric medical traumatic stress48, which can have an influence on their children and we therefore recommend that their distress is regularly monitored (once in every 6 months) with the DT-P.

Monitoring the adjustment of siblings to the cancer diagnosis of their sick brother or sister should form an important part of assessment as well. Just like their parents, siblings are at risk for pediatric medical traumatic stress reactions, a lower HRQoL, and school problems52. Often siblings’ needs are met inadequately compared to their sick brother or sister. During treatment and follow-up, we recommend screening for possible emotional and behavioral problems in siblings at least once in every 6 months, for example with the SDQ.

Family experience measures and assessing quality of care

The experience that a family has in the hospital can have an impact on their psychosocial outcomes and it is therefore important to also monitor parent and patient reported experience measures (PREMs). A promising PREM questionnaire that is currently available in Dutch is the PedsQL Healthcare Satisfaction Hematology/Oncology Module53, which measures parents satisfaction with information, inclusion of the family, staff technical skills, services, communication, emotional needs, and overall satisfaction with care. We are currently involved in a project that is going to use this measure within a new to be build pediatric oncology center: the Princess Máxima Center for pediatric oncology. This could lead to helpful insights into families psychological functioning and satisfaction with delivered care when looking at different healing environments.

Survival (5 years after end of treatment)

In the Netherlands, a guideline (LATER guideline) for children that are 5 years or above the end of their treatment has been developed. It includes a psychosocial guideline section, which advises to use the SDQ, and the GHQ. Unfortunately these Dutch psychosocial guidelines are only partly followed up. If we want to provide the care that patients and their families deserve, we should start to think of pragmatic ways to incorporate these guidelines into clinical practice. The KLIK method could offer a solution, since this saves time in scoring of questionnaires.

Next to the questionnaires described in the LATER guideline, other questionnaires could be helpful as well, such as the Benefit and Burden Scale. For patients after end of treatment, this instrument could inform clinical practice in how well patients have adjusted to the disease. A Dutch study that was performed by the Emma Children’s Hospital AMC in Amsterdam, found that disease-related burden of childhood cancer survivors was related to HRQoL, anxiety, posttraumatic stress symptoms and behavioral problems55.
### Summary and General Discussion

#### NEW DIAGNOSIS
- Shortly after diagnosis (preferably within 2 weeks)

#### DURING PEDIATRIC CANCER TREATMENT
- During treatment (once in every 3 months)

#### AFTER END OF TREATMENT
- Bi-annually (from 6 months post-diagnosis)

#### ≥ 5 YRS POST-DIAGNOSIS: LATER GUIDELINE
- Follow-up (every outpatient visit)

#### AGE 18+: TRANSITION
- Transition to adult care (once in every 3 months)

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<table>
<thead>
<tr>
<th>NEW DIAGNOSIS</th>
<th>DURING PEDIATRIC CANCER TREATMENT</th>
<th>AFTER END OF TREATMENT</th>
<th>≥ 5 YRS POST-DIAGNOSIS: LATER GUIDELINE</th>
<th>AGE 18+: TRANSITION</th>
</tr>
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<tbody>
<tr>
<td>Registration</td>
<td>KLIK website</td>
<td></td>
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<tr>
<td>Monitoring²:</td>
<td>- TAPQOL/PedsQL² generic</td>
<td>- PedsQL fatigue³</td>
<td>- PedsQL fatigue³</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- SDQ (siblings)⁷</td>
<td>- Open question to staff member⁵</td>
<td>- Open question to staff member⁵</td>
<td></td>
</tr>
<tr>
<td>Screening³:</td>
<td>- PAT (parents)⁶</td>
<td>- SDQ (patient)⁷</td>
<td>- GHQ (18+)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Or:</td>
<td>- SDQ (siblings)⁷</td>
<td>- DTP (parents)⁸</td>
<td></td>
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<tr>
<td></td>
<td>- Socio-demographic questionnaire (if diagnosis ≥ 3 months in the past)</td>
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</tbody>
</table>

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**Figure 2.** Overview of suggested patient and family electronic PRO assessment points during different stages of the pediatric cancer trajectory

- a results are reviewed and/or discussed by a member of the psychosocial team. In case of concerning results, targeted interventions are applied.
- b results are reviewed and/or discussed by a member of the medical staff. In case of concerning results, referrals to targeted supportive care are made.
- 1 Use for patients aged 0-1 years
- 2 Available in Dutch for patients aged 2-30 years (with different age versions for 2-4, 5-7, 8-12, 13-18, and 19-30 years)
- 3 Available in Dutch for patients aged 2-18 years (with different age versions for 2-4, 5-7, 8-12, and 13-18 years)
- 4 Use for patients aged 0-18 years
- 5 Use for patients aged 0-30 years and/or parents of patients aged 0-18 years
- 6 Use for parents of patients aged 0-18 years
- 7 Use for patients and/or siblings of patients aged 2-17 years
- 8 Available in Dutch for patients aged 2-30 years (with different age versions for 2-4, 5-7, 8-12, 13-18, and 19-30 years)

**Abbreviations:** PAT= Psychosocial Assessment Tool, TAPQOL= TNO-AZL Preschool Quality of Life questionnaire, PedsQL= Pediatric Quality of Life Inventory, HCSSQ-HO= Healthcare Satisfaction Questionnaire-Hematology/Oncology Module, DTP= Distress Thermometer for parents, SDQ= Strengths and Difficulties Questionnaire, GHQ= General Health Questionnaire
CONCLUSION

This thesis “Changing pediatric cancer care: development and implementation of electronic patient and parent reported outcomes”, was the first to determine the fidelity and influencing factors for the real-world implementation of electronic patient and parent reported outcomes in multi-center pediatric cancer care. This knowledge is important because it makes an additional step— from a highly controlled research environment to actual implementation in standard pediatric oncology care. Reliable and valid questionnaires were developed and can now be used in research and in pediatric cancer care. It was shown that the implementation of PROs is generally feasible and internationally valued, but crucial implementation barriers remain present. For the sustainable integration of PROs in clinical practice, joint efforts should be made to reach a common set of PRO topics and barriers should be tackled with adequate implementation strategies.

KEY MESSAGES

1. Reliable and valid ePRO measures are available for Dutch children with cancer and their families:
   o Overall, patient HRQoL (TAPQOL/PedsQL), parental distress (DT-P) and family psychosocial risk for psychosocial problems (ePAT) can be reliably measured in the Netherlands, and the questionnaires can be used to compare children and parents from the healthy population with children with cancer and their parents;
   o Patients, parents and healthcare professionals should start to work together to come to a common set of PRO topics;
   o To accomplish high response to PRO measures, and to collect efficient, precise, valid, and responsive parent– and child– reported PROs, smart and flexible technology systems should be adopted.

2. The implementation of ePROs is internationally valued in pediatric cancer care, but medical and psychosocial healthcare professionals experience substantial barriers to make this a standard part of their care process:
   o Mainly technological, practical, and organizational barriers remain present, but it is also important to look at less evident markers of resistance to change in individuals;
   o The implementation of international multidisciplinary guidelines are needed to improve the monitoring, screening, and application of PROs as part of integrative pediatric cancer care;
   o Only when an organization fully incorporates the use of PROs in the vision and the management system, the implementation of PROs will be successful.
Reference list


50. van Staa AL. On Your Own Feet: Preferences and Competencies for Care of Adolescents with Chronic Conditions 2012; http://hdl.handle.net/1765/32973.