From research to relief

Improving children's cancer pain management at home using digital health.

Julia Simon

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Van onderzoek naar pijnverlichting:
Het verbeteren van de pijnbehandeling van kinderen met kanker in de thuissituatie
met behulp van digitale zorg-interventies.

(met een samenvatting in het Nederlands)

Proefschrift

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Alles
wordt lichter

door erover te praten:

als we delen
wat we dragen

dan tillen we het samen.

- Bram Schweckhorst

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Chapter 1

General Introduction

PEDIATRIC ONCOLOGY

Coping with a childhood cancer diagnosis, and its intense and toxic treatment, has major implications for patients and their families. In The Netherlands, roughly 600 families are faced with this new reality on a yearly basis [1], and around 400.000 families worldwide [2,3]. Diagnoses include blood cancers, brain cancers, and solid tumors [2,3]. Thanks to advances in diagnostics and treatment, average overall survival rates for childhood cancer in The Netherlands are now roughly 83% five-year post treatment [4], and 78% ten-year post treatment [5]. In low- and middle income countries, the percentage of children that are cured is still much lower, around 30% [2]. As pediatric cancer is often associated with a high symptom burden, among which pain, nausea, fatigue, and psychosocial problems (such as fear, worry, and sadness) [6-9], the focus on symptom management has increased over the past decennia [10]. The adverse effects of the illness itself and its treatment jeopardize the quality of life (QoL) of those affected [9,11,12]. And thus, when care for children with cancer in The Netherlands was centralized at the Princess Máxima Center for Pediatric Oncology, its mission statement included a clear focus on QoL: *'Curing every child with cancer, with an optimal quality of life'.*

SUPPORTIVE CARE AND PSYCHO-ONCOLOGY

Improving QoL is also reflected in the core principles of supportive care (aimed at preventing and managing the adverse effects of the illness and its treatment [13]) as well as psycho-oncology (aimed at reducing the psychosocial risks for children and their families [14]). Recent studies in adult oncology have shown that timely monitoring of symptom burden can improve survival rates and patient's QoL [15-17]. Also, children with cancer are at risk of experiencing significant psychological distress during and after the cancer treatment, and thus, providing psychosocial support is key to maintaining their QoL [18]. In addition, as parents and caregivers are profoundly affected by a child's cancer diagnosis, ongoing assessment and interventions focusing on their emotional wellbeing is strongly recommended. Many parents are resilient and function well over time, but there is a subset of parents (often with pre-existing mental health problems) that struggle to cope and feel overwhelmed [19]. This may affect their child's recovery, as parental distress has been reported as an important predictor of the psychosocial adjustment and emotional wellbeing of children [20-22]. Furthermore, parental emotional issues can negatively influence the child's experience of and coping with cancer treatment, their own ability to support the child and their siblings, and threaten family stability in general [23-26]. Therefore, monitoring symptom burden of both children and their parents during their cancer care trajectory is of utmost importance [19].

DEFINITION AND TYPES OF PAIN

Pain is one of the most common and distressing adverse effects children experience during cancer treatment [27-32]. The International Association for the Study of Pain (IASP) defines pain as 'an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage' [33]. This definition takes into account the biopsychosocial model of pain, stating that a person's perception of pain is not only influenced by the nature of a certain stimulus, but also by a variety of biological (e.g. nervous system characteristics such as pain threshold), psychological (e.g. anxiety, coping skills), and environmental (e.g. social and cultural beliefs) factors [33-36]. For instance, previous experiences with painful and stressful situations, or learned perceptions about pain and coping strategies can influence an individual's experience of pain [37].

Sources of pain experienced during cancer treatment can be categorized in 1) treatment-related pain, resulting from chemotherapy, radiation or surgery (such as mucositis or vincristine-induced neuropathy), 2) procedure-related pain, resulting from blood draws, lumbar punctures, or bone marrow aspirations, and 3) illness-related pain, resulting from the tumor itself or its metastases inflaming or eroding bone, viscera or nerves [31,38,39]. In addition, pain can be categorized in nociceptive (from tissue injury), neuropathic (from nerve injury), and nociplastic (from sensitization of the nervous system) [34], of which nociceptive pain is the most common [40]. Finally, pain can be categorized as acute or chronic. Acute pain usually occurs in direct response to tissue trauma and related inflammatory processes. In contrast to chronic pain, which persists beyond the expected healing period and is generally defined as pain lasting three months or longer [39], acute pain dissolves and carries an important survival value (i.e. warning signal, promoting caution) [34]. In its complexity, chronic pain is considered a disease on itself with many serious psychological and physical implications [34]. The focus of this thesis lies mainly on acute pain.

PAIN PREVALENCE: HOSPITAL VERSUS HOME

A study on pain in children with cancer (during- and post treatment) revealed that 75% experienced pain over the past month [32]. In another study, over 50% of parents of children receiving cancer treatment reported that their child experienced chronic or recurrent pain in the past 3 months [29]. Similar numbers were reported by children and their parents or caregivers in qualitative interviews during the first three months after diagnosis (49%) [31], and during the first year of cancer treatment (i.e. 43%) [30]. Children

receiving palliative care reported a higher prevalence of pain (80-86%) [41]. The high variability of pain prevalence may be due to a large variety of patient populations in studies (focus on specific cancer diagnoses, treatment phases, or age groups) and pain assessment tools that were used.

Up until now, research has mainly focused on hospitalized children with cancer [42], and only a limited number of studies assessed pain at home [29,30,32,42]. However, these studies disregarded the youngest population (0-4 or 0-8 year old children). One study did include children aged 1-18 years old [32], yet only used parent proxy reporting.

PAIN ASSESSMENT IN CHILDREN

There are many different ways to assess pain in children and adolescents [43], yet to date, there is no consensus on one perfect assessment tool or analysis technique [44]. Given that pain is a highly subjective experience, self-reporting is generally the preferred method for its assessment [34]. When self-reporting is not possible (for instance with young children), researchers and clinicians depend on proxy-reports from caregivers or clinicians, which come with disadvantages. For instance, parents of children with cancer [45] as well as parents of children in a pediatric pain clinic [43] generally reported higher pain intensity compared to the children's self-reports. Another study with children with cancer showed that nurses consistently reported lower pain intensity than children did [46]. However, a study with children and adolescents with cerebral palsy (CP) found no significant difference between the proportion of self-reported versus proxy-reported pain [47]. Given these divergent results on the validity of proxy-reports, as well as the subjective nature of pain [34], researchers and clinicians should strive to use self-reporting whenever possible. Based on an extensive systematic review and quality assessment, strong recommendations were made for use of the Numerical Rating Scale-11 (NRS-11) across all types of pain (acute, chronic, postoperative) for children aged 8 years or older [43]. This is in line with another review supporting the reliability and validity of the NRS-11 as a self-report scale for pain intensity of children 8 years and up, and perhaps even as young as 6 years old [48]. No recommendations are made for children under the age of six, as most children in that age group will not have attained the cognitive abilities required for self-reporting pain intensity [49].

CONSEQUENCES OF PAIN FOR CHILDREN AND THEIR PARENTS

Pain is not only one of the most common symptoms during childhood cancer treatment, it also causes high distress [50], and it is the symptom most feared by children [51]. High distress and fear can lead to noncompliance with care (e.g. painful procedures) [52]. Furthermore, untreated or undertreated pain can create significant changes in the way pain is processed (causing an increased sensitivity to pain, sometimes persisting after recovery from cancer [28,53]), as well as increased distress and anxiety [54]. Moreover, undertreated pain can lead to poor sleep quality and morbidity, negatively impacting children's QoL [9,55].

In addition to pain felt by patients, it also affects their parents or caregivers. Watching their child in pain often makes them feel powerless [56]. Moreover, having a child that is in pain, on top of the increased caregiving demands that come with having a child with cancer, are risk factors for parental sleep problems, fatigue and distress [55,57-59]. In some cases, these problems are long lasting: a longitudinal study assessed sleep problems in parents of children with Acute Lymphoblastic Leukemia (ALL) and found that in general parental sleep improved over time, but that 33% of parents still reported clinically relevant sleep problems three years after the diagnosis (compared to 16% in general population). Half of those 33% of parents also reported clinical distress, both of which negatively affect their QoL [58]. The psychosocial burden on families of children with cancer also disrupts family dynamics, make it difficult to maintain social lives, and negatively impact caregiver-caregiver and sibling-caregiver relationships [60]. Use of proper pain management interventions can maintain and/or improve the QoL of patients and their families [29].

PAIN MANAGEMENT INTERVENTIONS

There is a wide range of pharmacologic as well as non-pharmacologic pain management interventions available for cancer-related pain. The WHO guideline for cancer pain relief and palliative care [61] has been proven effective in controlling pain in children and adolescents with cancer [62]. At the Princess Máxima Center for Pediatric Oncology, these interventions are carried out by a multidisciplinary team of healthcare professionals. The hospital's Pain Service consists of nurses and anesthesiologists focusing on the prevention and treatment of pain during hospitalization and surgeries. Moreover, child life specialists from the psycho-oncology department prepare children for and guide them through painful medical procedures using interventions such as active distraction. Psychologists are readily available to carry out a scale of interventions such as cognitive-

behavioral therapy (CBT), relaxation training, and hypnosis [63]. And finally, social workers provide (mental) support to parents and help them cope with stressful situations, as we know that parental responses to their child's pain can influence the development and maintenance of pain in children [64].

Studies have shown that non-pharmacologic interventions can significantly reduce pain intensity in children and adolescents with headache, fibromyalgia, and abdominal pain [65,66]. With regards to children with cancer specifically, a recently published clinical practice guideline made strong recommendations for the use of active distraction and hypnosis during painful procedures [67]. Based on a Cochrane review on needle-related procedural pain in children with cancer, the authors support the efficacy of hypnosis, distraction, and combined CBT and breathing intervention to reduce pain and/or distress [68]. Hypnosis and CBT were also found effective in reducing pain and pain-related anxiety in pediatric cancer patients undergoing bone marrow aspirations [69].

Another non-pharmacologic intervention gaining popularity is pain science education (PSE), a psychoeducational intervention primarily aimed at changing patients' understanding of the biopsychosocial aspects (biological, psychological and environmental factors) of pain [70]. PSE has yielded decreased pain intensity and pain catastrophizing in adult cancer survivors with chronic pain [71], and holds promise for children with cancer and survivors as well [72]. In pediatric oncology, psychoeducational interventions are generally aimed at educating children and families to better understand, and cope with the illness, treatment and its side-effects [73]. Well-informed pediatric oncology patients and families often feel more in control, which can lead to reduced levels of distress [74], and a psychoeducational intervention for coping and symptom management in children with cancer significantly reduced pain [75]. In conclusion, despite the existence of many evidence based pain management interventions for children and adolescents with cancer (both pharmacologic and non-pharmacologic) [62], cancer-related pain in children is still suboptimally managed at home [29].

SUBOPTIMAL PAIN MANAGEMENT AT HOME

Ineffective treatment of pain at home might be attributable to different factors. First, as new treatment regimens allow more flexibility to carry out parts of the treatment in an outpatient setting, and children spend less time hospitalized, there is an increased responsibility for the management of adverse effects of the illness and its treatment for families themselves [76,77]. After the diagnosis, families receive an overwhelming amount of information regarding (implications of) the illness and treatment, and may feel ill

prepared to take on the challenges they are faced with. During hospitalization, parents can ask healthcare professionals for advice day and night, yet this is more difficult for outpatients in the home setting. Some parents may feel a barrier to contact the hospital and ask for help ("aren't we asking for a lot already?"), or they are discouraged by long hospital phone queues.

Moreover, there are a lot of fears and misconceptions among parents about pain and its treatment in children. For instance, many parents think children only express pain through active, loud, and attention seeking behavior, as opposed to being quiet or withdrawn [78]. A study in children who had recently undergone surgery (e.g. tonsillectomy or to reset fractures) showed that parents with more misconceptions and fears about analgesic use, provided fewer doses of postoperative analgesics at home [79]. It has been established that misconceptions are also very prevalent in parents of children with cancer: some parents think pain is unavoidable during cancer [31]. They think that pain medication is addictive, and that it works best when given as little as possible [80]. Assessing and addressing parental and children's gaps in knowledge and misconceptions regarding pain (management) by using psychoeducational interventions might be an important step towards improving pain management at home [72].

THE POTENTIALS OF DIGITAL HEALTH

Digital health tools may be a solution for optimizing pain management in the home setting, as these tools provide us with the opportunity to bridge the distance between the hospital and the home setting. Digital health tools can be sub-categorized in either eHealth or mHealth. eHealth refers to "the use of information technology (internet, digital games, virtual reality, and robotics) in the promotion, prevention, treatment, and maintenance of health", whereas mHealth refers to "mobile and wireless applications, including text messages, apps, wearable devices, remote sensing, and the use of social media such as Facebook and Twitter, in the delivery of health related services"[81]. The focus of this thesis lies on mHealth specifically, as such interventions can be assessed anyplace and anytime and therefore enable real-time (i.e. prospective) pain monitoring, and thereby avoid recall bias [82].

Digital health tools hold great potential benefits, such as providing patients with real-time feedback and creating better accessibility to care for patients living remotely [83]. A previous randomized controlled trial (RCT) with adult cancer patients revealed promising advantages of weekly electronic symptom monitoring using patient-reported outcomes (PROs): the intervention group showed improvements in physical functioning and QoL,

as well as less frequent admissions to the ER or hospitalization compared to the control group [17,84]. As they enable more timely recognition of difficulties, PROs contribute to better prevention and management of acute as well as late (post treatment) psychosocial and physical symptoms in cancer patients [85,86]. Digital health tools using electronic symptom monitoring have also gained popularity in pediatric oncology, and these tools are mainly aimed at psychoeducation and improving symptom management [87-93]. The KLIK PROM method for instance, a web-based portal that monitors and enables healthcare professionals to discuss PROs, has shown to improve health-related Quality of Life (HRQoL) of children with cancer [94]. Another example is ePROtect, a web-based portal carrying out daily assessments of children's symptom burden (appetite loss, fatigue, nausea, pain, physical functioning, cognitive impairments, and sleep quality) [95]. First results on use of ePROtect reveal that daily symptom monitoring was feasible for children with cancer aged 5-18 years old, and that it assisted in the management and intervention of adverse events [96].

With regards to pain specific mHealth tools for pediatric oncology: some had already been developed at the start of this project (2018), such as the Pain Squad app [97], the Pain Buddy app [98], and the Kræftværket app [99]. However, these tools all disregard the youngest cancer population: Pain Squad and Pain Buddy were developed for children between the ages of 8 and 18 years, and Kræftværket for 16- to 32-year olds. Moreover, no results of these mHealth interventions effectiveness in clinical care had been published.

IMPLEMENTATION IN CARE

Over the past years, many digital health tools aimed at better pain management have been developed [93]. Unfortunately, even though these very costly digital tools are often developed to improve access to care, the evidence suggests that patients do not have access to these tools in the real-world setting [100]. Implementation science focuses on this specific problem, and uses methods and theories to guide the process of translating research into practice [101]. In the past, it could take up to 15-20 years before innovations were successfully implemented and used in clinical care [101,102]. As a result, only 14% of evidence based tools were actually implemented, leaving a large amount of 'research waste' [100,101]. For instance, one systematic review identified 47 papers on mHealth interventions (apps) for pain, of which none were publicly available in app stores [103]. And thus, implementation has been one of the top priorities since the start of our research project.

Assessing determinants that might hinder (i.e. barriers) or facilitate (i.e. facilitators) implementation in a real-world setting is a key aspect of implementation science [104]. A previous study with a digital PROM intervention (the KLIK method) for HRQoL in pediatric oncology revealed that barriers for its use were mainly related to organizational issues (e.g. organizational change), whereas facilitators were mainly related to end-users (e.g. positive outcome expectations) and the intervention itself (e.g. simplicity of use) [105]. Another study assessed barriers and facilitators of digital pediatric pain assessment tools, and found researchers' intrinsic motivation (e.g. personal beliefs in the importance of making tool available to end users) to be the most common facilitator, whereas system-level issues (e.g. lack of time and infrastructure to support intervention availability) were the most common barriers [104]. Including end-users in the design phase (user-centered design) was associated with intervention availability in routine care [104]. This is consistent with other reviews on digital tools stressing the importance of involving key stakeholders (all people and/or organizations that affect or are affected by the outcomes of a project) throughout the entire process to attain buy-in from these parties [87,93,100,106].

At the start of this research project, there was little information available on barriers and facilitators of implementation of digital health tools for pain in pediatric oncology. One systematic review had been carried out on digital health tools for pain management in adults [93], and one in pediatrics [88]. However, the latter did not focus on oncology patients specifically. Given that pediatric cancer treatment is particularly intense and toxic relative to other diagnoses, this group might have specific digital health needs (such as real-time feedback from healthcare professionals). As the field of digital health is still rapidly evolving, there is a need to update and zoom in on barriers and facilitators of implementation of digital health tools focusing on pain in children with cancer.

SUMMARY AND KNOWLEDGE GAPS

- Pain is highly prevalent during childhood cancer treatment and it negatively affects the QoL of children and their families;
- Timely access to supportive- and psycho-oncological care can improve the QoL of children and their families;
- Research has mainly focused on hospitalized children, and little is still known about pain prevalence and management in children with cancer at home;
- Despite the availability of evidence based pain management interventions (pharmacologic and non-pharmacologic) for children with cancer, pain is still sub optimally managed at home;
- Psychoeducational interventions can help assess and address parental and children's knowledge gaps and misconceptions regarding pain(management), and have the potential to improve pain management at home;
- Digital health tools can bridge the distance between the hospital and home setting, and have potential to improve pain management at home;
- Unfortunately, even though digital health tools are often developed to improve access to care, evidence shows that patients do not have access to these tools in the real-world setting (research-to-practice gap);
- Implementation science, which includes the assessment of barriers and facilitators, has the potential to decrease the research-to-practice gap;
- Existing digital health tools for pain in children with cancer disregard the youngest population. Tools that include this group are needed.

AIMS AND OUTLINE OF THE THESIS

In response to the existing challenges and knowledge gaps, we started the *RELIEF* project which was primarily aimed at improving pain management of children with cancer aged between 0 and 18 years old in the home setting by using a digital health tool. The *RELIEF project* had three sub-aims: first, to explore pain prevalence in children with cancer at home (chapter 2). Second, to develop and test feasibility (chapter 3) and effectiveness (chapter 4) of a pain monitoring app for the home setting (the *KLIK Pijnmonitor app*). And third, to explore barriers and facilitators of implementation in clinical care (chapters 5 and 6). The figure below illustrates the project timeline with corresponding thesis chapters.

Chapter 2

This chapter describes an explorative clinical study with 73 children (or one of their parents) with cancer (between 0 and 18 years old) receiving ambulatory chemotherapy at the outpatient clinic. We assessed pain severity, pain prevalence, pharmacologic use, and pain interference with daily life. This study was the only one to be carried out at the Sophia Children's Hospital in Rotterdam before the Princess Máxima Center opened its doors in 2018.

- Main question: What is the prevalence of pain in children with cancer at home?

Chapter 3

Chapter 3 describes the development and feasibility testing of the *KLIK Pijnmonitor app*. In addition to feasibility, we assessed user adherence to the app, user experiences with the app, and determinants of implementation. In total, 27 children (or one of their parents) with cancer (between 0 and 18 years old) participated. Results were used to improve the *KLIK Pijnmonitor app* and the processes involved for the next step: effectiveness testing.

- Main question: Is use of the app feasible for children with cancer and their parents?

Chapter 4

In this chapter, a Randomized Controlled Trial (RCT) to assess effectiveness of the *KLIK Pijnmonitor app* in reducing clinically significant pain at home is described. We also assessed whether use of the app affected different aspects of pain (duration, interference, pain management strategies), and parental emotional wellbeing (i.e. distress, anxiety, depression, anger). Finally, we evaluated the app with users. In total, 158 children (or one of their parents) with cancer (between 0 and 18 years old) participated.

- Main question: Do fewer children report clinically significant pain at home when they have the app at their disposal (intervention group) versus when they receive care as usual (control group)?

Chapter 5

This chapter shows the results of a scoping review in which we systematically identified and characterized existing mHealth interventions for pain monitoring in children with cancer. Moreover, through semi-structured interviews with project leaders of these interventions, we assessed common barriers and facilitators of implementation.

- Main question: Which digital health tools have been developed for pain monitoring in pediatric oncology worldwide, and what are common barriers and facilitators for implementation of these tools?

Chapter 6

Chapter 6 describes our use of an implementation framework (Knowledge-to-Action (KTA)) to prepare for implementation of the app in clinical care. KTA is a commonly used theoretical approach to guide the process of translating research into practice. This chapter also describes barriers and facilitators that may influence future implementation of the app at the Princess Máxima Center for Pediatric Oncology, based on healthcare professional's attitudes.

- Main question: What are important barriers and facilitators of implementation of the *KLIK Pijnmonitor app* in clinical care?

Chapter 7

provides a summary of the main findings of the thesis, followed by implications for clinical practice and future research, strengths, methodological considerations and limitations of the research, and a conclusion. An overview of the studies and main findings presented in this thesis are also summarized in Table 1 attached to chapter 7.

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2

Chapter 2

Pain at Home During Childhood Cancer Treatment: Severity, Prevalence, Analgesic Use and Interference with Daily Life

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ABSTRACT

Background: Pain is a common symptom in childhood cancer. Since children spend more time at home, families are increasingly responsible for pain management. This study aimed at assessing pain at home.

Procedure: In this longitudinal observational study (April 2016-January 2017), pain severity and prevalence, analgesic use, and pain interference with daily life (Brief Pain Inventory Short Form) were assessed for 4 consecutive days around the time of multiple chemotherapy appointments. Descriptive statistics (frequencies and percentages) were used to report pain severity (with clinically significant pain defined as: score ≥ 4 on "worst pain" or "average pain in the last 24 h"), pain prevalence, and analgesic use. Mixed models were estimated to assess whether patient characteristics were associated with pain severity, and whether pain severity was associated with interference with daily life.

Results: Seventy-three children (50.7% male) participated (1-18 years). A majority (N = 57, 78%) experienced clinically significant pain at least once, and 30% reported clinically significant pain at least half the time. In 33.6% of scores ≥ 4, no medication was used. We found an association between pain severity and interference with daily life: the higher the pain, the bigger the interference (estimated regression coefficient = 1.01 [95% CI 0.98-1.13]).

Conclusions: The majority of children experienced clinically significant pain at home, and families frequently indicated no medication use. A stronger focus on education and coaching of families seems essential, as well as routine screening for pain in the home setting.

Keywords: Pain, pediatric oncology, psychosocial, quality of life, support care

INTRODUCTION

Due to major advances in treatment over the past years, the overall 5-year survival rate of children with cancer has now increased to approximately 80% [1]. With the improvement in survival, emphasis on improving quality of life and managing cancer related symptoms such as pain [2-4], has grown. This is an important development, as pain has been identified as the most frequent and severe cancer-related symptom by pediatric patients [5]. Pain in children with cancer can be divided into treatment-related pain (due to chemotherapy, radiation, surgery), procedure-related pain (due to blood draws, lumbar punctures, bone marrow aspirations) and illness-related pain (due to the infiltration of the tumor in organs or tissues) [6,7]. Studies have found treatment-related pain to be the most prevalent [7-9], with neuropathic pain as a result of chemotherapy being one of the most common forms of treatment-related pain [10,11].

A study on pain in children with cancer (in active treatment and post-treatment) revealed that 75% experienced pain over the past month (a score >0/10 for worst, least or average pain) [8]. In another study, over 50% of parents said their child experienced chronic or recurrent pain in the past three months [12]. Similar pain prevalence percentages were reported by children and their parents/guardians in qualitative interviews during the first three months after diagnosis (49%) [7], and during the first year of cancer treatment (i.e. 43%) [13]. The percentage of pain in children with cancer varies between studies. This may be due to rapid changes in treatment options over the years and the large variety of study populations (focus on specific cancer diagnoses, treatment phases or age groups) and pain assessment tools. Taking into account this wide range of studies, pain prevalence varies between 43 and 75%.

Until now, research on pain in children with cancer has focused mainly on hospitalized children [14]. However, as a result of changing patterns in health care systems and therapeutic regimens, children with cancer spend less time in the hospital and more time at home [15-19]. Therefore, families are becoming increasingly responsible for the child's pain management [15,18].

Little is still known about pain experiences of children with cancer in the home setting. There have been some studies focusing on this group [8,12,13,20]. However, the youngest population is often disregarded (0 - 4/8 year olds). One study did include children aged 1 - 18 years old [8]. However, only parent proxy-reporting was used. The aim of our study was to include the entire patient population (children aged 0 - 18 years) and use parent- as well as self-report measures of acute pain as recommended by previous studies [21].

Since pain in children with cancer receiving outpatient care (i.e. at home or at the outpatient clinic) has been reported in a limited amount of studies, the effect of families' increased responsibility for the child's pain remain unclear. One study reported that parents tend to undertreat pain in the home setting [12]. Parental concerns about analgesic use and misconceptions about the expression and treatment of pain in children could be related. For instance, a study focusing on parental attitudes regarding analgesic use in children with cancer showed that 63% of parents think that pain medication is addictive and 42% of parents think that pain medication should be given as little as possible in order to minimize side effects [22]. Another study carried out interviews with patients and parents and revealed that about half of the interviewees thought of pain as an unavoidable symptom during cancer treatment [7]. This is worrisome, as pharmacological as well as non-pharmacological treatments such as psychosocial interventions aimed at social, behavioral, cognitive or psychoeducational aspects [23] seem to have an effect on pain control in children when handled correctly [24,25]. Moreover, the way pain is being dealt with during childhood can permanently impact the child's pain processing (i.e. sensitization to pain), sometimes persisting into survivorship (post-treatment) [26].

Pain is an often present and disconcerting symptom during all stages of childhood cancer and many patients will experience pain as a consequence of their illness and/or treatment [6,14,27-29]. The existing literature suggests that pain management at home is not optimal and thus many children may be experiencing pain unnecessarily[12]. In some cases, undertreatment of pain during childhood cancer treatment can cause sensitization to pain stimuli, causing pain to persist post-cancer treatment [26]. Pain has been reported as very stressful by children with cancer [30], and it interferes with their quality of life [31]. Furthermore, it has been associated with high levels of patient distress [27,32], greater burden from physical and psychological symptoms [33], negative affect [34], and sleeping problems [7,33]. In childhood cancer survivors, it has been associated with greater emotional distress and suicidal ideation [26].

Since research on pain in the home setting is still scarce, the first aim of this study was to gain more insight into pain experiences of children at home during childhood cancer treatment in order to determine whether interventions focusing on pain management at home are needed. Therefore, we assessed the severity and prevalence of pain, as well as analgesic use. Furthermore, we investigated whether patient characteristics (i.e. age, gender, and diagnosis) were associated with pain severity, and whether pain severity was associated with interference in daily life.

METHODS

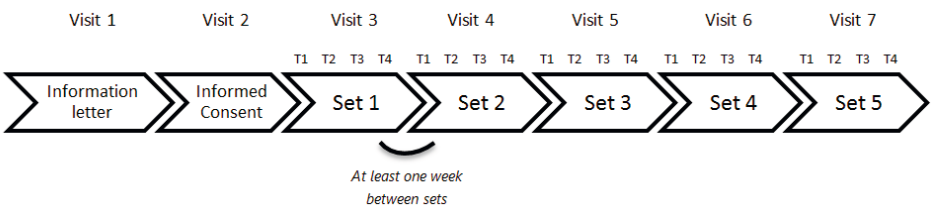
Procedure and participants

This explorative longitudinal observational study included families of children with cancer receiving chemotherapy at the outpatient clinic of Sophia Children's Hospital/ Erasmus University Medical Center in Rotterdam, the Netherlands between April 2016 and January 2017. Inclusion criteria were as follows: children with cancer between 0 and 18 years old with cancer receiving chemotherapy at the outpatient clinic at the time of study, with either patient or parent having a sufficient understanding of the Dutch language to complete the questionnaires. Approval for the study was obtained from the Internal Review Board of the Sophia Children's Hospital.

All patients meeting the inclusion criteria were invited to participate. Eligible families were identified through the electronic patient database and were approached by a research assistant. Families received both oral and written information about the study. If they agreed to participate, an informed consent form was signed.

Participating families received one set of questionnaires at the outpatient clinic. Each set of questionnaires consisted of four printed copies of the Brief Pain Inventory Short Form (BPI-SF). These four copies of the BPI-SF were completed at different moments (i.e. time points (T)) around chemotherapy appointments at the outpatient clinic, namely *T1*: while waiting for the appointment at the outpatient clinic (focused on the 24 hours before initiation of chemotherapy), *T2*: on the same day, after chemotherapy had been initiated, *T3*: one day after chemotherapy, and *T4*: two days after chemotherapy. Families were asked to complete multiple sets of questionnaires. On each visit to the outpatient clinic for chemotherapy, families were handed a new set. There was one requirement: a minimum time of one week between the start of two subsequent sets (Figure 1).

Figure 1. Data collection over the course of multiple visits to the outpatient clinic



Note. Each set consists of four questionnaires (BPI-SF) completed at different time points (*T*): *T1* in the waiting room before initiation of chemotherapy; *T2* on the same day, after chemotherapy had been initiated; *T3* one day after chemotherapy; *T4* two days after chemotherapy.

Measures

Brief Pain Inventory Short Form

The BPI-SF is a validated questionnaire focusing on three domains: 1) pain severity, 2) pain management (i.e. analgesic use and other forms of pain treatment), and 3) interference of pain with daily life [35-37]. The BPI-SF has been used to assess pain in multiple cancer populations in different countries and internal consistency of the questionnaire has been proven with coefficient alphas ranging between .75 and .91 [38-46]. The current study showed similar coefficient alphas ranging between .83 and .94, dependent on the subscale and moment of measurement (time point). The questionnaire was originally developed in English to assess pain in adults. Since then, it has also been used in children [47,48]. Stinson et al. (2015) [49] included items on pain severity, analgesic use, and interference of pain in daily life comparable to the BPI-SF items in their smartphone-based pain assessment app, and these were validated for self-report in children with cancer between the ages of 8 - 18 years old. For children aged 0 - 8, the literature suggests the usefulness of parent proxy-reporting of pain. Birnie et al. (2019) published a systematic review [21] on the measurement properties of self-report pain intensity measures in children and adolescents. For children aged 6 and up, strong recommendations were made for the NRS-11 scale, which is used in the BPI-SF. For children younger than 6 however, no self-report recommendations were made. Hagglund et al. (2020)[50] assessed whether the prevalence of pain in children (1 - 18 years) with cerebral palsy differed based on self- or proxy reporting, and found no statistically significant difference. Building of these findings, the questionnaires in this study were completed by one of the parents (children aged 0 - 4), jointly (children aged 5 - 8) or by the children themselves (aged 9 - 18).

For the purposes of this study, the Dutch version of the BPI-SF has been slightly changed and adapted to the participants (i.e. children). Instead of asking to what degree the pain has interfered with normal work (original BPI-SF), we asked how the pain interfered with school/playtime/hobby's.

The pain severity section of the BPI-SF consists of four items in which participants are asked to rate pain on a Numeric Rating Scale (NRS-11) ranging from 0 (no pain) to 10 (worst pain imaginable) for different situations: '*please rate your pain/your child's pain by circling the number that best describes the pain at its worst in the last 24 hours'* (i.e. worst pain), '*please rate your pain/your child's pain by circling the number that best describes the pain at its least in the last 24 hours'* (i.e. least pain), '*please rate your pain/your child's pain by circling the number that best describes the pain on the average in the last 24 hours'* (i.e. average pain in the last 24 hours), and '*please rate your pain/your child's pain by circling*

the number that best describes the pain right now (i.e. pain right now). As Hicks et al. (2001) [51] have demonstrated that the Faces Pain Scale Revised (FPS-R) is an appropriate tool for children's pain intensity in children aged 4 and up, we decided to use this scale rather than the NRS-11 in the age group 4 - 8. Clinically significant pain was defined as a score ≥4 on the NRS or the FPS-R (face number 3 equals a score of 4) on either 'worst pain' or 'average pain in the last 24 hours' [52,53].

The pain management section of the BPI-SF consists of one open-ended item in which treatments/medications received for the pain are assessed *(i.e. 'What treatments or medications did you receive for your pain/did your child receive for their pain?')*. Afterwards, responses were dichotomized to assess whether any pain treatments/medications were used (yes/no categories).

Finally, the interference of pain with daily life section consists of seven items in which the influence of pain on daily activities is assessed on a scale ranging from 0 (no interference) to 10 (complete interference). Daily activities include school, hobbies, and sleep. An average interference score was computed based on these items, as recommended in the BPI-SF user guide [37]. The higher scores, the higher the interference with daily life.

Demographics

Age, gender and diagnosis were retrieved from the electronic patient database.

Analytic Strategy

Pain severity

Descriptive statistics (frequencies and percentages) were used to report the severity of pain at each time point. A mean pain score was calculated per patient on all completed questionnaires for each specific time point (i.e. T1, T2, T3 or T4). This was done separately for three pain items of the BPI-SF (i.e., 'worst pain', 'least pain', and 'average pain in the last 24 hours'). We then divided the means into categories of pain severity: none (0), mild (1-3), moderate (4-6), and severe (7-10) [53].

Prevalence of clinically significant pain

Descriptive statistics (frequencies and percentages) were used to report how many patients experienced clinically significant pain at least once across all completed time points (i.e. reported a score ≥4 on either 'worst pain' or 'average pain in the last 24 hours'). We also assessed how many patients experienced clinically significant pain at least 50% of the time (i.e. percentage of clinically significant pain scores in the total amount of completed questionnaires per patient).

Analgesic use

Chi-Squared tests were used to assess how often patients/parents indicated medication use (yes/no categories) when logging a clinically significant pain score (yes/no categories). We reported in which percentage of these scores medication was used.

Mixed models

To study the association between pain severity and patient characteristics (gender [*Male, Female]*, age group [*0-3, 4-8, 9-18]*, diagnosis [*ALL, Lymphoma, Brain tumor, Others/Solid tumor]*), mixed models were estimated to account for the repeated measure design. 'Worst pain' and 'average pain in the past 24 hours' were used to assess pain severity (i.e. outcome measures). For both items, a mixed model was estimated.

We used the same methodology to study the association between pain severity and interference with daily life. Here, 'average pain in the past 24 hours' was used to assess pain severity and the average interference score was used to assess interference with daily life (i.e. outcome measure).

SPSS version 25.0 was used for all analyses.

RESULTS

One hundred and ten eligible families were invited to participate in the study, of which 89 families agreed to participate and 21 families declined (response rate: 81%). Among the 89 families who signed informed consent, 16 families dropped out. The characteristics of the remaining 73 patients are summarized in Table 1.

Cancer related treatment of patients during the study period was limited to chemotherapy (i.e. no radiotherapy or major surgeries). Moreover, no major surgeries (amputation, limb sparing, thoracotomy) had occurred in any patient within four months preceding the study.

On average, the assessment period (number of days participants were in the study) was 42.9 days (min = 4 days; max = 178 days). There was a variability in the number of completed sets (*one set consisted of four printed copies of the BPI-SF*) per patient. The majority of families completed three sets (N=35), and some completed four (N=15) or five sets (N=15). A small group completed one (N=3) or two sets (N=5). We evaluated whether the number of completed sets was associated with the level of pain severity. We divided the families into two groups: group 1 (one or two completed sets) and group

Table 1. Patient characteristics

Parameters	
Age in years	
Mean (SD), min-max	8.33 (4.87), 0-18
Gender	
Male, n (%)	37 (50.7)
Female, n (%)	36 (49.3)
Diagnose group	
ALL, n (%)	37 (50.7)
Lymphoma, n (%)	12 (16.4)
Brain tumor, n (%)	15 (20.5)
Others/solid tumor, n (%)	9 (12.4)

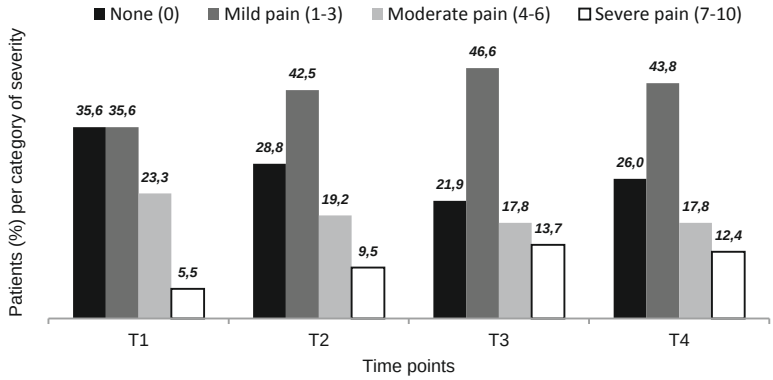
Note. N = 73
Abbreviations: SD, standard deviation; n, number of patients per subgroup.

2 (three, four of five completed sets). On the 'worst pain' item, group 1 and group 2 had a mean pain severity equal to 3.41 and 1.81 respectively. On the 'least pain' item, group 1 had a mean of 1.16, and group 2 a mean of 0.67. On the 'average pain in the last 24 hours' item, group 1 and 2 had a mean equal to 2.40, and 1.21 respectively. On the 'pain right now' item, group 1 had a mean equal to 1.78, whereas group 2 had a mean equal to 1.07. Group 1 consistently had a higher mean pain severity score than group 2. However, one-way Analysis of Variance showed no significant difference between groups. Thus, all sets were included in the analyses.

Pain severity

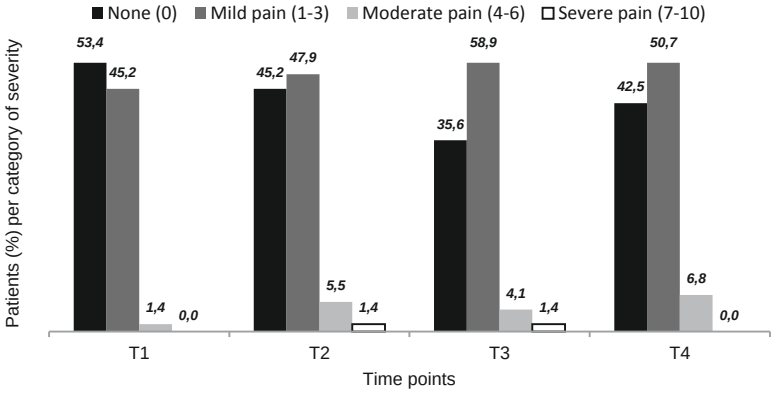
Figures 2-4 show the severity of reported pain at home. These figures illustrate the mean pain score per patient for each specific time point (T1, T2, T3 or T4) divided into categories of pain severity. Figure 2 illustrates 'worst pain', Figure 3 'least pain', and Figure 4 'average pain in the last 24 hours'.

Figure 2. Pain at its worst in the last 24 hours



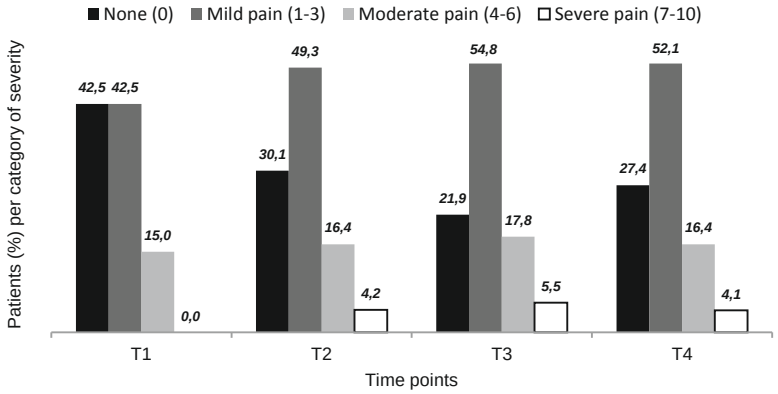
Note. Mean pain score per patient for each specific time point (T1, T2, T3 and T4), divided into categories of pain severity (N=73).

Figure 3. Pain at its least in the last 24 hours



Note. Mean pain score per patient for each specific time point (T1, T2, T3 and T4), divided into categories of pain severity (N=73).

Figure 4. Average pain in the last 24 hours



Note. Mean pain score per patient for each specific time point (T1, T2, T3 and T4), divided into categories of pain severity (N=73).

Prevalence of clinically significant pain

Fifty-seven patients (78.1%) experienced clinically significant pain (i.e. reported a score ≥4 on 'worst pain' or 'average pain in the last 24 hours') at least once. The remaining 16 patients (21.9%) did not report clinically significant pain. Twenty-one patients (30%) reported clinically significant pain at least 50% of the time.

Analgesic use

'Worst pain' scores reveal that in 38.1% of scores ≥4, no pain medication was used. For 'average pain in the last 24 hours' scores, this is 33.6%. Thus, in roughly one third of scores of scores ≥4, no medication was used (Table 2).

Table 2. Medication use during scores ≥4

BPI-SF item	Number of scores per item	Number of scores ≥4 per item	Medication use (%) in scores ≥4	Missing
'Worst pain'	1013	352	218 (61.9%)	1
'Average pain in the last 24 hours'	1013	247	164 (66.4%)	1

Note. N = 1013 (total number of completed BPI-SF). Missing = in the same questionnaire in which a score of ≥4 occurred, the question on analgesic use had been left unanswered.

Mixed models

No association between pain severity and patient characteristics (gender [*Male, Female]*, age group [*0-3, 4-8, 9-18]*, diagnosis [*ALL, Lymphoma, Brain tumor, Others/solid tumor]*) was found.

We found an association between pain severity and interference with daily life, adjusted for gender, age and diagnosis. The more severe the pain, the bigger the interference (estimated regression coefficient = 1.01 (95% CI 0.98 – 1.13).

DISCUSSION

This study is among the few that assessed pain in children with cancer in the home setting [8,12,13,18]. We found that a majority of patients (78%) experienced clinically significant pain at least once during the study period, and that a large proportion (30%) experienced clinically significant pain at least 50% of the time. We also found that in roughly one third of all clinically significant pain incidences, the pain was not being treated with medication. This is in line with previous studies. One study found that parents tended to use physical and psychological strategies rather than medication to reduce pain [8]. Another study found that despite the fact that most children experienced chronic pain, analgesic use at home was still low [12]. As our questionnaire did not assess the rationale behind medication use, no conclusions can be drawn as to why medication was used so scarcely. Yet, previous studies imply that misconceptions (i.e. 'pain is simply unavoidable') and fears regarding medication and side effects may lie at the root of this [7,22].

Furthermore, no association was found between pain severity, gender, age, and diagnosis. This is in line with previous studies in children during cancer treatment that also did not find significant differences in pain severity when controlling for patient characteristics [5,8,54]. A study with survivors of pediatric brain tumors found pain to be more prevalent in females and in younger age groups [55]. However, participants were post-treatment with ages ranging between 13 - 32, as opposed to participants in the current study (aged 0 - 18 years), who were assessed during treatment.

We did find an association between severity of pain and interference with daily life. The more severe the pain, the bigger the interference with daily life. This is in line with previous studies which show pain to be correlated with distress [30], sleeping problems [7,33] and greater burden from physical and psychological symptoms [33], affecting the quality of life of patients in both pediatric [7,30,33] and adult populations [56].

Overall, our findings have several clinical implications. The calculation of mean scores per patient (Figs. 2, 3, and 4), reveals that a majority fits the none/mild category of pain severity. Thus, based on the days that data was collected, the majority seems to have no issues to adequately cope with pain at home. However, assessment of clinically significant pain scores per patient reveals that the majority did experience clinically significant pain (78%), some more than half of the time (30%). This implies that pain management could potentially be improved for this group. Previous studies have also revealed the negative impact of pain on quality of life, distress, burden of physical and psychological symptoms, affect, and sleep [7,27,31-34]. It is therefore imperative to closely monitor pain in these children in the home setting. We believe that the use of ecological momentary assessments (i.e. real time pain assessment in the subject's natural environment [57]) over a prolonged period of time is the most reliable source to collect data on pain in the home setting. In the current study, subjects reported pain in their natural environment (i.e. at home) with a recall period of 24 hours. In the future, real time pain assessment will be taken into account to minimize recall bias and gain a more reliable dataset.

Firstly, we propose interventions aimed at educating families on recognizing and addressing pain in their children, and on the available pain management strategies, both pharmacological and non-pharmacological. Currently, families are often insufficiently prepared to effectively manage pain symptoms in the home setting [19]. As parents' knowledge about pain recognition and management is less extensive than that of health care professionals, the focus should be on educating and coaching parents during the early stages of the illness in order to effectively recognize and manage their child's pain [58]. By providing them with timely education about pain recognition and management, treatment may be improved and pain decreased [15].

Secondly, our study highlights the importance of better communication about pain in the home setting. Regular screening increases the opportunity to intervene with pain before escalation. Studies have already shown that routine use of Patient Reported Outcomes (PROs) in clinical practice increases the detection of psychosocial problems, the discussion of the reported problems during consultations and enhances the satisfaction with care [59-61]. Several research groups have acted on this and developed eHealth interventions to keep track of pain in children with cancer [62,63]. Following the results of the current study, our group has developed a mobile app (the KLIK Pain Monitor) to assess pain in the home setting, enabling healthcare professionals to respond to families of patients in need as quickly as possible. Furthermore, the app features information concerning pain recognition and treatment, taking into account the need for education and coaching. Results of the feasibility study of the KLIK Pain Monitor will soon be available, and we are currently planning an effectiveness study.

The current study has some limitations. Firstly, there is no data available on the time since diagnosis. This can be relevant information, as one previous study has shown children to experience pain most often in the first three months after diagnosis [7]. However, as all patients who received chemotherapy between the ages om 0 - 18 years old were approached for participation at random, we expect our group to be representative for the patient population, with a wide variety of time since diagnosis. Still, in the future this data should be collected and analyzed.

Secondly, we did not ask why families chose not to participate, and thus there might be a participation bias. To minimize this bias, we approached all families visiting the outpatient clinic for chemotherapy consecutively.

Thirdly, the BPI-SF Dutch version has not been formally validated for children. However, taking into account the massive use in context with different languages and wide range of cultures [38,39,41-43,45], and the validation of items (English language) comparable to the BPI-SF for children with cancer aged 8 - 18 [49], we believe that the BPI-SF can be used in our population.

Fourthly, the pain management section of the BPI-SF does not distinguish clearly between analgesic and non-analgesic interventions used to decrease pain. In this study, only one participant reported using a non-analgesic method (i.e. cannabis oil). As another study found parents to use more physical and psychological strategies (e.g. deep breathing, massage/rubbing) than pharmacological strategies to manage their child's pain [8], we suspect that due to a lack of clear instructions, participants might have underreported on non-analgesic interventions. Thus, based on our results we can not conclude definitively in which percentage of cases pain was being under treated (i.e. no interventions, analgesic or non-analgesic, used). In future studies, a clear distinction should be made between analgesic and non-analgesic interventions.

Fifthly, as cancer treatment was limited to chemotherapy in our study population, the results cannot be generalized to patients receiving other treatments such as radiation therapy or major surgery. Therefore, future studies should also look at the specific effects these treatments may have on pain prevalence and severity in children with cancer.

Finally, there was a variety in the number of completed questionnaires (i.e., time points) per patient. However, we found no difference concerning mean pain severity between patients who completed one or two sets versus patients who completed three, four or five sets.

In conclusion, a large proportion of children receiving outpatient cancer treatment experience clinically significant pain. Moreover, medication is not always used in situations of clinically significant pain. Therefore, pain might not be optimally managed, with the result that children might be experiencing pain unnecessarily. Thus, interventions aimed at pain management at home are warranted. By educating and coaching families in pain management during the early stages of the illness, and using e-health tools to monitor pain and bridge the distance between the hospital and home, we hope to improve pain management at home and decrease pain in children with cancer.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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3

Chapter 3

Reducing Pain in Children with Cancer at Home: A Feasibility Study of the KLIK Pijnmonitor App

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ABSTRACT

Purpose: This study assessed adherence to, feasibility of, and barriers and facilitators of implementation of an app developed to monitor and follow-up with pain in children with cancer at home.

Methods: Children (8–18 years) receiving cancer treatment (all diagnoses) or their parents (of children aged 0–7 years) used the KLIK Pain Monitor app for 3 weeks. Pain was assessed twice daily using an 11-point numeric rating scale (NRS-11) (ranging from 0 to 10). Healthcare professionals (HCP's) from the hospital's Pediatric Pain Service were instructed to follow-up with clinically significant pain scores (≥ 4) within 120 min (scores 4–6) or 30 min (scores 7–10). Adherence, feasibility, and implementation outcomes were assessed using questionnaires, app log data, and interviews.

Results: Twenty-seven children (*M* age = 7.3 years, 51.8% male) and six HCP's participated. Sixty-three percent (*N* = 17) of families used the app on a daily basis during three weeks, and 18.5% (*N* = 5) reported pain scores twice daily during that time (*family adherence*). Twelve out of 27 children (44.4%) reported a clinically significant pain score at least once. In 70% (14/20) of clinically significant pain scores, HCP's followed-up with families within the set timeframe (*HCP adherence*). Outcomes reveal feasibility for the majority of app functions (i.e., positive evaluation by ≥ 70% families/HCP's), and non-feasible aspects could be resolved. Identified barriers and facilitators were used to improve future implementation efforts.

Conclusion: Use of the KLIK Pain Monitor app seems feasible. Future research will determine its effectiveness in reducing pain in children with cancer at home.

Keywords: Pediatric Oncology, mHealth/eHealth, feasibility, implementation

INTRODUCTION

Pain is a common and disconcerting symptom during all stages of childhood cancer with prevalence rates varying between 40-78% [1-5]. Changes in therapeutic regimens cause children to spend less time in the hospital and more time at home [6-10], making families increasingly responsible for the management of pain [6,9]. Studies on pain management at home reveal parental misconceptions (e.g. pain is unavoidable during cancer) [1] and concerns regarding analgesic use (e.g. pain medication is addictive) [11]. A previous study in children (1-18 years old) receiving outpatient chemotherapy revealed that in one third of clinically significant pain incidents (score ≥4 on scale of 0-10 [12,13]) occurring in the home setting, no analgesic medication was used [5]. It seems that despite the availability of effective pain interventions (either pharmacologic [14,15] or non-pharmacologic [16-19] in nature) for children with cancer, parents tend to undertreat pain [3]. As pain has been related to poor quality of life, suffering and morbidity [20], combined with the notion that suffering from persistent pain during the treatment of cancer can extend into survivorship [21], it is imperative to address this problem.

Interventions for the home setting are warranted. Some efforts have already been made to address this using mHealth, such as the Pain Squad+ smartphone app [22], the tablet-based Pain Buddy program [23], and the Color me Healthy app [24], which were all developed to improve pain management in children with cancer. The KLIK Pain Monitor app, named after the existing KLIK PROM (patient reported outcome measures) portal [25], was developed to reduce pain in children aged 0-18 years old at home during cancer treatment with the aim to (1) monitor pain in the home setting, enabling healthcare professionals (HCP's) to follow-up with families and offer help more quickly, and (2) provide families with psycho-educational information about pain. A future goal is to integrate data from the app into the KLIK PROM portal, which has already been implemented at the hospital. The distinction between the KLIK Pain Monitor app and most previously developed mHealth-initiatives lies in its target user (i.e. all children with cancer versus 6/8-18 year olds). By creating an app that bridges the gap between the hospital and home setting, we aim to improve pain management and decrease pain in children with cancer.

Stakeholder (i.e. end user) involvement is a prerequisite for the development of purposeful mHealth interventions fit for effective use in practice [26]. This study therefore aims to assess user adherence to, feasibility of, and barriers/facilitators of implementation based on family and HCP experiences with the app. Outcomes will be used to improve the app and processes involved.

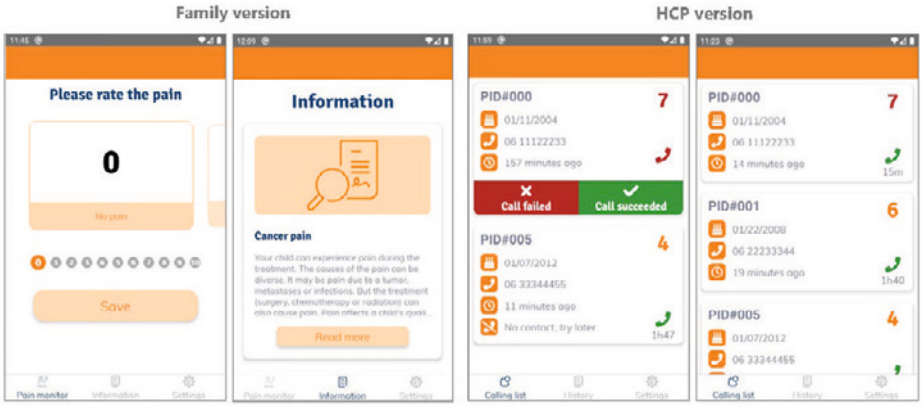
METHODS

The KLIK Pain Monitor app

The KLIK Pain Monitor app for Apple and Android was commissioned by the Princess Máxima Center for Pediatric Oncology and the software was developed according to secure and controlled processes (ISO72001/NEN75010 approved Information Security Management System) by an external web design company (Biomedia). To ensure user privacy, the app uses Two-Factor Authentication (2FA) login, and a Data Protection Impact Assessment (DPIA) was carried out and approved by the hospital's Data Protection Officer. Currently, there are three versions of the app: a parent version (for kids aged 0-7 years old), a child version (for kids aged 8-18 years old, for which language was adapted and approved by the Dutch children's cancer association) and a HCP-version. Screenshots of the translated parent/child and HCP version of the app can be found in Figure 1. The parent/child version of the app featured psycho-educational information about pain, medication and non-pharmacologic interventions suitable to the home setting. This information was composed by a medical psychologist, pediatric oncologist specialized in palliative care, and a representative of the center's Pain Service, based on the WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses [27], the Dutch Pediatrics Association Guideline on the treatment of pain [28], and a clinical practice guideline on the pharmacological and psychological management of pain in children with cancer [17].

The family version of the app allowed children (aged 8-18) or parents (children aged 0-7) to report pain intensity at the time on an 11-point numeric rating scale (NRS-11) ranging from 0 (no pain) to 10 (worst pain imaginable). When a score ranging between 0-3 was reported, families were redirected to interventions suitable to the home setting on the psycho-educational information page of the app. When a clinically significant pain score was reported (≥4), a notification was forwarded to the family (stating the time in which they would be contacted, and instructions to contact the hospital themselves in acute situations requiring immediate follow-up), as well as the calling list of the HCP version of the app. They were instructed to call the family within a set time frame (i.e. within 2 hours for pain scores 4-6 and within 30 minutes for scores 7-10). In the HCP calling list, the reported pain intensity score, remaining time for follow-up (based on set time frame), a patient identification number (PID), date of birth, and a phone number provided by the family for the purposes of this study were visible. The attending HCP would use the PID (and date of birth as cross check) to find the patient in the hospital's electronic patient dossier to read up on essential medical background information, before calling the family. During follow-up, HCP's were instructed to use a standardized questionnaire and decision tree for pain management based on the center's Pediatric Pain Service standard of care.

Figure 1. Family and HCP version of the KLIK Pain Monitor app (English translation)



Procedure and participants

This study included children aged 0-18 years old (all diagnoses) receiving chemotherapy at the Princess Máxima Center for Pediatric Oncology in Utrecht, The Netherlands. In this national center, all care for children with cancer is centralized. Participants needed to have a sufficient understanding of the Dutch language to participate. Finally, as the app was developed to decrease pain in children in the home setting, children needed to be home at the time of the study (i.e. not hospitalized). Participating HCP's consisted of members of the hospital's Pediatric Pain Service (N = 4 nurses specialized in pediatric pain treatment), and two pediatric oncologists. Approval for the study was obtained from the Internal Review Board of the hospital.

Families of eligible children received both oral and written information about the study. If a family agreed to participate, an informed consent form was signed. The coordinating researcher offered support with downloading the app, after which families received their login information via email. For children aged 0-7 years old, a parent was asked to use the app and report pain scores based on their evaluation of the child's pain (i.e. parent proxy-reporting) [29,30]. Children aged 8-18 years old were assumed capable to scoring self-reports of pain intensity using the NRS-11 scale [31]. However, not all children in this age group owned a smartphone or were capable of using the app independently. Thus, parents were allowed to help (i.e. using their phone and offering support with pain reporting). Still, the focus for this age group was self-reported pain (child's self-assessment of the pain). Families were clearly instructed that whoever used the app (child/parent) during the study, should also complete the evaluative questionnaire and interview at the end of the study. Thus, if a parent assisted in using the app, they also assisted in completing the evaluative questionnaire and were present during the interview.

Families were asked to use the KLIK Pain Monitor for three consecutive weeks and report pain at least twice daily (morning and evening), and whenever deemed necessary (ad hoc). Daily reminders were sent in the morning and evening, for which families were able to set the exact times. The minimum requirement of two pain assessments per day created the opportunity to test all functionalities of the app.

Adherence was assessed using log data from the app. All app-users (families and HCP's) completed a feasibility questionnaire after completion of the study. To identify barriers of, and facilitators to future implementation, app-users were interviewed (semi-structured) about their experiences with the app.

Measures

This study used a mixed-method design, consisting of quantitative (standardized questionnaires and log-data from the app) as well as qualitative (semi-structured interviews) methods.

Background and medical characteristics

The child's age, sex, and medical characteristics (diagnosis, time since diagnosis, stage/risk levels and treatment modalities [surgery, chemotherapy, radiation, transplant]) were obtained from the medical chart. Medical characteristics were used to complete the Intensity of Treatment Rating (ITR-3) [32]. Intensity levels were as follows: level 1 (least intensity), 2 (moderately intensive), 3 (very intensive), and 4 (most intensive). The ITR-3 was completed individually by two pediatric oncologists (WT and EM), after which scores were discussed and consensus was reached on the intensity level of treatment of each patient.

Adherence

Adherence reflected the extent to which families and HCP's were able to use the app as intended [33]. For families, this meant reporting pain scores at least twice daily for 3 weeks. If patients were admitted to the hospital during this period, families were asked to stop using the app temporarily and resume once they returned home. For HCP's, adherence related to responding to clinically significant pain scores within the defined time range: 120 minutes for scores 4-6, and 30 minutes for scores 7-10. Adherence to the app was assessed using log data obtained through the app server.

Feasibility

Feasibility was assessed using a questionnaire (separate version for families and HCP's) with statements regarding app functions. The questionnaire was adapted from Hochstenbach et al. (2016) [34] and two versions were composed: for families and for HCP's. The questionnaires focused on learnability (*N*=4 items), usability (*N*=6 items), and

Table 1. Child and HCP characteristics *n (%)*

Child characteristics (N=27)	
Mean child age (years (SD), range)	7.33 (5.00), 1-17
Child sex (male)	14 (51.9)
Diagnosis category	
Leukemia/Lymphoma	18 (66.7)
Brain/CNS tumors	4 (14.8)
Solid tumors (Non-CNS)	5 (18.5)
Time since diagnosis	
< 3 months	5 (18.5)
< 4-6 months	3 (11.1)
6 mo - 11months	7 (25.9)
1 - 2 years	12 (44.4)
Intensity of Treatment Rating (ITR)	
1 (least intensive)	0 (0.0)
2 (moderately intensive)	20 (74.1)
3 (very intensive)	4 (14.8)
4 (most intensive)	3 (11.1)
HCP characteristics (N=6)	
Mean HCP age (years (SD), range)	48.2 (9), 35-57
HCP sex (male)	1 (16.6)
Mean work exp. (years (SD), range)	9.42 (10), 0.5-27

Note. HCP Healthcare professional; SD standard deviation; *n* individuals in each category; CNS Central Nervous System; Exp experience.

desirability (*N*=4 items [families], *N*=7 items [HCP's]) of the app. Learnability reflected the time and effort required for families and HCP's to learn how to use the application as intended (e.g. *"It was easy to learn how to use the app"*). Usability reflected the extent to which families and HCP's could use the app with effectiveness, efficiency and satisfaction (e.g. *"The information provided by the app on pain (treatment) was easy to understand"*). Desirability reflected the extent to which the application was pleasant and engaging to use [34] (e.g. *"I liked that HCP's called me when I reported high pain scores"*). The questionnaire contained an additional item to assess whether users would recommend the app to others. App-users rated their agreement with these statements on a 5-point Likert-scale (1 = strongly disagree, 2 = disagree, 3 = undecided, 4 = agree, 5 = strongly agree). Higher scores indicated better learnability, usability and desirability. Internal consistency was evaluated. Cronbach's alphas for the family version were .54 (learnability scale), .40 (usability scale), and .79 (desirability scale). For the HCP version these were .84 (learnability scale), .60 (usability scale), and .80 (desirability scale).

Barriers and facilitators of implementation

Interviews were carried out with all app-users (families and HCP's). Whoever used the app (parent or child) was interviewed. A semi-structured interview guide was composed and focused on three main themes: use and general satisfaction with the app, technical functioning of the app, and supportiveness of the app regarding pain management.

Analytic Strategy

Adherence

In order to determine adherence to the *KLIK Pain Monitor app*, descriptives were used to assess the percentage of patients that reported scores twice daily in the home setting for 3 weeks (i.e. 21 days) (*family adherence*), and the percentage of incidences in which healthcare professionals called within the set time range when clinical scores were reported by families (*HCP adherence*). The threshold was reached if at least 70% of families/HCP's adhered to app use as intended. If adherence was below that cut-off point, the process involved was re-evaluated and measures were taken to make improvements.

Feasibility

We assessed responses on the feasibility questionnaire for families and HCP's separately. A statement (each relating to specific app functions) was found feasible if it was rated with a 4 (agree) or higher by at least 70% of families/HCP's. Conversely, if a statement was rated with a 2 (disagree) or lower by at least 30% of families/HCP's, the corresponding app-function was closely re-evaluated and measures were taken to make improvements.

Barriers and facilitators of implementation

Transcripts of the interviews were made and all interviews were audio recorded. Transcripts were then thoroughly read and thematic analysis was performed by the interviewer (JS) to identify recurring topics and meaningful themes within the data [35,36]. The following main themes emerged: technical functioning, user friendliness, content and functionalities, and impact on pain care. Subsequently, the transcripts were analysed by two researchers (JS and SS) independently to identify barriers and facilitators for future implementation. These were categorized into either one of the main themes. Afterwards, the researchers discussed their findings during several meetings and consensus was reached on which barriers and facilitators were mentioned. To identify relevance of specific topics, a list was composed with all identified barriers and facilitators, and how often they were mentioned. If a barrier or facilitator was mentioned by at least 30% of families/HCP's, it was marked 'relevant' by the researchers. For relevant facilitators, efforts were made to reinforce their impact on successful future implementation; for relevant barriers, measures were taken to prevent their impact on successful future implementation.

RESULTS

Forty-one families of children with cancer were invited to participate in the study. Of those, 28 families agreed to participate and signed informed consent (response rate: 68%). No families were ineligible for participation due to a lack of devices. The most common motivation for non-participation was the absence of pain at the time of intended inclusion. One family dropped out after signing informed consent but before they started using the app due to bad timing with regards to the child's treatment (feeling overwhelmed). The characteristics of the remaining 27 children are summarized in Table 1.

Of the participating children, eight children (29.7%) used the app themselves and two children (7.4%) used the app with the help of a parent. For the remaining children, the app was used by a parent (mothers: *N*=12, 44.4%; fathers: *N*=2, 7.4%, both parents: *N*=3, 11.1%).

Adherence

Families

Log data from the app shows that 63% (*N*=17) of families used the app at home on a daily basis during the three study weeks, and 37% (*N*=10) used the app for a shorter period (*minimum number of days = 7*). Of all families, 18.5% (*N*=5) used the app at home for three weeks and reported pain scores twice daily during that time (*family adherence*).

Of the total of 976 reported NRS-11 pain scores, twenty clinically significant pain scores were reported by twelve families. Thus, 44.4% (12/27) of families reported a clinically significant pain score at least once. Of the clinically significant reported pain scores, 50% (*N*=10) occurred during the nights/evenings/weekends, and 50% (*N*=10) on working days between 8 a.m. -5 p.m.

HCP's

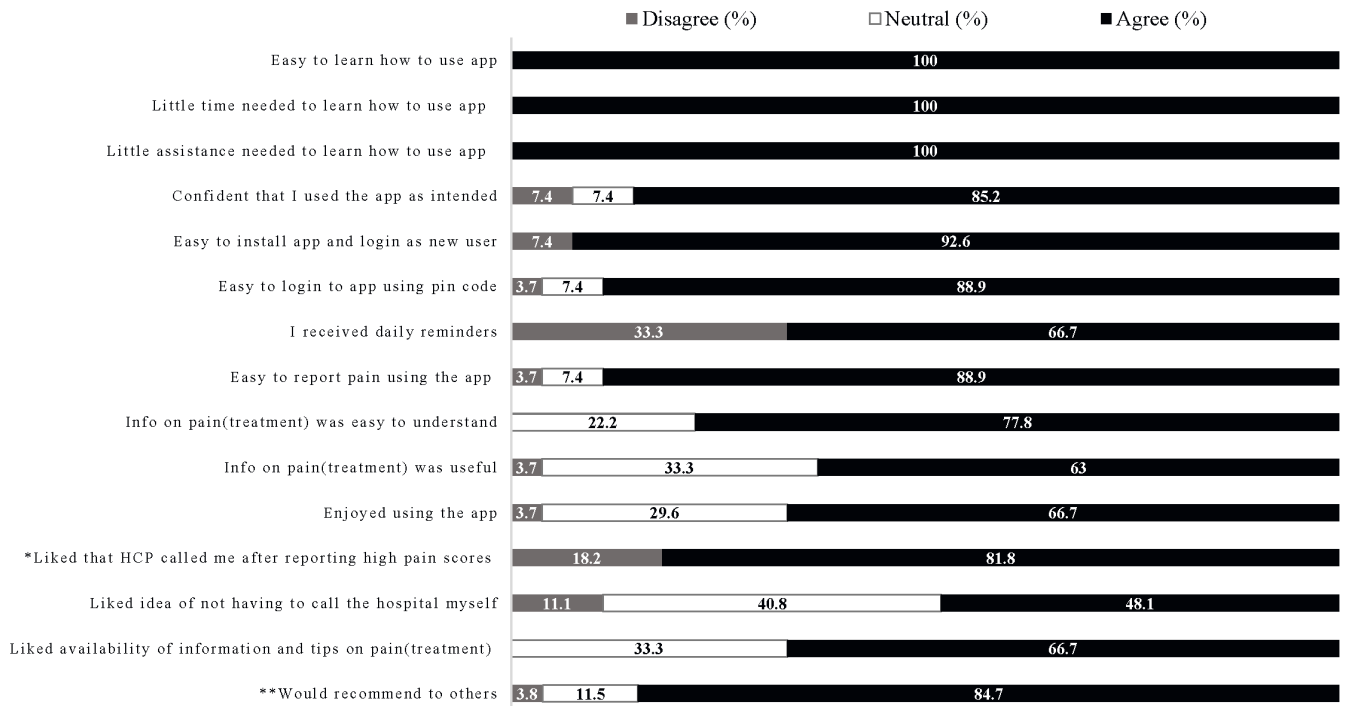
In 70% (14/20) of clinically significant incidences, HCP's called families within the set timeframe (HCP adherence).

Feasibility

Families

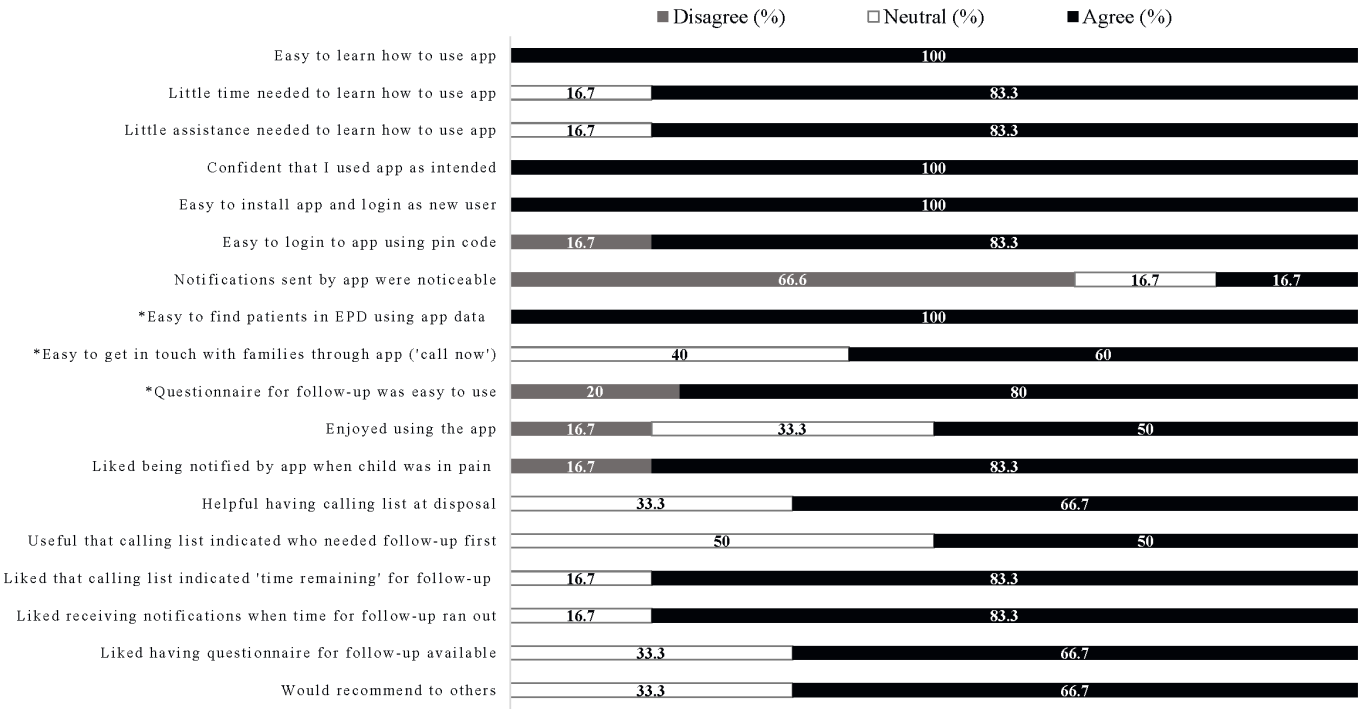
The majority of statements (9/15) were rated with a 4 (agree) or higher by at least 70% of families and were found feasible (Figure 2). One statement ("*I received daily reminders at the times I chose*") was rated with a 2 (disagree) or lower by at least 30% of families, and was found not feasible. The remaining statements did not reach the cut-off for feasibility nor non-feasibility due to neutral responses (score 3).

Figure 2. Feasibility (usability, learnability, desirability) rated by families



Note. $N = 27$ families. Responses rated on five-point Likert-scale divided into categories of disagree (scores 1, 2), neutral (score 3) and agree (scores 4, 5). $N = 11$ for item with * (only families called by HCP during study included); $N = 26$ for item with ** (one missing).

Figure 3. Feasibility (usability, learnability, desirability) rated by HCP's



Note. $N = 6$ HCP's. Responses rated on five-point Likert-scale divided into categories of disagree (scores 1, 2), neutral (score 3) and agree (scores 4, 5). $N = 5$ for items with * (only HCP's who called families during study included).

HCP's

The majority of statements (14/18) were rated with a 4 (agree) or higher by at least 70% of HCP's (Figure 3) and were found feasible. One statement (*"Pop-ups (reminders, notifications) sent by the app were noticeable")* was rated with a 2 (disagree) or lower by at least 30% of HCP's, and was found not feasible. The remaining statements did not reach the cut-off for feasibility nor non-feasibility due to neutral responses (score 3).

The feasibility questionnaire included one added item assessing whether users would recommend the app to others. Of the families, 81.5% said that they would recommend the app to other children/parents, and 66.7% of HCP's said that they would recommend the app to other HCP's.

Barriers and facilitators of implementation

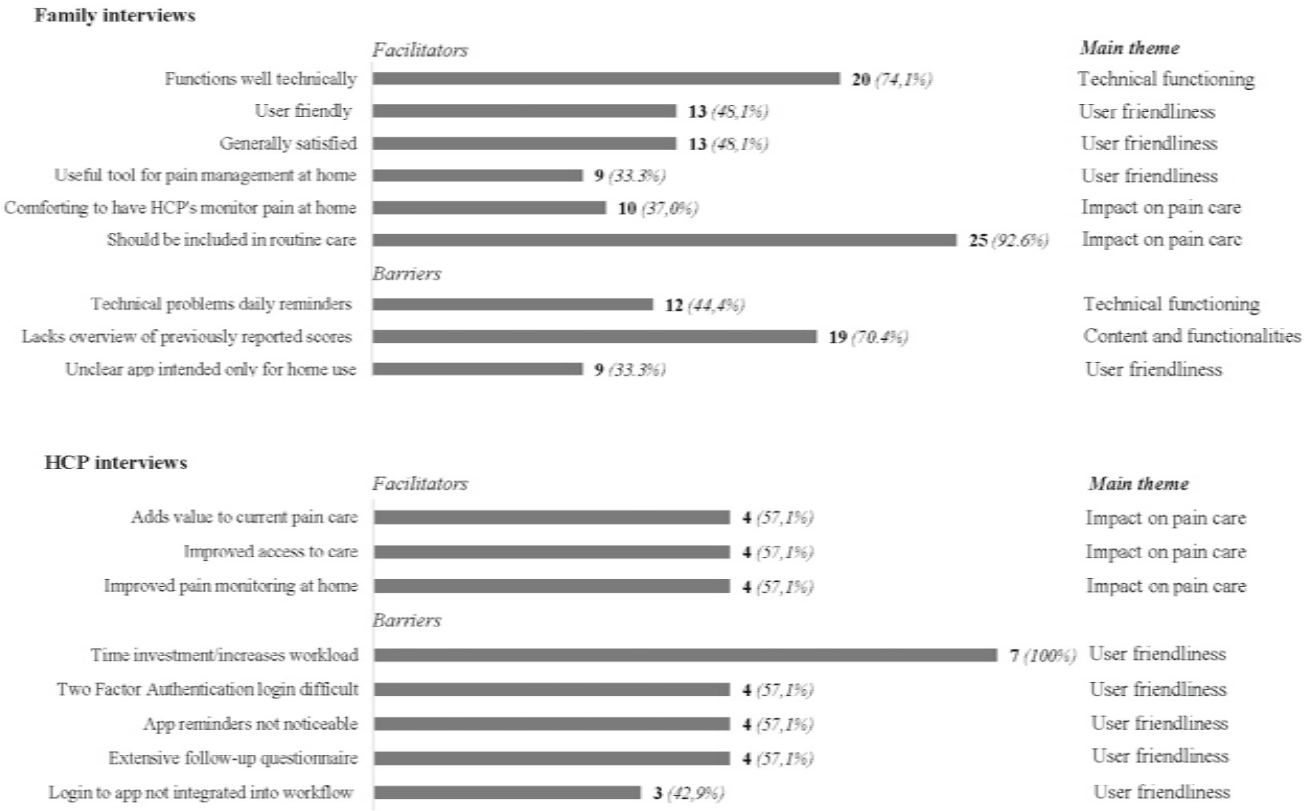
Families

Results of the interviews can be found in Figure 4. Based on the interviews with families, six relevant facilitators and three relevant barriers were identified (i.e. mentioned by at least 30% of families). The facilitators related to technical functioning (*'It worked perfectly: customer friendly, intuitively, simple. I didn't experience any problems'*), impact on pain care (*'We don't want to call the hospital all the time. With the app, you get the sense that pain is being monitored and they call us when we report high pain scores. That is very comforting. It gives you the sense that you're being taken care of*'), and user friendliness of the app (*'It was really easy and clear how to use the app')*. The identified barriers related to technical problems with daily reminders (*'I didn't always receive the daily reminders. At one point, I didn't receive them for two days'*), content and functionalities (*'The only thing that was missing, was an overview of previously reported scores. That way, you get a sense of patterns of pain'*), and user friendliness *('It wasn't immediately clear to us that the app was only meant for use at home and not during hospitalization'*).

HCP's

Based on the interviews with HCP's, three relevant facilitators and five relevant barriers have been identified (i.e. mentioned by at least 30% of HCP's). Facilitators mainly related to impact on pain care (*'I think that the app will increase our knowledge on how often kids are in pain at home. And it enables us to provide them with care much quicker'*). The identified barriers related to user friendliness of the app (*'If we start using the app there will be extra shifts, extra workload*').

Figure 4. Facilitators and barriers identified in family and HCP interviews



Note. N = 27 families and N = 7 HCP's. Facilitator/barrier included if mentioned by at least 30% of families/HCP's

DISCUSSION

This study aimed to assess adherence to, feasibility of, and barriers and facilitators of implementation of a newly developed app to reduce pain in children with cancer at home, by providing HCP's and families with a tool for real-time feedback and educational information about pain(management).

Family adherence (i.e. reporting pain scores twice daily for three weeks) was 18.5%. Log data from the app reveals that families did not receive daily reminders for pain reporting during one third of the study period. This was the only adjustment made to the app over the course of the study. A consecutive study will closely monitor the effects of the specific adaptations made to the app and processes involved as a result of this feasibility study. During the month the technical bug was active, zero family adhered to our request of reporting pain twice daily for three weeks. After the bug had been resolved, family adherence increased to 38.4%, indicating that the bug affected family adherence. However, 38.4% is still low compared to another study with a similar app and patient population (children with cancer aged 8-18 years old), in which adherence to pain assessment was 62% [37]. Another possible explanation for low family adherence in the current study, might be a relatively low prevalence of pain in the study sample. Of the total of 976 reported pain scores, twenty scores were clinically significant (2%). This is in shrill contrast with the 78% pain prevalence found in children with cancer in a previous study [5]. Thus, adherence and prevalence will be closely monitored in consecutive studies.

For HCP's, adherence (i.e. follow-up with families within the set timeframe) was 70%, reaching the pre-defined threshold for adherence. However, as feasibility questionnaires as well as interviews reveal that HCP's did not always notice the notifications sent when a clinically significant score was reported, we believe profit can still be made. Thus, the notifications have been assigned a more distinctive sound and the effect on HCP adherence will be assessed in consecutive studies.

The cut-off for feasibility (learnability, usability, desirability) was reached for the majority of app functionalities and non-feasible functions have been addressed (i.e. technical bug daily reminders, non- distinctive sound of HCP notifications). Generally, families (81.5%) and HCP's (66.7%) said they would recommend the app to others.

Barriers and facilitators mentioned in the interviews have been taken into account as well. Some families said the app should have an overview of previously reported scores. This was not one of the original aims of the app, but it has been added to the list of possible future functionalities. Also, since it was not clear to all families that the app was

only meant for use at home, a flyer with clear instructions was developed to hand out to families in consecutive studies and future implementation. Facilitators mentioned by families related to improved care for patients and user friendliness of the app.

Barriers identified in HCP interviews mainly related to time consumption and increased workload. The list of questions used by HCP's as a guideline for follow-up with patients (based on the hospital's Pediatric Pain Service standard of care) was rated 'too extensive' and has since then been reviewed by the Pediatric Pain Service. HCP's indicated that the login process was not yet integrated into their workflow and could be easily forgotten. This is something we cannot resolve immediately, and we think that this is a matter of time to get used to. With regards to the 2-FA login process ('time consuming'), as this is a privacy requirement we were unable to make alterations. Facilitators mainly related to improved care for patients, and user friendliness of the app. Thus, although HCP's are generally positive about use of the app and its potential benefits for patient care, their worries relating to workload need to be addressed. Worries related to workload might also account for the fact that one third of HCP's indicated that they would not recommend the app to other HCP's. In view of the fact that only a small number (*N*=20, 2%) of reported scores required follow-up, it is possible that external factors have also influenced HCP's attitudes towards working with the app. As the Princess Máxima Center is a relatively new hospital in which HCP's are still getting used to new workflows and division of tasks, it is possible that HCP's experience a resistance to (additional) change [38]. This will be addressed in consecutive studies.

These outcomes are in line with a previous study assessing barriers and facilitators of implementation of an online tool monitoring electronic patient-reported outcomes (KLIK) [25]. Similar to the current study, barriers mainly related to organizational context (i.e. time), whereas facilitators related to the intervention (i.e. simplicity of use) and outcome expectations (i.e. more efficient detection of problems). Addressing organizational aspects such as capacity, financial resources, and time is an essential prerequisite for the successful implementation of innovations [39], and will be taken into account in future efforts.

The current study has some limitations. Firstly, a technical bug caused the daily reminders for pain reporting not to be sent to families for a majority of the study period, affecting family adherence. However, it should be noted that the daily reminders were merely instituted to guarantee sufficient pain scores to test all functionalities of the app. As the final goal of the app is to provide families with a tool to report pain when necessary (not at set times), the daily reminders will be optional. Secondly, this study reflects the experiences of a small sample of children and parents, whose perspectives might not be representative for all children with cancer receiving treatment in the home setting. However, with regards to patient characteristics (age, gender, diagnosis, intensity of treatment), this group reflects

a realistic cross section of the patient population. Thirdly, as the app is currently only available in Dutch, non-Dutch speaking families could not participate. Translation of the app to different languages is an important goal for the future. Fourthly, only families with access to a smartphone and access to internet were able to participate in this study. However, as The Netherlands is one of the leading European countries with regards to households with internet access (98%) and smartphones (87%) [40], we do not believe this has impacted the outcomes. And fifthly, not all sub scales of the feasibility questionnaires for families and HCP's showed good internal consistency. However, as we wanted to analyze individual items to assess specific functionalities of the app, rather than calculate mean scores for sub scales, we see the questionnaire as a valid tool for this purpose.

We can conclude that patients, parents, and HCP's are generally positive about the KLIK Pain Monitor and use of the app seems feasible for implementation at the Princess Máxima Center for Pediatric Oncology. This study is an important preliminary step in the implementation process, as tailoring interventions based on evaluation with stakeholders (patients, parents, HCP's) will ultimately benefit effective use in practice [26]. As feasibility has been established, the next step is to assess effectiveness of the app in reducing pain in children at home, in a Randomized Controlled Trial (RCT). If found effective, the KLIK Pain Monitor app will be implemented and function as a bridge between the hospital and home setting, improving pain management at home and decreasing pain in children with cancer.

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Conflicts of interest

The authors declare that there is no conflict of interest to disclose.

Availability of data

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability

SPSS version 25.0 was used for all analyses.

Author's contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Julia D.H.P. Simon and Sasja A. Schepers. The first draft of the manuscript was written by Julia D.H.P. Simon and all authors

commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

This study was approved by the appropriate institutional research ethics committee (METC Utrecht [medical ethics review committee, Utrecht], registration number 20/680) and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent to participate and for publication

Informed consent was obtained from all individual participants included in the study. The authors affirm that all participants consented to the publication of their data.

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4

Chapter 4

Pain Monitoring App Leads to Less Pain in Children With Cancer at Home: Results of a Randomized Controlled Trial

Submitted.

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ABSTRACT

Purpose: Despite major advances in pediatric cancer treatment and supportive care, the majority of children still experience pain. During hospitalization, pain management support is readily available, but at home this is more difficult. Digital health can help bridge the distance between the hospital and home setting. For this purpose, a pain monitoring app was developed to improve pain management at home by providing families with educational information, and real-time HCP feedback when clinically significant pain (score ≥4 on NRS-11) was reported.

Patients and methods: We conducted a Randomized Controlled Trial (RCT) comparing an intervention group (app, n=79) to a control group (care as usual, n=79) assessing whether use of the app yielded less clinically significant pain at home. We also assessed whether use of the app affected different aspects of pain (duration, interference, pain management strategies), and parental emotional wellbeing (i.e. distress, anxiety, depression, anger). Finally, we evaluated the app with families.

Results: Analyses reveal that use of the app in the intervention group resulted in less clinically significant pain (29%) compared to the control group (52%, *p*=.004). No differences were found for pain duration, interference, and pain management strategies, but parents in the intervention group reported significantly less distress compared to the control group (β -.84, 95% CI [-1.61; -.03], *p* = .04). Family evaluations revealed that being called by a HCP following reported clinically significant pain was deemed the most relevant feature of the app.

Conclusion: Results indicate the effectiveness of the app in reducing clinically significant pain in children with cancer at home. The working mechanisms through which the app affects pain (e.g. HCP feedback, educational information, increased sense of safety) should be further elucidated.

Keywords: Pediatric Oncology, Pain, Digital Health, App, Effectiveness

INTRODUCTION

Pain is one of the most common (prevalence: 40-78%) and distressing symptoms of childhood cancer[1-5]. Cancer-related pain may be caused by illness itself, or by the treatment[1,6]. While new treatment regimens allow more flexibility to carry out parts of the treatment at home and spend less time hospitalized, this also brings along the burden of responsibility for pain management[7,8]. In a previous study, we found that clinically significant pain (score ≥4 on NRS-11 scale) often remained untreated in the outpatient pediatric cancer setting[5]. Studies on pain management at home reveal that this might be due to parental misconceptions (e.g. pain is unavoidable during cancer[1], pain medication is addictive[9]). Despite existing evidence for effective interventions[10-15], pain management at home is still sub optimal, and interventions are warranted[3].

Digital health interventions provide healthcare professionals (HCP's) with the opportunity to bridge the distance between the hospital and home setting, and hold great potential benefits (e.g., providing patients with real-time feedback at a distance, greater accessibility for patients that live remote)[16]. We therefore developed a pain monitoring app (*KLIK Pijnmonitor app*) to improve pain management of children with cancer at home. The app provides families with educational information regarding pain(management), and real-time HCP feedback following clinically significant pain scores. A previous study revealed feasibility of the app[17].

In this Randomized Controlled Trial (RCT), we compared an intervention group (*app*) to a control group (care as usual) to assess whether use of the pain monitoring app yielded a lower prevalence of clinically significant pain. Secondary, we assessed different aspects of pain (duration, interference, pain management strategies), and parental emotional wellbeing. Finally, we evaluated the app with the intervention group.

METHODS

Pain monitoring app

The *KLIK Pijnmonitor app* is suitable for Apple and Android smartphones, and uses Two-Factor Authentication (2FA) login to ensure user privacy[17]. There were two versions of the app: a family version and a HCP version. The family version featured educational information about pain, including analgesic and non-analgesic (e.g. distraction and breathing techniques) pain management strategies. The app allowed families to report on pain 24/7, and families were instructed to use the app when necessary (no set times for pain reporting). The HCP version featured a calling list, with the reported pain

intensity score, remaining time for contacting the family (based on the set time frame), a patient identification number (PID), date of birth, and a phone number provided by the family for the purposes of the study.

In the app, pain intensity was assessed using a 11-point numeric rating scale [NRS-11], ranging from 0 (no pain) to 10 (worst pain imaginable). For scores 1-3, families were redirected to the educational information page of the app. For scores ≥4 (clinically significant pain score), families were called by a HCP within the set timeframe (within 2 hours for scores 4-6 and within 30 minutes for scores 7-10). HCP's advised families based on the hospital's Pediatric Pain Service standards of care[17].

The study was approved by the ethical committee, registration number: NL75263.041.20s, and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Participants

Children in active treatment for a malignancy at the Princess Máxima Center for Pediatric Oncology were eligible for inclusion. They also had to be aged between 0-18 years, ≥ 3 months after diagnosis, ≥ 2 months of treatment remaining, understand and speak the Dutch language, and own a smartphone/tablet on which the application could be downloaded. Users of Huawei phones were excluded from the study as US legislation prohibited this company from using Google Mobile Services in Android at the time of study.

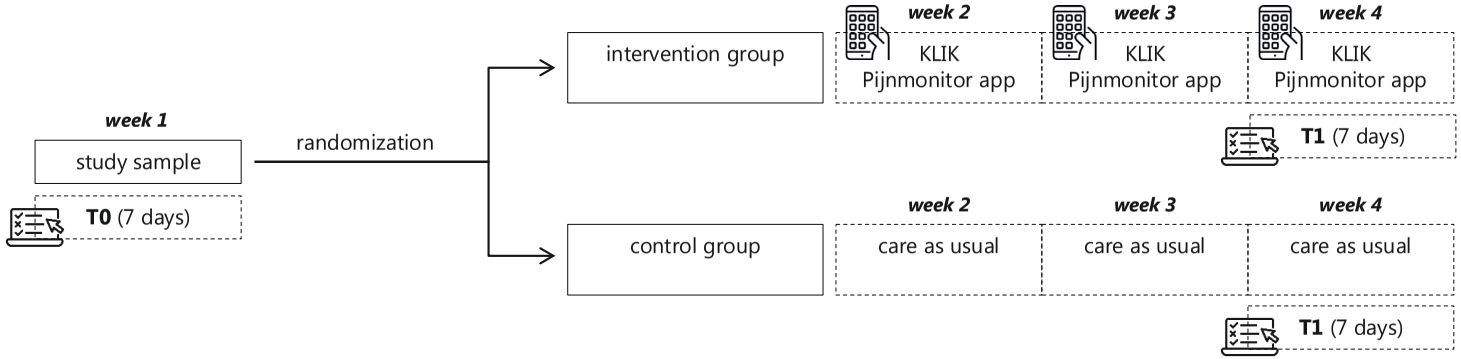
For children aged 0-7 years, a parent/guardian completed the study questionnaires and used the app, whereas children aged 8-18 were able to self-report pain severity[18].

Procedure

See Figure 1 for the study design. In week 1 (T0) and week 4 (T1) of the study, a daily pain assessment was conducted by all participants. Both pain assessments (T0, T1) consisted of seven days of pain reporting to obtain a reliable overview of pain. A minimum of four assessments per participant was required. Parental emotional well-being was assessed once on the final day of both T0 and T1 (optional and to be completed by one parent).

After T0 completion, participants were randomized into the intervention or control group with a 1:1 ratio. Randomization was stratified based on diagnosis (neuro-oncology, hemato-oncology, solid tumors), as well as distribution of age and gender. For randomization, *ALEA Clinical* was used, a digital service that supports online patient randomization.

Figure 1. Study design Randomized Controlled Trial



Note. In weeks 1 and 4, T0 and T1 were carried out and consisted of daily pain assessment using Brief Pain Inventory Short Form (BPI-SF), and the Emotion Thermometer (ET) (once on final day). After completion of T1, intervention group completed evaluation questionnaire on app. App was available to intervention group during weeks 2, 3, and 4.

After randomization, participants in the intervention group had the *KLIK Pijnmonitor app* at their disposal for three weeks, and completed an evaluation questionnaire after study completion. Participants in the control group received care as usual (they called the hospital themselves whenever they required help).

As we aimed to assess pain in the home setting, children hospitalized during the study were instructed to pause all study activities. When hospitalization occurred during the T0 or T1 pain assessment periods (i.e., one questionnaire per day for seven days), the missing days were completed upon discharge.

Sociodemographic and medical characteristics

The child's age, sex, and medical characteristics were obtained from the electronic patient record (Table 1). Treatment intensity was rated independently by two pediatric oncologists (EM and WT) using the Intensity of Treatment Rating (ITR-3)[19].

Measures

All questionnaires in this study were administered through the KLIK PROM Portal[20].

Brief Pain Inventory Short Form (BPI-SF) (assessed daily at T0 and T1)

Clinically significant pain (primary outcome), pain duration, pain management strategies, and interference with daily life were assessed using the validated Brief Pain Inventory - Short Form (BPI-SF) [21-23]. The questionnaire was originally developed for adults but has also been used in children[24,25].

Participants were asked to rate pain on a Numeric Rating Scale (NRS) ranging from 0 (no pain) to 10 (worst pain imaginable) for different situations: pain at its worst in the last 24 hours, and average pain in the last 24 hours. Clinically significant pain was defined as a score $\geq$4 on either of these two items[26,27]. Participants also completed multiple choice questions assessing pain duration and analgesic (e.g. paracetamol, morphine) and non-analgesic interventions (e.g. distraction, hypnotherapy) they used. Finally, participants rated the influence of pain on daily activities on a scale ranging from 0 (no interference) to 10 (complete interference). These include school, hobbies, and sleep. An average interference score was computed for each patient based on these items, as recommended in the BPI-SF user guide[23]. The current study showed internal consistency of the interference section, with a coefficient alpha of .95.

Emotion Thermometer (ET) (assessed on the final day of T0 and T1)

Parental emotional well-being was based on the Emotion Thermometer (ET) in which parents rated their level of distress, anxiety, depression, anger, on a range from 0 (not at all) to 10 (very much)[28].

App evaluation intervention group (assessed after T1)

Use of the app was evaluated with families in the intervention group using a questionnaire consisting of three items: 'How satisfied are you with the app?' Answer categories range from 0 (not at all) to 10 (very much). 'Should the app become part of standard care at the hospital?' and 'To what degree do you perceive the following app functionalities as relevant?: (1) pain is being monitored, (2) HCP's call when we report high pain scores, (3) the availability of tips and information about pain (management strategies). Answer categories ranged from 0 (definitely not) to 10 (absolutely).

Analytic Strategy

Sample size calculation

Group sample sizes of 79 in both the intervention and control group achieve 80% power to detect a difference between the groups of 21% with $p<0.05$ based on a two-sided Z-test with pooled variance.

Clinically significant pain and pain severity

To study the primary aim, we compared the following two outcomes between groups: 1) the proportion of days (0-100%) clinically significant pain was reported, and 2) the percentage of patients reporting clinically significant pain at least once. For outcome 1), we performed a linear regression analysis with the proportion at T1 as dependent variable, and randomization group (intervention/control) as independent variable. The model was adjusted for the proportion of days with pain at T0. To obtain standardized coefficients (β) with confidence intervals, continuous variables were standardized. For outcome 2), we performed a logistic regression analysis with having had clinically significant pain at least once at T1 as dependent variable, and randomization group as independent variable.

A mean score was calculated for the daily report of severity of 'worst pain'. Scores were then categorized into no pain (score 0-2), mild pain (scores 1-3), moderate pain (scores 4-6), and severe pain (scores7-10), and compared between control and intervention groups using Chi-square tests with Cramer's V as effect size.

Duration, interference, and pain management strategies used

Pain duration, interference and pain management strategies used for clinically significant pain incidences were compared between groups using generalized Estimating Equations (GEE) with an exchangeable correlation structure to correct for dependency between repeated assessments in children who reported clinically significant pain on more than one day. For pain interference, differences between groups were assessed using Linear Mixed Models with a random intercept.

Parental emotional well-being

To assess differences between intervention and control groups, a linear regression analysis was carried out, with the Emotion Thermometer scores at T1 as dependent variable, and randomization group as independent variable. The model was adjusted for the Emotion Thermometer score at T0. To obtain standardized coefficients (β) with confidence intervals, continuous variables were standardized.

App evaluation intervention group

Mean scores and standard deviations (SD) were reported for the evaluation questionnaire.

For all analyses, the significance level was targeted at 0.05[29-33]. After Cohen, mean differences between two groups (regression coefficients of categorical variables) of .2, .5 and .8 and correlations (regression coefficients of continuous variables, Cramer's V and *r*) of .1, .3 and .5 were considered small, medium and large[34].

RESULTS

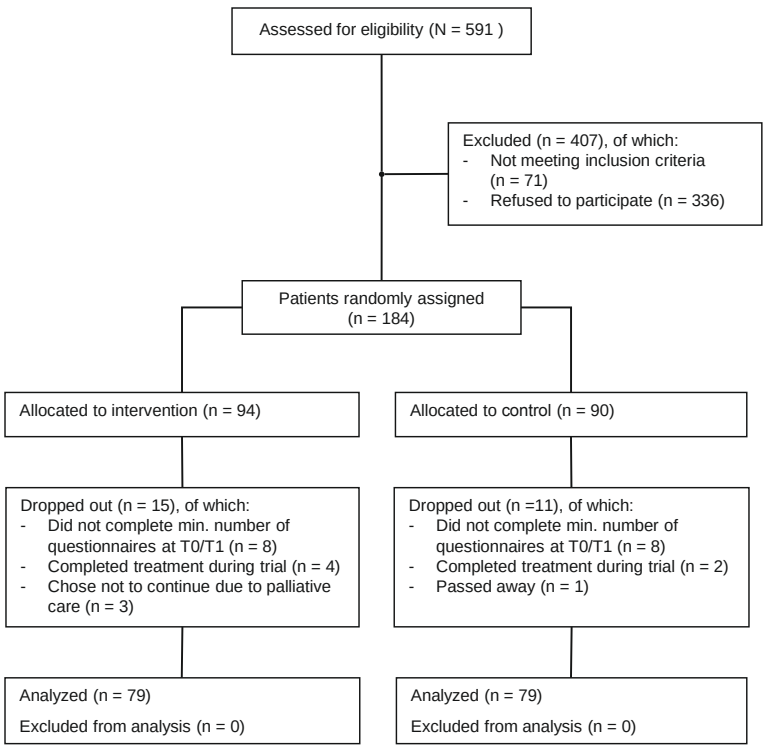
591 families of children with cancer were assessed for eligibility. Of those, 520 families met the inclusion criteria and were invited to participate, of which 184 signed informed consent (response rate: 35%). Most common reason for non-participation was that families already participated in multiple studies and did not have the time/want to participate in another one. 94 Patients were allocated to the intervention group (of which 15 dropped out), and 90 patients to the control group (of which 11 dropped out). 158 Patients successfully completed the study between February 2021 and August 2022 (18 months) (see Figure 2). Characteristics of participating patients are summarized in Table 1. Next to age, gender, and diagnosis (on which the stratification of randomization was based), the distribution of other characteristics was also similar.

Variability in the amount of completed BPI-SF at T0 and T1 ranged between 4 (min required) and 7 (max). The variability in number of completed questionnaires was accounted for in the analysis of the mean percentage of days (proportion) of clinically significant pain.

In total, 1710 scores were reported via the app. Of those scores, 1319 were 0 ('no pain'), and 50 scores ≥4 were reported in the app, of which 8 were cancelled by the family within five minutes. The remaining 42 clinically significant pain scores were reported by 23 different families; thus 29% of the intervention group reported at least one clinically significant pain score via the app. In 52% (n=22/42), families were contacted by a HCP within the set timeframe.

17 Children (21.5%) used the app themselves and 11 children (13.9%) used the app with the help of a parent. For the remaining children, the app was used by a parent: mothers (n=39, 49.4%), fathers (n=7, 8.9%), or 'other' (i.e. both parents/grandparent(s) (n=5, 6.3%).

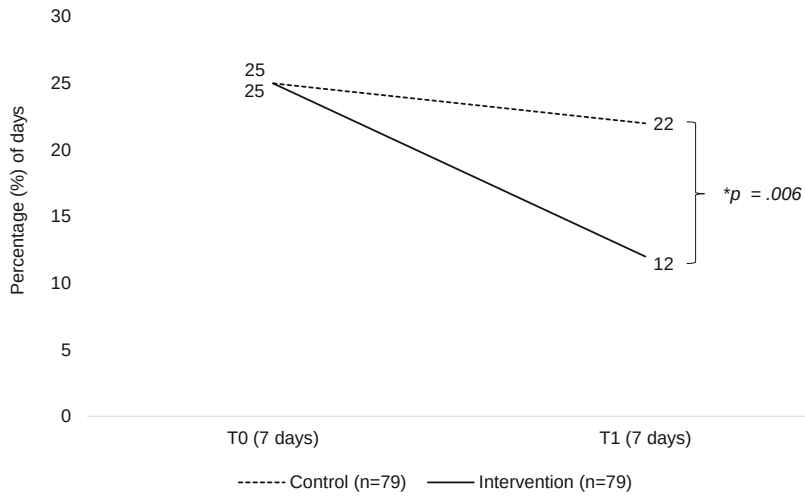
Figure 2. CONSORT flow diagram



Clinically significant pain and pain severity

Figures 3 and 4 reflect the mean proportion of days (0-100%) clinically significant pain was reported and the percentage of patients reporting clinically significant pain at least once. For the mean proportion, a significant difference between groups was found at T1 (p = .006) with a small to medium effect size (β=0.39, 95% CI [.277; .509])[34]. For the percentage of patients reporting clinically significant pain at least once, there also was a significant difference between groups at T1 (p=0.004, OR=.38, 95% CI [.198; .734]). Figure 5 reflects mean pain severity (divided into categories of none, mild, moderate, severe pain) at T1 for the BPI-SF 'worst pain' item. A significant difference was found between groups (p=.017): the intervention group reported lower pain severity (Cramer's V=.25, with a small to medium effect).

Figure 3. Clinically significant pain: mean percentage of days ('proportion')

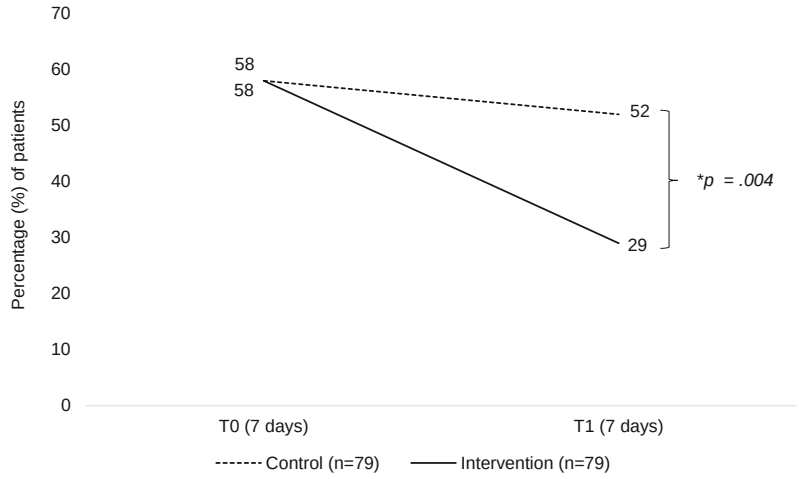


Note. Mean percentage of days on which clinically significant pain was reported at T0 and T1. Clinically significant pain was defined as score ≥4 on either 'worst pain' or 'average pain' item. Difference between groups was assessed at T1.

Duration, interference, and pain management strategies used

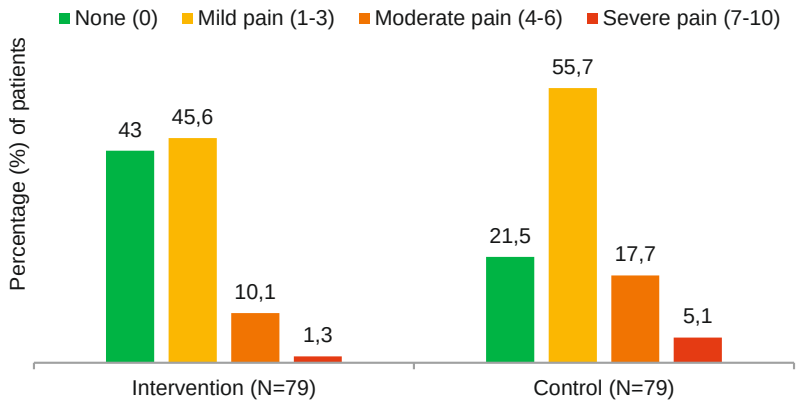
For pain duration, (non-)analgesic use and pain interference of clinically significant pain incidences reported at T1, no significant differences were found between groups (Appendix A). Appendix B and C show which specific analgesic/non-analgesic interventions were used (no significant differences between groups).

Figure 4. Clinically significant pain 'at least once'



Note. Percentage of patients reporting clinically significant pain at least once at T0 and T1. Clinically significant pain was defined as score ≥4 on either 'worst pain' or 'average pain' item. Difference between groups was assessed at T1.

Figure 5. Pain severity

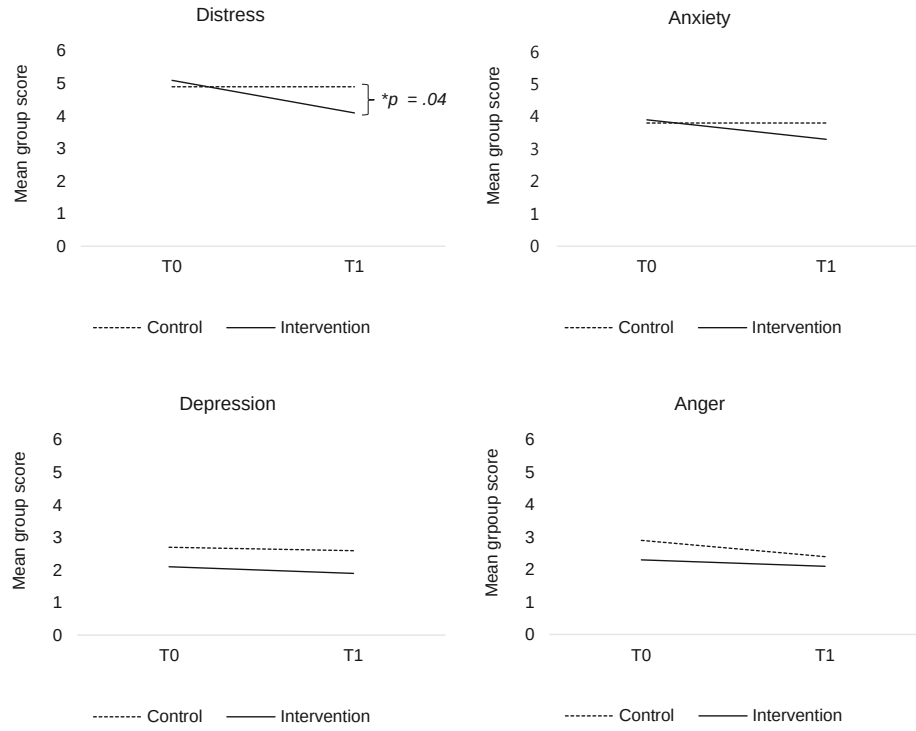


Note. Percentage of patients in each category of pain severity, based on their mean pain severity score at T1 (based on 'worst pain' item).

Parental emotional well-being

In total, 116 parents (59 control, 57 intervention) completed the Emotion Thermometer at T0, and 126 families (62 control, 64 intervention) at T1. Figure 6 reflects parental well-being at both time points. For distress, a significant difference between groups was found at T1: the intervention group reported lower distress levels compared to the control group (p = .04).

Figure 6. Parental emotional well-being



Note. Mean parental emotional well-being at T0 and T1. Differences (beta [95% CI]) between groups were assessed at T1. The model was adjusted for the mean score at T0.

App evaluation intervention group

All 79 families completed the evaluation questionnaire (Appendix D). On average, families scored 7.3 (range 0-10) for satisfaction. When asked whether the app should become standard of care, families scored 7.6. With regards to the relevance of specific app functionalities, 'HCP call when high pain is reported' had the highest relevance score with 7.7, followed by 'pain being monitored' (7.4), and 'tips and information regarding pain(treatment)' (6.6).

DISCUSSION

These results show that the use of a pain monitoring app in the home setting led to less clinically significant pain incidences, less pain severity in general, and less parental distress. Our results are in line with previously published preliminary data[35,36], but these are the first definitive results of a randomized controlled trial with a digital health intervention for pediatric cancer pain.

With regard to pain duration, interference, and pain management strategies, no significant differences were found between groups. Remarkably, even though there was a significant lower number of clinically significant pain incidences in the intervention versus control group, there was no significant difference in use of pain management strategies between the two groups. Pain is a highly subjective experience which, aside from the actual use of (analgesic or non-analgesic) strategies, can be influenced by many factors[37]. Placebo induced hypoalgesia refers to the reduction of pain experience due to cognitive modulations[38], such as the expectation of a beneficial or therapeutic outcome[37]. It might be that simply having the app at their disposal and knowing that help was within arm's reach, provided families with a sense of relative safety which has been correlated with reduced pain ratings[39]. This relative sense of safety might also explain the significant lower parental distress in the intervention group. It is known that parental responses to children's pain play a central role in the development and maintenance of pain[40]. Thus, parental distress might play an important role in the differences found in clinically significant pain in children between the groups.

Also noteworthy is the fact that the percentage of patients using no pain management strategies despite having clinically significant pain was much smaller in this study compared to an earlier study in 2017 (7,8 % intervention group, 12,4% in the control group, vs 33% in the 2017 study). This improvement in pain management might be attributable to the fact that since 2017, care for children with cancer has been centralized at the Princess Máxima Center, which likely resulted in more united communication regarding adequate pain treatment options. Another possible explanation lies in the framing of the question used to assess pain interventions. In the previous study, we asked families *"What treatments or medications did you/your child receive for the pain?",* whereas in the current study we made a clear distinction between analgesic and non-analgesic interventions, and provided families with multiple choice options. It is possible that due to framing, families only reported on analgesic use in the previous study, rather than including non-analgesic options as well, resulting in a lower reported use of interventions.

Families (patients and parents) who used the app were generally positive about the intervention itself, and whether it should become part of standard care at the hospital. However, it is likely that not all clinically significant pain was reported via the app. Throughout the study, several families reported that they did not always needed to be contacted by a HCP, as in time they felt capable to manage the pain themselves, and thus they did not report the pain in the app (study limitation). Thus, adding an option to the app enabling families to indicate whether they would like to be contacted by a HCP or not might be a relevant addition. This could also decrease HCP's time investment and workload, which is one of the main barriers identified for implementation of digital health interventions in clinical practice[41].

HCP's called families within the set timeframe in 52% of cases. HCP's relatively low adherence may have resulted in the fact that no significant difference in pain duration was found between the intervention and the control-group (study limitation). We expected that the app would result in quicker feedback and hence, lower average pain duration. Considering the fact that families rated 'HCP's call following high pain scores' and 'pain being monitored' as the most relevant functionalities of the app despite not always being called in time, raises the question whether real-time feedback from HCP's is always necessary. Alternatively, algorithm-informed feedback might be sufficient in some cases. These are important aspects to take into account for future implementation of the app in clinical practice.

This study has demonstrated the benefit of a pain monitoring app in reducing clinically significant pain in the home setting, and opens up a scale of opportunities for symptom monitoring, not only for pediatric oncology, but for a wide range of pediatric and adult illnesses as well. Future research should further investigate the working mechanisms through which the app affects pain (e.g. HCP feedback, educational information, increased sense of safety).

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Chapter 5

Digital Health Tools for Pain Monitoring in Pediatric Oncology: a Scoping Review and Qualitative Assessment of Barriers and Facilitators of Implementation

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ABSTRACT

Purpose: We aimed to systematically identify and characterize existing digital health tools for pain monitoring in children with cancer, and to assess common barriers and facilitators of implementation.

Methods: A comprehensive literature search (PubMed, Cochrane, Embase, and PsycINFO) was carried out to identify published research on mobile apps and wearable devices focusing on acute and/or chronic pain in children (0-18 y) with cancer (all diagnoses) during active treatment. Tools had to at least include a monitoring feature for one or more pain characteristic(s) (e.g. presence, severity, perceived cause interference with daily life). Project leaders of identified tools were invited for an interview on barriers and facilitators.

Results: Of 121 potential publications, 33 met inclusion criteria, describing 14 tools. Two methods of delivery were used: apps (*n*=13), and a wearable wristband (*n*=1). Most publications focused on feasibility and acceptability. Results of interviews with project leaders (100% response rate), reveal that most barriers to implementation were identified in the organizational context (47% of barriers), with financial resources and insufficient time available mentioned most often. Most factors that facilitated implementation related to end-users (56% of facilitators), with end-user cooperation and end-user satisfaction mentioned most often.

Conclusion: Existing digital tools for pain in children with cancer were mostly apps directed at pain severity monitoring and little is still known about their effectiveness. Paying attention to common barriers and facilitators, especially taking into account realistic funding expectations and involving end-users during early stages of new projects, might prevent evidence based interventions from ending up unused.

Keywords: Pain, pediatric oncology, digital health, mHealth, implementation

INTRODUCTION

Children with cancer experience a wide range of symptoms as a result of their illness and/or treatment [1]. These symptoms include pain, nausea, and fatigue [2]. As survival rates of pediatric cancer improve [3,4], the focus on supportive care (i.e., the management and prevention of adverse symptoms of the illness and its treatment) has increased [5]. Pain is one of the most common adverse symptoms during childhood cancer treatment with prevalence rates varying between 40 and 78% [2,6-11]. It is also the symptom most feared by children [12]. Cancer-related pain is often caused by the treatment (chemotherapy, surgery, or radiation), by procedures (lumbar punctures, blood draws, or bone marrow aspirations), or by the illness itself (tumor infiltration in tissues or organs) [10,13].

A previous study on pain in children receiving chemotherapy at the outpatient clinic showed that the majority (78%) experienced clinically significant pain (score ≥ 4), some even more than half of the time (30%) [9]. In one-third (33%) of the clinically significant pain incidences reported in this study, no interventions were used to reduce the pain. This might be due to parental misconceptions (e.g., pain in cancer is inevitable) [10] or concerns regarding analgesic use in children (e.g., pain medication is addictive and works best when used as little as possible) [14]. Despite existing evidence for a variety of effective pain prevention and pain management strategies [15], the management of pain in the home setting is still suboptimal [9]. Digital health provides healthcare organizations with an opportunity to bridge the distance between the hospital and home setting, and to offer support remotely. Digital health includes electronic health (eHealth) and mobile health (mHealth) [16] and has many potential benefits such as accessibility and availability to a wider public (anywhere, anytime), the ability to provide real-time strategies in everyday settings, and to finetune interventions to end users' individual needs [17].

Over the years, the amount of digital health tools for pain management has grown rapidly [18-21]. The range of features used in existing digital tools for pain seems to vary widely, from more basic tools providing information about pain(management) or using symptom diary tracking, to more advanced tools including real-time feedback from healthcare professionals (HCPs) and game elements (i.e., gamification) such as personalized avatars or in-app rewards to increase user engagement and motivation to symptom reporting [22,23]. The literature shows growing evidence for the feasibility, acceptability, and effectiveness of digital tools in adult cancer patients and survivors [19,24]. In the pediatric oncology population, the feasibility and acceptability of some digital tools for cancer-related symptoms, including pain, have been assessed as well [25], yet results on their effectiveness are scarce. One systematic review looked at the effectiveness and efficacy of digital health tools for children and young adults undergoing cancer treatment and survivors [25]. The

results of the two identified studies examining the impact on pain were mixed: one study using virtual reality did not demonstrate a significant change in self-reported pain intensity [26], and one study using an app did [27], yet this was a pilot study with preliminary results.

The rapid development and rise of these, often very costly, tools raise the urgency of implementation science [18]. It generally takes approximately 15–20 years to successfully implement a new evidence-based intervention in healthcare settings [28,29], and only 14% of interventions are successfully adopted in routine care [29], resulting in a large amount of "research waste." Implementation science uses strategies to adopt and integrate evidence-based health interventions into a clinical setting and describes "the effects of deliberate and purposive actions to implement new treatments, practices, and services" [29]. In order to prevent evidence-based interventions from ending up unused, it is imperative to assess and address determinants that are slowing down (i.e., barriers) and/or facilitating (i.e., facilitators) implementation [30]. In order to make optimal use of this knowledge and focus on areas that need more attention, barriers, and facilitators need to be identified at an early stage. A review on the availability of pain-related eHealth interventions in routine pediatric care found researchers' intrinsic motivation (i.e., personal beliefs in the importance of making their tools available to end users) to be the most endorsed facilitator, whereas system-level issues (e.g., lack of time and infrastructure to support intervention availability) were common barriers [30]. Including end users in the design phase (user-centered design) was associated with intervention availability in routine care [30]. This is consistent with other reviews on digital tools stressing the importance of involving key stakeholders throughout the entire process to attain buy-in from these parties [25,31-33]. Stakeholders are defined as all people and/or organizations that affect or are affected by the outcomes of a project [34].

In children with cancer, pain has been identified as one of the most common symptoms during all phases of cancer treatment (acute as well as follow-up). Relative to other pediatric diagnoses, their treatment is particularly intense and toxic. Moreover, with new treatment regimens allowing patients to spend more time at home, the responsibility of managing pain lies with families themselves more than ever [35,36]. Therefore, there is a need to identify digital health tools aimed at the pediatric population specifically, as these might help parents and children cope better. Two systematic reviews (2020) reported on the availability of digital health tools for cancer-related symptoms in pediatric patients [20,25], yet in both studies, only a limited number (n=2) of tools aimed at pain were identified. As the field of digital health is still rapidly evolving, we expect that an update on the subject will yield more results.

Moreover, this review will focus on mobile applications ("apps") and wearable devices specifically. The reasoning behind this is that we want to include digital health tools that are always at hand and enable real-time (i.e., prospective) pain assessments, in order to avoid

recall bias [37]. Thus, we aim to identify and characterize existing digital health tools (i.e., mobile apps and wearable devices) for pain in children with cancer. For each tool, we aim to provide an overview of research findings (e.g., feasibility, acceptability, effectiveness), and to assess common barriers and facilitators (i.e., lessons learned). By doing so, we hope to gain insight into existing digital tools for pain in pediatric oncology specifically, and secondly to compile valuable lessons for future digital health developers and researchers, not only in pediatric oncology but in a broader range of pediatric healthcare settings.

METHODS

Design and reporting

We used Arksey and O'Malley's methodological framework for scoping reviews to examine the extent, range, and nature of research activity, and to summarize and disseminate our research findings [38]. The framework consists of (step 1) identifying an aim, (step 2) identifying relevant studies (i.e., carry out a literature search), (step 3) selecting studies based on inclusion and exclusion criteria, (step 4) charting the data, and (step 5) collating, summarizing, and reporting the results and is in accordance with the extended PRISMA guideline for Scoping Reviews [39]. No review protocol exists for the current review.

Search strategy and eligibility criteria

A search strategy was created with a medical librarian and carried out on February 9th 2022. Eligible publications were identified through searches of PubMed, Cochrane, Embase, and PsycINFO. The search consisted of four main search terms (ehealth/mhealth, pain, children, and cancer), each consisting of multiple keywords. A detailed overview of the included keywords and search string used for PubMed can be found in Appendix 1. Medical Subject Headings (MeSH), or equivalent terms, were used. No date range was used to limit the search and only English publications were considered. Additional publications were manually searched by scanning reference lists of identified publications.

We included publications (a) concerning mobile apps and wearable devices aimed at pain (b) with (at least) a monitoring feature for one or more pain characteristic(s) (e.g., presence, severity, perceived cause, interference with daily life), (c) for children with a cancer diagnosis (all diagnoses) (d) aged between 0 and 18 years old (or their parents) (e) during active treatment.

The literature management program EndNote was used to remove duplicates, after which the remaining publications were transported into Rayyan [40], which was used to remove

the remaining duplicates and to enable multiple authors to screen the publications independently. Two reviewers (JDHPS and ISH) screened the publications independently for eligibility based on abstract and title. Disagreements were resolved by discussion and consensus. A final review of full-text versions of the selected publications was carried out by JDHPS and ISH to determine eligibility.

Semi-structured interviews

The second objective was to assess the determinants of implementation of the identified tools. For this purpose, the corresponding authors of these tools were approached for a semi-structured interview about their tool via a live video communication platform (Zoom). The interviews were audio-recorded after obtaining permission from the interviewees and consisted of three sections: (1) current project phase and parties involved (i.e., professionals who contributed to the project and key stakeholders), (2) use of implementation theory/ model/framework, (3) and key barriers and facilitators encountered during the project. Finally, demographic information and working experience of interviewees were collected.

The Measurement Instrument for Determinants of Innovations (MIDI) was used to guide section 3 of the interview (key barriers and facilitators encountered during the project) [41]. The MIDI categorizes barriers and facilitators into 4 main themes and 29 subthemes. The main themes are a tool (e.g., complexity, compatibility), end user (e.g., personal benefits/drawbacks, satisfaction), organization (e.g., formal ratification by management, replacement when staff leave), and socio-political context (e.g., legislation and regulations). We added an additional subtheme to socio-political context (collaborating with external stakeholders, i.e., other disciplines/hospitals/cultures) since external collaboration barriers/facilitators were not included in the MIDI. An overview of the MIDI (sub)themes was sent to the interviewees prior to the interview and was displayed during the interview when barriers and facilitators were discussed [41]. After a barrier/facilitator was mentioned by an interviewee, the interviewer and interviewee collaboratively categorized it into a corresponding MIDI theme and subtheme. The interview guide, including the overview of MIDI (sub)themes, can be found in Appendix 2.

Data charting and synthesis of results

The data from the publications identified in the literature search was charted by giving an overview of tool characteristics based on published research, namely method of delivery, features, end users, and published research (including outcome measures and main findings) in table form. Published studies were categorized by study design based on what was reported in articles. During interviews, aspects that remained unclear based

on published research were verified with the project leaders. Finally, all project leaders were requested to verify the data in the table via email (Table 1).

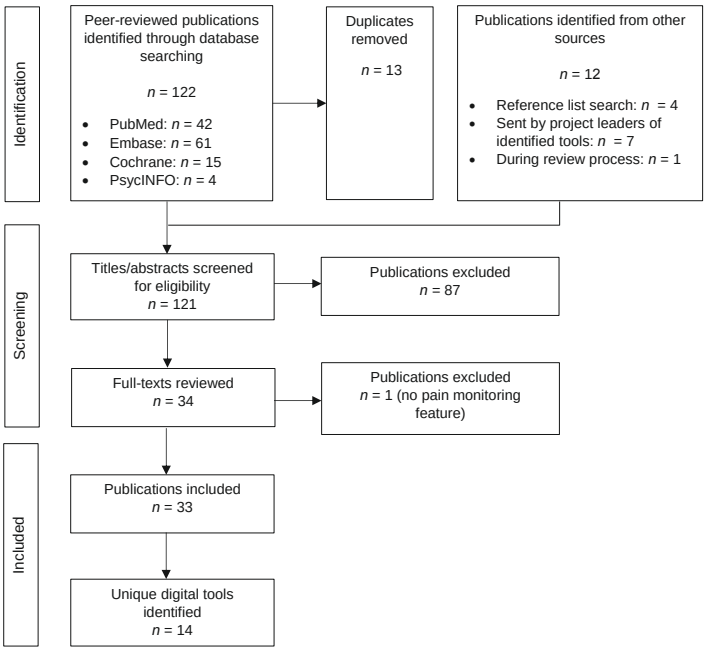
The outcomes of the interviews on barriers and facilitators were summarized based on audio recordings and represented in table form and visualized in graphs. Each interviewee was requested to verify the data in the table (Appendix 3).

RESULTS

Publication selection process

We identified 122 publications across databases, and 11 additional publications through alternative routes (Figure 1). After duplicates had been removed, 120 publications were screened based on titles and abstracts, and 33 full-text publications were reviewed. Finally, 32 publications were included. In total, 14 tools for pain in pediatric oncology were identified.

Figure 1. Flow diagram scoping review



Results scoping review

An overview of included studies and characteristics of the digital tools can be found in Table 1.

Table 1. Identified tools, characteristics, and published research (N=14 tools)

Digital tool	Tool characteristics	Publications (N=33 included in total)	
Color Me Healthy app *Main goal:* To acquire child-centric symptom reports	Method of delivery Mobile application (tablet) Feature(s) *Pain monitoring (among other symptoms):* - Severity (4-point Likert scale) *Game-element(s):* - Users can pick/customize their avatar - Sketch pad to locate pain End-user(s) Children with cancer and one of their parents Age: 6-12 Inpatients and outpatients	Feasibility/acceptability study (*N*=19 patients) (2020)[1]	
		Outcome measures: Acceptability Feasibility	**Main finding(s):** Preliminary acceptability and feasibility established
		Secondary analysis: self-reports of pain (*N*=19 patients) (2021)[2]	
		Outcome measures: Pain frequency Pain severity Pain bother Pain location	**Main finding(s):** 100% reported pain at least once. Most frequent reported severity: 'mild'. Most frequent reported bother: 'mild'. Most frequent reported location: 'head'
		Secondary analysis: parental feedback (*N*=19 parents) (2022)[3]	
		Outcome measures: Parental perceived benefits	**Main finding(s):** Parents perceived tool to 1) elicit child's voice about symptom experience, 2) provide supportive/safe environment for child to report symptoms, 3) create opportunity to facilitate communication between child, parent, and clinical team
		Descriptive study (*N*=19 patients) (2022)[4]	
		Outcome measures: Reported symptoms Reported daily experiences	**Main finding(s):** 100% reported symptoms at least once, and *n*=14 reported at least one day with symptom of moderate or higher severity

Table 1. Identified tools, characteristics, and published research (N=14 tools) (continued)

Digital tool	Tool characteristics	Publications (N=33 included in total)	
Computerized Symptom Capture Tool (C-SCAT) *Main goal:* To better understand symptom experiences of patients	Method of delivery Mobile application (tablet) Feature(s) *Pain monitoring (among other symptoms):* - Pain presence (Memorial Symptom Assessment Scale [MSAS], adult version) - Severity (4-point Likert scale) - Interference with daily life (5-point Likert scale) - Perceived causes (free text) - Alleviating and exacerbating factors (free text) *Communication:* - Discuss reported scores during planned clinic visit End-user(s) Adolescents and Young Adults (AYA's) with cancer Age: 13-29 Inpatients and outpatients	Feasibility/acceptability study (*N*=72) (2014)[5]	
		Outcome measures: Feasibility Acceptability Reported symptoms Reported symptom clusters	**Main finding(s):** Tool demonstrated feasibility and acceptability
		Mixed-methods descriptive study (*N*=72) (2015)[6]	
		Outcome measures: Experienced symptoms Symptom clusters	**Main finding(s):** Most frequently reported symptoms were nausea, feeling drowsy, lack of appetite, and lack of energy. The most common symptom cluster was nausea/eating problems/ appetite problems
		Descriptive study (*N*=72) (2017)[7]	
		Outcome measures: Self-management strategies used	**Main finding(s):** 772 reported self-management strategies were organized into three overarching themes (and 16 sub themes): "Things I take..or not", "Physical care things I do", and "Psychosocial care things I do". Medications was the most frequently reported strategy
		Descriptive study (*N*=86) (2019)[8]	
		Outcome measures: Frequency and characteristics of priority symptoms Self-management strategies used for priority symptoms	**Main finding(s):** Lack of energy, nausea, difficulty sleeping, and pain comprised 39% of all (189) priority symptoms. Self-management strategies included "Physical care strategies", "Things I take (or not)", and "Psychosocial care strategies"

Table 1. Identified tools, characteristics, and published research (N=14 tools) (continued)

Digital tool	Tool characteristics	Publications (N=33 included in total)	
Computerized Symptom Capture Tool (C-SCAT)		Effectiveness study (*N*=88) (2019)[9]	
		Outcome measures: Effect on self-efficacy for symptom management and self-regulation related to symptoms Communication with HCP's	**Main finding(s):** 85% showed improved self-efficacy for managing symptoms. Qualitative data suggest usefulness for enhancing self-regulation abilities. AYA's reported that tool facilitated communication with HCP's about symptom (management).
		Feasibility study (*N*=86) (2020)[10]	
		Outcome measures: HCP's perceptions of usefulness HCP's perceptions of ease of use	**Main finding(s):** Use of tool enhanced HCP's understanding of AYA's symptom experiences
		Descriptive study (*N*=118) (2021)[11]	
		Outcome measures: Symptom experiences of AYA's across five cancer diagnostic groups based on individual factors	**Main finding(s):** Across diagnostic groups, symptoms varied little based on individual factors. This supports a heterogeneous approach to symptom research with AYA's
Empatica E4 wristband *Main goal:* To provide more effective individualize care to patients	Method of delivery Wearable device (wristband) Feature(s) *Pain monitoring:* - Heart rate - Skin temperature - Electro dermal activity End-user(s) Children with cancer and sickle cell disease, admitted for acute/chronic pain Age: 7-20 Inpatients	Feasibility/acceptability study (*N*=12) (2021)[12]	
		Outcome measures: Ability of wireless device to obtain vital signs Children's perception of wristband	**Main finding(s):** Data collected with tool correlated with manually obtained vital signs. Children responded favourable to wearing the tool

Table 1. Identified tools, characteristics, and published research (N=14 tools) (continued)

Digital tool	Tool characteristics	Publications (N=33 included in total)	
ePROtect *Main goal:* To acquire symptom self-reports for a more patient-directed cancer control approach	Method of delivery Mobile application (phone and tablet) Feature(s) *Pain monitoring (among other symptoms):* - Severity (smiley scale three faces (<8 years), 5-point Likert scale (>8 years) - Interference with daily life (5-point Likert scale) *Communication:* - Real-time feedback from Healthcare Professionals (HCP's) End-user(s) Children with cancer being treated with chemotherapy Age: 0-18 Inpatients and outpatients	Feasibility study (*N*=12) (2021)[13] **Outcome measures:** Patient satisfaction Usefulness Completion rate and time Symptom prevalence Frequency of interventions based on patient-reported outcome measures (PROMs)	**Main finding(s):** Over 80% of patients/proxies provided feedback with a high rating for satisfaction and usefulness of tool. The median percentage of completion days was 85.3%, and mean time to complete was 47.6 seconds. Severe symptoms were reported in 14.7% of measurements, which led to interventions in 57 cases
KLIK Pain Monitor app *Main goal:* To improve pain management in the home setting	Method of delivery Mobile application (phone and tablet) Feature(s) *Pain monitoring:* - Severity (Numerical Rating Scale [NRS]-11) *Information about pain(management)* *Communication:* - Real-time feedback from HCP's End-user(s) Children with cancer Age: 0-18 Outpatients	Feasibility study (*N*=27) (2021)[14] **Outcome measures:** Family adherence HCP adherence Feasibility Barriers and facilitators of implementation	**Main finding(s):** 18.5% Of families reported pain twice daily (family adherence). In 70% of high pain scores, HCP's followed-up within set timeframe (HCP adherence). The majority of app functions are feasible. Facilitators related to user friendliness, and barriers related to technical problems with daily reminders

Table 1. Identified tools, characteristics, and published research (N=14 tools) (continued)

Digital tool	Tool characteristics	Publications (N=33 included in total)	
Kræftværket app *Main goal:* To create a virtual community that empowers patients and improves their quality of life	Method of delivery Mobile application (phone) Feature(s) *Pain monitoring (among other symptoms):* - Severity (smiley scale five faces) *Information about pain(management)* *Communication:* - Community forum End-user(s) AYA's with cancer and during follow-up Age: 16-32 Inpatients and outpatients	Prototype development study (*N*=17) (2018)[15]	
		Outcome measures: User-involved development of prototype app	**Main finding(s):** Three key features to be included in prototype were identified during co-creation workshops: 1) community forum, 2) information library, 3) symptom and side-effect tracking tool
		Usability study (*N*= 20) (2020)[16]	
		Outcome measures: Usability of prototype based on think-aloud test	**Main finding(s):** AYA cancer apps should be relevant, targeted, and unique, and include a tracking function and AYA-produced videos
		Feasibility study (*N*=17) (2021)[17]	
		Outcome measures: Patient reported relevance Patient reported usefulness	**Main finding(s):** Tool was perceived most relevant at disease onset. During treatment, diagnosis-specific information and communities were requested
Mobile Oncology Symptom Tracker (mOST) *Main goal:* To record symptoms in real-time	Method of delivery Mobile application (phone) Feature(s) *Pain monitoring (among other symptoms):* - Severity (Faces Pain Scale Revised [FPS-R], Color Analog Scale [CAS]) End-user(s) AYA's with cancer Age: 13-21 Inpatients and outpatients	Usability/acceptability study (*N*=10) (2012)[18]	
		Outcome measures: Patient adherence Usefulness and acceptability	**Main finding(s):** Adherence to daily symptom reports exceeded 90%. Patients experienced few technical difficulties and reported benefits from daily symptom reports

Table 1. Identified tools, characteristics, and published research (N=14 tools) (continued)

Digital tool	Tool characteristics	Publications (N=33 included in total)	
OPBG (Ospedale Pediatrico Bambino Gesu Tool) *Main goal:* To track pain in the home setting	Method of delivery Mobile application (phone and tablet) Feature(s) *Pain monitoring:* - Severity (Combination between the NRS-11, FPS-R, CAS, VAS): sliding from left to right the face gradually changes expression until it becomes a crying face at the score of 10 End-user(s) Children with cancer or their parents Age: 4-21 Outpatients	Adherence to use and pain prevalence study (*N*=124) (2021)[19] **Outcome measures:** Pain levels App use Patient satisfaction	**Main finding(s):** 75.8% reported pain (>1) at least once during one month, of these, 56.4% reported mild pain, 35.1% moderate pain and 8.5% severe pain. 124 participants used the app for at least a month. The median number of times participants used the app during that time was 6. Most participants were satisfied with app

Table 1. Identified tools, characteristics, and published research (N=14 tools) (continued)

Digital tool	Tool characteristics	Publications (N=33 included in total)	
Pain Buddy *Main goal:* To enhance pain management and foster improved quality of life during cancer treatment	Method of delivery Mobile application (phone and tablet) Feature(s) *Pain monitoring:* - Pain presence (MSAS, yes/no) - Severity (VAS, 0-100) - Frequency (4-point Likert scale) - Bothersomeness (5-point Likert scale) - Pain location (Adolescent Pediatric Pain Tool [APPT], VAS, 0-100) - Intensity (word graphic rating scale) - Quality (list of pain descriptors) *Information about pain(management)* *Communication:* - Real-time feedback from HCP's through web-interface *Gamification:* - Users can pick their three-dimensional avatar - Adherence-based reward system End-user(s) Children with cancer Age: 8-18 Outpatients	Pilot development study (*N*=12) (2016)[20] **Outcome measures:** Overview of development phase Feasibility Preliminary outcome data	**Main finding(s):** Key aspects: daily pain and symptom diaries, remote monitoring, cognitive and behavioral skills training, interactive avatars, and an incentive system to motivate engagement. Children were highly satisfied. Pain and appetite disturbances were most frequently endorsed
		Preliminary effectiveness study (*N*=48) (2020)[21] **Outcome measures:** Reduction in average daily pain over study period (intervention vs control)	**Main finding(s):** Both groups experienced significant reductions, with no evident group differences. Intervention group did report significantly fewer instances of moderate to severe pain compared with control group

Table 1. Identified tools, characteristics, and published research (N=14 tools) (continued)

Digital tool	Tool characteristics	Publications (N=33 included in total)	
Pain Squad app *Main goal:* To assess pain in real-time during cancer treatment	Method of delivery Mobile application (phone and tablet) Feature(s) *Pain monitoring:* - Severity (VAS, 0-10) - Interference with daily life (VAS, 0-10) - Pain management control (VAS, 0-10) *Gamification:* - Users play the role of law-enforcement officers - Adherence-based reward system End-user(s) Children with cancer Age: 8-18 Inpatients and outpatients	Development, usability and feasibility study (*N*=47) (2013)[22]	
		Outcome measures: Usability Feasibility Compliance Satisfaction	**Main finding(s):** App was overall appealing to patients. They endorsed game-based nature of app and its virtual reward system. Compliance was high (mean 81%) and patients found app to be likeable, easy to use, and not bothersome to complete
		Psychometric validation study (*N*=106) (2015)[23]	
		Outcome measures: Construct validity Reliability Feasibility	**Main finding(s):** Results provide evidence of construct validity, reliability, and feasibility of tool
		Pilot implementation study (*N*=6) (2018)[24]	
		Outcome measures: Implementation outcomes (acceptability, appropriateness, cost, feasibility, fidelity, penetration, and sustainability)	**Main finding(s):** Tool was well received by small number of children, yet user uptake, engagement, and adherence were significant barriers to implementation in a natural setting

Table 1. Identified tools, characteristics, and published research (N=14 tools) (continued)

Digital tool	Tool characteristics	Publications (N=33 included in total)	
Pain Squad + app *Main goal:* To assess pain in real-time and provide patients with real-time pain management support	Method of delivery Mobile application (phone and tablet) Feature(s) *Pain monitoring:* - Severity (VAS, 0-10) - Interference with daily life (VAS, 0-10) - Pain management control (VAS, 0-10) *Information about pain(management)* *Communication:* - Real-time, algorithm informed feedback *Gamification:* - Users play the role of superheroes - Adherence-based reward system End-user(s) Children with cancer Age: 12-18 Inpatients and outpatients	Development study (*N* = 9 HCP, 10 patients) (2014)[25]	
		Outcome measures: Pain management advice algorithm System design requirements	**Main finding(s):** A systematic literature review and 2-day consensus conference established which clinically important pain inputs would require action (pain management advice) from tool, the appropriate advice the tool should provide and the functional requirements of the tool
		Iterative usability testing study (*N*=16) (2017)[26]	
		Outcome measures: Ease of use Ease of understanding Efficiency Acceptability	**Main finding(s):** Patients required an average of 4.3 minutes to complete pain assessment. Overall, the tool was acceptable. Problematic issues related to software malfunction, interface design flaws and confusing text
		Implementation and preliminary effectiveness study (*N*=40) (2017)[27]	
		Outcome measures: Intervention fidelity (implementation outcome) Outcome measure completion Adherence Acceptability Preliminary effectiveness	**Main finding(s):** Intervention fidelity was impacted by technical difficulties, and a prolonged time for HCP contact in event of sustained pain. Outcome measure completion rates were high and tool was acceptable. Trends in improvements in pain intensity, pain interference, and Health Related Quality of Life (HRQL) were significant
		Nested qualitative study within multicenter pilot feasibility study (*N*=20) (2018)[28]	
		Outcome measures: Acceptability Perceived helpfulness Suggestions for improvement Satisfaction with pilot study protocol	**Main finding(s):** Overall, the tool was acceptable to patients. Suggestions for tool and study improvements were identified and will be incorporated into future RCT design
		Protocol for RCT (*N*=74 per arm; *arm 1= control waitlist, 2= app with nurse, 3 = app no nurse)* (2020)[29]	
		Outcome measures: Effect on pain intensity Effect on pain interference, HRQOL, pain self-efficacy and cost Satisfaction with treatment regarding tool	**Main finding(s):** Not applicable: research protocol

Table 1. Identified tools, characteristics, and published research (N=14 tools) (continued)

Digital tool	Tool characteristics	Publications (N=33 included in total)	
PicPecc (Pictorial support in person-centred care for children) *Main goal:* To acquire self-reports of symptoms experienced by ALL patients	Method of delivery Mobile application (phone and tablet) Feature(s) *Pain monitoring (among other symptoms):* - Severity (Faces Thermometer Scale [FTS]) *Information about pain(management)* *Communication:* - Real-time feedback HCP's and visual feedback via app (pictorial support) End-user(s) Children with ALL, undergoing high-dose methotrexate treatments Age: 5-17 Inpatients and outpatients	Protocol for crossover design study (2021)[30] **Outcome measures:** Distress levels (intervention vs control group) Level of person-centered care Symptom assessment frequency	**Main finding(s):** Not applicable: research protocol
		Development study (*N*=7 children, 8 parents, 19 HCP [phase 1], *N* = 10 children, 9 parents, 21 HCP [phase 2] (2022)[31] **Outcome measures:** Symptom-reporting needs Evaluation of patients' tool interaction Parents' views and HCP's expectations and requirements for tool	**Main finding(s):** Various symptom-reporting needs were identified. The findings of this study indicate that the tool is a potential solution for providing communicative support to patients. Interview data also highlighted symptoms that are at risk of being overlooked if not included in the tool
Telemonitoring System for Paediatric Oncology *Main goal:* To increase the quality of life of patients during cancer treatment by monitoring symptoms in the home setting	Method of delivery Mobile application (phone) Features(s) *Pain monitoring (among other symptoms):* - Severity (6-point Likert scale) *Communication:* - Web-interface for HCP's to evaluate data End-user(s) Children with cancer Age: 0-18 Outpatients	Development/feasibility study (2015)[32] **Outcome measures:** Acceptability Telemonitoring workflow	**Main finding(s):** Nine vital signs and toxicities have been identified as most significant to monitor in pediatric cancer patients. Experiences from the user centred design process indicate a high level of usability and acceptability

Table 1. Identified tools, characteristics, and published research (N=14 tools) (continued)

Digital tool	Tool characteristics	Publications (N=33 included in total)	
RESPONSE *Main goal:* To monitor symptoms in children undergoing systemic cancer treatment	Method of delivery Mobile application (phone and tablet) Features(s) *Pain monitoring (among other symptoms)* - Bothersomeness (5-point Likert scale) *Information about pain(management)* *Communication:* - Web-interface for HCP's to evaluate data - Algorithm-informed alerts advising families to discuss with HCP at next hospital visit (moderate concern), or phone hospital (immediate concern) End-user(s) Parents of children with blood cancer and solid tumors (or adolescents themselves) Age: 2-18 Inpatients and outpatients	Protocol for controlled hybrid effectiveness implementation trial (2021)[33]	
		Outcome measures: Effectiveness on total symptom burden of children Effects on health-related quality-of-life Feasibility Acceptability Satisfaction Sustainability	**Main finding(s):** Not applicable: research protocol

Method of delivery

Two methods of delivery were used: apps (n=13, 92.9%), and a wearable wristband (n=1, 7.1%).

Features

Tool features were grouped into four main themes: (1) monitoring feature for one or more pain characteristic(s) (e.g., presence, severity, perceived cause, interference with daily life, bothersomeness), (2) information about pain(management), (3) communication, and (4) game elements. In 13/14 tools, the pain characteristic "severity" was monitored (n=14, 92.9%), of which 12 tools used self and/or parent reports with several rating scales (details in Table 1), and one wearable tool used heart rate, skin temperature, and electrodermal activity to monitor pain [42]. One tool just assessed the pain characteristic "bothersomeness" (mouth sores, headache, hurt of pain other than headache) [43]. Information about pain(management) was provided in six tools (42.9%), and nine tools (64.3%) included a communication feature, of which n=3 provided real-time feedback from healthcare professionals, n=2 provided real- time algorithm-informed feedback, n=3 included a web-interface for healthcare professionals to evaluate and give feedback on data, n=1 included a community forum for peers, and n=1 provided pain reports for healthcare professionals during clinic appointments. One tool had two communication features and thus was counted twice [43]. Gamification elements were used in four tools (24.6%) and included users picking their own avatar (n=2), playing the role of a superhero or law-enforcer (n=2), having a sketch pad available (n=1), and reward systems for adherence to pain diary completion (n=2).

End users

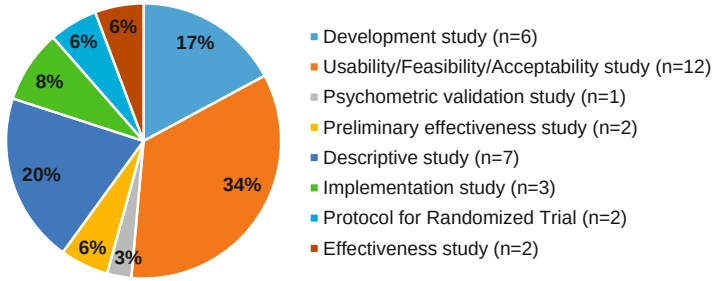
All tools were developed for children during cancer treatment, yet one was also available during follow-up after treatment, and one was available for children with sickle cell disease as well. Age groups of children varied, with one tool (7.1%) solely focusing on young children (ages 0–12), three tools (21.4%) on adolescents and young adults (AYAs) (ages 13–32), and ten tools (71.4%) on both young children and AYAs. With regard to setting, one tool (7.1%) could be used solely in the hospital (i.e., inpatients), five tools were meant for an outpatient setting (i.e., not during hospitalization) (35.7%), and eight tools were available for in- as well as outpatients (57.1%).

Included studies

The research was published between 2012 and 2022. An overview can be found in Fig. 2. The majority of studies focused on the development and usability/feasibility/acceptability testing. For two tools (Pain Squad+ and Pain Buddy [44,45]), preliminary data on their effectiveness in reducing pain has been published, yet no definitive results are available. For another tool (C-SCAT [46]), an effectiveness study was published. However,

this study focused on the tool's effectiveness in increasing AYA self-efficacy for symptom management, rather than pain reduction.

Figure 2. Study designs of published research (N=35*)



Note. n = number of studies per category. *33 publications were included in this review, yet two publications focused on both implementation and (preliminary) effectiveness and were counted twice in this figure.

Results semi-structured interviews

Thirteen project leaders were invited for a semi-structured interview on barriers and facilitators to (future) implementation of their tools (100% response rate). Table 2 describes the interviewee characteristics. For the RESPONSE app [43], no interview was conducted as this tool was added during the review process.

Table 2. Interviewee characteristics *(N*=13)	*n (%)*
Gender (female)	10 (76.9)
Age (mean, range)	51.2 (39-58)
Place of residence	
EU	6 (46.2)
USA	5 (38.5)
Canada	2 (15.4)
Background (schooling)	
Nurse	7 (53.8)
Physician	3 (23.1)
Psychologist	2 (15.4)
Other	1 (7.7)
Years working in care (mean, range)	20.8 (min: 0, max: 37)
Years working in research (mean, range)	18.7 (min: 5, max 32)
Years working with digital health (mean, range)	12.3 (min: 2, max: 22)

Note. n = number of individuals per category.

A comprehensive overview of outcomes of the semi-structured interviews (including quotes illustrating the context in which barriers and facilitators were encountered) can be found in Appendix 3.

With regard to professional input, 60.3% of the professionals were healthcare professionals (e.g., physicians, nurses, physiotherapists, psychologists, pain experts, child life specialists), 27.9% were digital technique specialists (e.g., computer scientists, engineers, software developers, applied IT specialists), and 11.8% were other professionals (e.g., lawyers, patient organization members, communication experts, measurements experts, health economists).

With regard to key stakeholders, 41.4% of all mentioned stakeholders were families (e.g., patients, parents, and extended families), 37.9% were healthcare professionals (includes the hospital as an organization), 10.3% were cancer aid organizations, 6.9% were research funders, and 3.4% were IT companies.

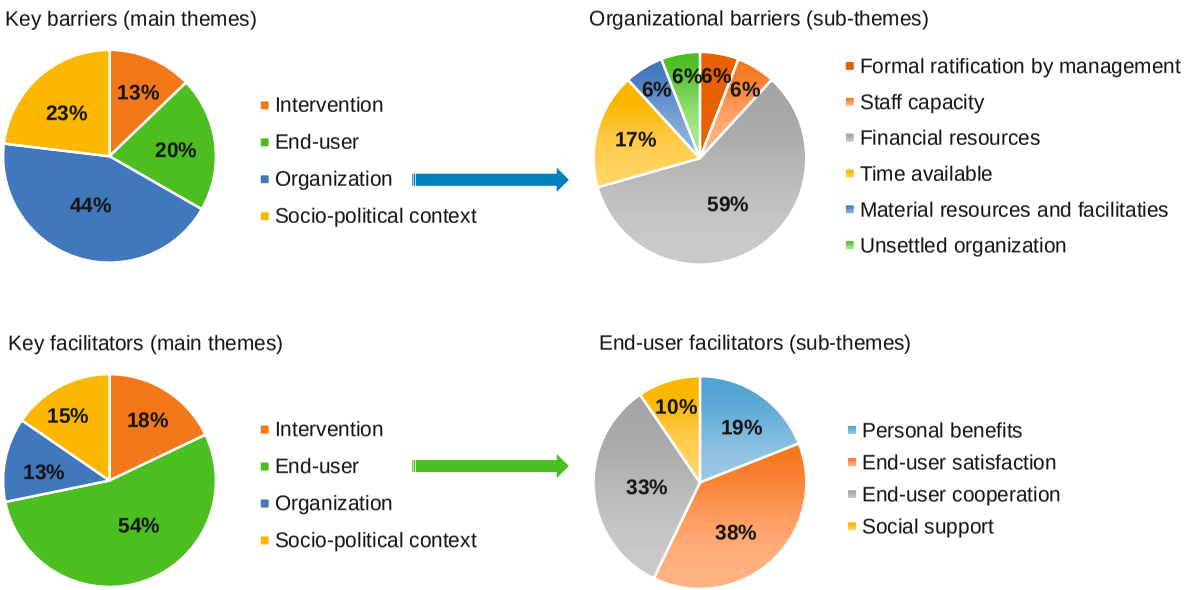
Five interviewees (38.5%) reported having used or using a theoretical model for implementation, namely the Consolidated Framework for Implementation Research (CFIR) (n=2), the Knowledge-to-Action (KTA) Framework (n=1), the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) Framework (n=1), and the MRC (Medical Research Council) Framework for Development and Evaluation of Complex Tools (n=1).

The key barriers and facilitators can be found in Fig. 3. Most barriers related to the organization (i.e., financial resources: “During effectiveness testing, a nurse is paid from research funding. But how will we fund this down the road, when we want to implement/scale up?”) and the socio-political context (i.e., legislation/regulations: “When you work with different hospitals and institutions they may have different juridical regulations”). Most facilitators related to the end users (i.e., client/patient cooperation: “Children are more likely to accept new technology and to incorporate new technology into their house”) and the tool itself (i.e., complexity: “It was really easy and clear how to use the app”).

DISCUSSION

This review identified fourteen unique digital tools for pain monitoring, with the ultimate goal of improving pain management and reducing pain in children and/or AYAs with cancer. Identified tools in this study were mostly mobile apps that can be used in both in- and outpatient settings, by young children as well as AYAs, and were directed at pain severity monitoring using self- and/or proxy reporting rating scales. The feasibility and/

Figure 3. Identified key barriers and facilitators categorized in MIDI* themes and sub-themes



Note. *MIDI: Measurement Instrument for Determinants of Innovations

or acceptability of all but one tool (RESPONSE [43]) has been established, yet very little is still known about their effectiveness in accurately monitoring and/or reducing pain [47]. Moreover, little is also known about their (future) chances of successful implementation in care. During the interviews, project leaders mostly mentioned organizational barriers and end-user facilitators in the process of implementation.

In addition to pain severity monitoring, another commonly used feature was "communication." Seven tools included a communication feature with healthcare professionals (50% of all tools), and one tool included a community forum for communication with peers (7.1%). Communication options with healthcare professionals ranged from real-time feedback on reported pain scores, to feedback on pain scores during clinic visits (i.e., delayed feedback). A previous review on the benefits of mobile apps for cancer pain management in (mostly) adults revealed evidence for improved quality of life and decreased pain catastrophizing for digital tools with a real-time communication functionality between patients and healthcare professionals [19]. This shows promise for the future effectiveness of tools which included real-time feedback from healthcare professionals.

Most included publications focused on the development and user experiences. The biggest knowledge gap lies in these tools' effectiveness in successfully monitoring and/or reducing pain. One effectiveness study found a significant effect on self-efficacy for symptom management in AYAs, yet no results on symptom (i.e., pain) reduction were included [46]. Two preliminary effectiveness studies on pain reduction were published and found a significant effect on pain severity (decreased) [27,48], pain interference (decreased), and Health-Related Quality of Life (HRQOL) (increased) [27]. The tools described in these two studies (Pain Buddy and Pain Squad+) both included real-time feedback (from healthcare professionals or algorithm informed based on healthcare professionals' input) and game elements. Game elements and in-app incentives have previously been found to increase medication adherence [49] and thus might also be useful to improve symptom reporting adherence of digital tools. However, since both studies were preliminary with small sample sizes (N=40/48), no definitive recommendations can be made.

A strength of this scoping review lies in the added value of the semi-structured interviews aimed at identifying key barriers and facilitators. This mixed-method design informs readers on the state of the field based on published literature but also incorporates project leaders' experiences that may form valuable lessons for future researchers. The high response rate (100%) for interview participation in this study reflects the project leaders' willingness to share experiences with colleagues to contribute to implementation awareness. Digital tools have the potential of being more cost-effective

than regular face-to-face care [50], that is, when success- fully implemented in care. A key pillar of implementation science lies in the involvement of stakeholders, and user-centered designs have previously been associated with successful implementation in care [30]. In this review, only five out of 12 interviewees reported using a theoretical model for implementation. However, all interviewees did report getting input from a diverse group of professionals (i.e., healthcare professionals, specialists in digital technique, lawyers, patient organizations) and stakeholders (i.e., families, healthcare professionals, cancer aid organizations, research funders, IT companies) throughout their projects. Healthcare professionals were by far the most involved professionals, and they were also the second most commonly mentioned key stakeholders, after families. Thus, despite the sparse use of formal theoretical models for implementation, end users' input was highly valued as they were involved in the majority of projects. Based on the literature, this increases the chance of successful future implementation of these tools in care. The close involvement of project leaders globally in this review might lead to more international collaborations, larger sample sizes, and higher cost-effectiveness in the future. At the same time, international collaborations might cause barriers in the socio-political spectrum of the MIDI [41], such as legislation and regulations and collaborating with external stakeholders (i.e., other disciplines/hospitals/cultures).

The importance of including end users is also reflected in the results of the interviews with project leaders on barriers and facilitators. The most common facilitators were often connected to end users (56% of all mentioned facilitators), with end-user cooperation and end-user satisfaction mentioned most often. This is in line with several reviews stressing the importance of user-centered designs to accomplish successful use in routine care [25,31-33]. In contrast to previous findings in which researchers' intrinsic motivation (personal beliefs in the importance of making their tools available to end users) was mentioned as an important facilitator [30], this was not found in the current study. The most common barriers were identified in the organizational context (47% of all mentioned barriers), with financial resources and time available being the most common. This is in line with a previous review on digital health tools for pediatric pain (not cancer-specific) in which lack of time and infrastructure to support tool availability were identified as barriers as well [30]. The overarching aim of assessing barriers and facilitators is to identify and understand factors that influence implementation [51]. However, solely assessment of barriers and facilitators does not suffice. It is also important to act on this knowledge and focus on areas that need more attention. For this purpose, Nilsen et al. have described several models which guide the process of translating research into practice and provide more practical planning and execution of implementation endeavors [51]. Future digital health researchers should incorporate such models in their projects in order to increase implementation success.

A limitation of this study lies in the fact that the RESPONSE tool [43] did not come up in our initial literature search and was brought to our attention during the review process. As a result, we were unable to carry out the interview about barriers and facilitators. We did include this tool in Table 1 (overview tool characteristics based on published research).

This review provides an update on digital tools for acute and/ or chronic pain in children with cancer that have been developed in research settings. Thirteen unique digital tools were identified, and these are mostly apps directed at pain severity monitoring. Feasibility and acceptability were established for all tools, yet definitive data on their effectiveness in accurately monitoring and/or reducing pain is lacking. Qualitative assessment of common determinants (barriers and facilitators) of successful implementation yielded valuable findings that can inform and guide future digital health researchers and implementers, not only in pediatric oncology, but also in a wide variety of both pediatric and adult healthcare populations.

APPENDIX 1.

Included keywords and search string used for PubMed

The following keywords were included: mobile health, telemedicine, telehealth, mhealth, ehealth, mobile intervention, mobile application, app, smarthphone, teleconsult, pain, cancer pain, headache, migraine, neuralgic, ache, neuropathic, child, kid, youth, juvenile, pediatric, infant, schoolchild, childhood, preschooler, adolescent, teen, teenager, cancer, neoplasm, tumor, malignant, and leukemia.

("Pain"[MeSH Terms:noexp] OR "Pain"[Title/Abstract] OR "Cancer Pain"[MeSH Terms] OR "headache*"[Title/Abstract] OR "migraine*"[Title/Abstract] OR "neuralgi*"[Title/Abstract] OR "ache"[Title/Abstract] OR "aches"[Title/Abstract] OR "aching"[Title/Abstract] OR "neuropath*"[Title/Abstract])
AND
("child"[MeSH Terms] OR "child"[Title/Abstract] OR "children*"[Title/Abstract] OR "kid"[Title/Abstract] OR "kids"[Title/Abstract] OR "youth"[Title/Abstract] OR "juvenile"[Title/Abstract] OR "pediatric*"[Title/Abstract] OR "paediatric*"[Title/Abstract] OR "infant"[MeSH Terms] OR "infant*"[Title/Abstract] OR "infancy"[Title/Abstract] OR "schoolchild*"[Title/Abstract] OR "childhood"[Title/Abstract] OR "preschooler*"[Title/Abstract] OR "girl"[Title/Abstract] OR "girls"[Title/Abstract] OR "boy"[Title/Abstract] OR "boys"[Title/Abstract] OR "adolescent*"[Title/Abstract] OR "adolescent"[MeSH Terms] OR "teen"[Title/Abstract] OR "teens"[Title/Abstract] OR "teenager*"[Title/Abstract])
AND
("Neoplasms "[MeSH Terms] OR "neoplas*"[Title/Abstract] OR "tumor*"[Title/Abstract] OR "tumour*"[Title/Abstract] OR "cancer*"[Title/Abstract] OR "malignan*"[Title/Abstract] OR "leukemia*"[Title/Abstract] OR "leukaemia*"[Title/Abstract])
AND
("mobile health"[Title/Abstract] OR "Telemedicine"[MeSH Terms:noexp] OR "Telemedicine"[Title/Abstract] OR "tele medicine"[Title/Abstract] OR "telehealth"[Title/Abstract] OR "tele health"[Title/Abstract] OR "teleconsult*" OR "tele consult*"[Title/Abstract] OR "mhealth"[Title/Abstract] OR "m health"[Title/Abstract] OR "ehealth"[Title/Abstract] OR "e health"[Title/Abstract] OR "mobile intervention"[Title/Abstract] OR "mobile application"[Title/Abstract] OR "app"[Title/Abstract] OR "apps"[Title/Abstract] OR "smartphone*"[Title/Abstract])

APPENDIX 2.

Interview guide Determinants of implementation of Digital Health Interventions for Pain in Pediatric Oncology

INTRODUCTION

"Are you ok with us recording this session as a back-up? We will not publish these recordings. If so: could you also shortly introduce yourself?"

"We invited you to do this interview as part of a scoping review on digital health interventions for pain in pediatric oncology. We wanted to add a qualitative aspect to the review, focusing on determinants of implementation researchers encounter. Our aim with these interviews is to develop an overview with lessons for future digital health developers and researchers."

"This interview will take up to 60 minutes, and has three sections. First, I will ask a few questions about the current status of the [intervention] project and the parties involved. Second, we will focus on which barriers and facilitators you have encountered during the [intervention] project. Third, we will talk about future plans. And finally we will ask some questions about you and your working experience."

CURRENT STATUS AND PARTIES INVOLVED

1. Please describe your role (job description) in the [intervention] project:
   Prompt: Are you currently still working in the [intervention] project?
2. Which phase is [intervention] currently in? For example: development, evaluation, implementation..
   Prompt: which phase specifically: development, feasibility testing, effectiveness testing, implementation, dissemination?
3. With regards to future implementation of [intervention], are you using OR are you planning to use an implementation theory/model/framework? And if so, which one?
   Prompt: for example, CFIR, PARIHS, Knowledge to Action Cycle, Theoretical Domains Framework, COM-B
4. We're wondering which professions have been involved in the project. Could you give an overview?
   Prompt: (if not mentioned) and how about researcher(s), clinician(s), IT-specialist(s), lawyer(s), policy maker(s), economic evaluator(s), OTHER, namely:
5. Stakeholders are people or organizations who have an interest in your research project, or affect or are affected by its outcomes. Which people or organizations are key stakeholders for your project?

Prompt: (if not mentioned) and how about parents, children, board of directors, healthcare professionals, researchers, OTHER, namely:

6. Are these key stakeholders now, or have they previously been, involved in the project? *Prompt: please describe their involvement*

BARRIERS AND FACILITATORS

Barriers and facilitators describe factors helpful to ór hindering the development and/or implementation process of new interventions. They can play a role at different levels, namely on the intervention level, the end-user level, the organization-level or the socio-political level. To give you an idea, we have sent an overview of possible barriers and facilitators prior to the interview and asked you to look at these (see 'overview MIDI-themes').

1. Which are the three major BARRIERS that you have encountered during the project?
2. Which are the three major FACILITATORS that you have encountered during the project?

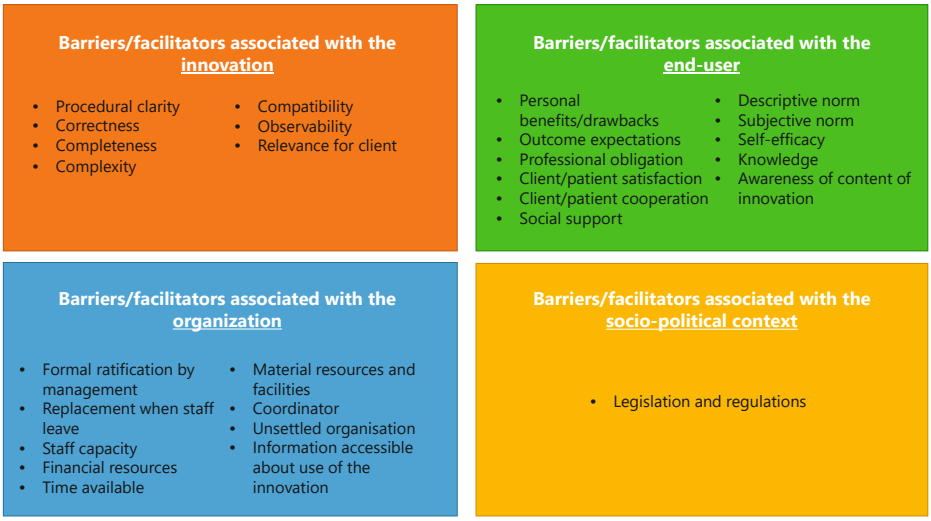
FUTURE PLANS

1. What are your future plans for the intervention?

DEMOGRAPHICS INTERVIEWEE

1. Which pronouns do you prefer?/i.e. what is your gender?
2. Age:
3. Country of residence:
4. Do you work in a hospital/university setting:
5. Clinical role: PHYSICIAN / PHARMACIST / PHYSIOTHERAPIST / NURSE / DIETITIAN / PSYCHOLOGIST / OTHER, namely:
6. Years working in clinical care:
7. Research/academic position: PROFESSOR / POST DOC / PHD STUDENT / RESEARCH ASSISTANT / OTHER, namely:
8. Years working in research:
9. Years working with digital health interventions:

OVERVIEW MIDI-THEMES



Source: Fleuren, M.A.H. Paulussen, T.G.W.M., Van Dommelen, P., & VanBuuren, S. (2014). Measurement instrument for determinants of innovations (MIDI). Leiden: TNO

DEFINITONS

Feasibility (testing)	(Testing) the practicality of the intervention, for example in terms of learnability, usability, desirability.
Effectiveness (testing)	(Testing) the degree to which the intervention is successful in meeting the desired results.
Implementation	The process of integrating the intervention into clinical settings. Putting interventions into use in real-world settings.
Dissemination	Effective dissemination is about actively getting the findings of your research to the people who can make use of them, to maximize the benefit of the research without delay.
Stakeholder	Stakeholders are people or organisations who have an interest in your research project, or affect or are affected by its outcomes. Stakeholders include those who are both supportive of your research, as well as those who may be less supportive or indeed critical of it (i.e. patients or healthcare professionals).
Champion	Individuals who support, market, or 'drive through' implementation in a way that helps to overcome indifference or resistance by key stakeholders (i.e. head nurse or member of patient counsil).
Implementation theory	Explains what influences implementation outcomes. Explains how or why an intervention does or does not work.
Implementation model	Describes and/or guides the process of translating research into practice. Describes the temporal sequence of implementation endeavours.
Implementation framework	A proposed model of factors/elements/determinants likely to impact implementation and sustainment of the intervention. Often includes multiple levels (system, organization, provider, patient) and phases (implementation occurs over time, often in phases).
Barrier	Prevents or hinders the intervention from further development and/or slows down the process of implementation.

Appendix 3. Overview outcomes semi-structured interviews

Intervention	Context research project	Stakeholder involvement	Use of implementation theory, model or framework	Identified key barriers and facilitators categorized in MIDI* main and sub-themes
Color Me Healthy app	• **Interviewee(s) role in project:** Principal investigator • **Current project phase:** Second cycle of development phase • **Professionals contributed to the project**: Nurses, nurse practitioners, physicians, specialists in videogame design, specialists in informatics	· **Key stakeholders involved:** Children, parents, nurses, nurse practitioners, physicians, child life specialists · **During which project phase(s) were they involved?** Throughout the development of the app	No	Key barriers · **Main: organization, sub: financial resources** "A really big challenge is maintaining some source of funding to keep the project going." · **Main: organization, sub: time available** "Even small bugs in the code can be a setback. Having the time and dedicated team to support the work are essential." · **Main: organization, sub: staff capacity** "We work with students, so their work is completed on a semester basis as opposed to having a constantly available team." Key facilitators · **Main: socio-political context, sub: collaborating with external stakeholders, i.e. other disciplines/hospitals/ cultures** "A key facilitator is having committed interdisciplinary team-members with different perspectives." · **Main: end-user, sub: cooperation** "If I don't have a parent who is supportive of working with their child in using the digital technology, then the project is less likely to be successful." · **Main: end-user, sub: personal benefits** "Cloud-based data repositories can be future facilitators to access data remotely."

Appendix 3. Overview outcomes semi-structured interviews (continued)

Intervention	Context research project	Stakeholder involvement	Use of implementation theory, model or framework	Identified key barriers and facilitators categorized in MIDI* main and sub-themes
C-SCAT	· **Interviewee(s) role in project:** Principal investigator · **Current project phase:** Seeking funding for a RCT to evaluate the efficacy of the C- SCAT to improve symptom self-management · **Professionals contributed to the project**: Nurses, nurse scientists, computer scientists and game design experts	· **Key stakeholders involved:** AYA's · **During which project phase(s) were they involved?** AYA's reviewed general concept for the C-SCAT while the initial grant to support the development of the C-SCAT was written	No	Key barriers · **Main: socio-political context, sub: collaborating with external stakeholders, i.e. other disciplines/hospitals/ cultures** "With our initial study, app development was relatively new, so we needed help identifying collaborators for programming support." · **Main: end-user, sub: personal drawbacks** "Initial version proved to be overly time consuming for patients with multiple complex symptoms." · **Main: end-user, sub: cooperation** "Some AYAs required more prompting than others to use their C- SCAT image in the context of a clinical visit." Key facilitators · **Main: socio-political context, sub: collaborating with external stakeholders, i.e. other disciplines/hospitals/ cultures** "Access to individuals who could facilitate connections to identify collaborators for programming support." · **Main: end-user, sub: satisfaction** **"**Novelty for users of interacting with a tablet computer-based app." · **Main: socio-political context, sub: collaborating with external stakeholders, i.e. other disciplines/hospitals/ cultures** "Multi-site collaborators to facilitate accrual of an adequate sample size."

Appendix 3. Overview outcomes semi-structured interviews (continued)

Intervention	Context research project	Stakeholder involvement	Use of implementation theory, model or framework	Identified key barriers and facilitators categorized in MIDI* main and sub-themes
Empatica E4 wristband	· **Interviewee(s) role in project:** Principal investigator · **Current project phase:** Empatica E4 wristband has been validated in a feasibility study, patient satisfaction has been studied, next step will be effectiveness testing in a multi-site study · **Professionals contributed to the project**: Data analysts, computer scientists, physicians	· **Key stakeholders involved:** Patients, parents of patients, clinicians (oncologists, hematologists), technology companies (Fitbit, Google Health) · **During which project phase(s) were they involved?** Patients, parents and clinicians are involved in designing the research. Technology companies provide the devices, they will be contacted while writing the grant.	No	Key barriers · **Main: end-user, sub: compatibility** "I'm having to make the devices work for children, rather than the devices be specifically designed for children. When it comes to innovation, children aren't necessarily the clientele." · **Main: end-user, sub: satisfaction** "Kids don't want to wear anything that will draw attention to them. It has got to be cool. I had to find something that records the data that I need, and fits with their personal brand." · **Main: intervention, sub: correctness** "The way that the medications were entered into the electrical health record were not always matched when the child received the medication." Key facilitators · **Main: end-user, sub: cooperation** "Children are more likely to accept new technology and to incorporate new technology into their house." · **Main: end-user, sub: satisfaction** "The children's hospital and my colleagues were supportive of the project." · **Main: intervention, sub: observability** "The time stamp, and vital information was really visualized on the researcher view of the innovation"

Appendix 3. Overview outcomes semi-structured interviews (continued)

Intervention	Context research project	Stakeholder involvement	Use of implementation theory, model or framework	Identified key barriers and facilitators categorized in MIDI* main and sub-themes
ePROtect	· **Interviewee(s) role in project:** Leader of the research group · **Current project phase:** Validity testing of measurement instrument used in intervention · **Professionals contributed to the project**: Healthcare professionals (psychologists, nurses, medical doctors), scientists, PhD students, study nurses, IT specialists	· **Key stakeholders involved:** Patients, parents of patients, medical doctors and nurses, cancer aid society, the hospital · **During which project phase(s) were they involved?** Throughout the entire project	No	Key barriers · **Main: organization, sub: time available** "The patient needs to be educated and reminded to fill out the measurements daily. It needs to be explained why this is important." · **Main: end-user, sub: cooperation** "The research group works very hard on establishing new ways to measure symptoms, but the other members of the ward (e.g., medical doctors, nurses) need to be involved in order for them to accept the new ways of measurement." · **Main: end-user, sub: knowledge** "It takes a lot of time to run the project and motivate the patients. In the phase of development and implementation it's consuming a lot of resources." Key facilitators · **Main: organization, sub: time available** "The pandemic gave us more time to concentrate on this project, because we had less patients." · **Main: end-user, sub: personal benefits** "The advantages that digital technique has, like the speed of time, the way of producing big data. That is a clear advantage of digital technique." · **Main: end-user, sub: personal benefits** "Our web portal was not just an instrument to ask something from the patient, but it was also an instrument to give the patient a lot of information about his treatment."

Appendix 3. Overview outcomes semi-structured interviews (continued)

Intervention	Context research project	Stakeholder involvement	Use of implementation theory, model or framework	Identified key barriers and facilitators categorized in MIDI* main and sub-themes
KLIK Pain Monitor app	• **Interviewee(s) role in project:** Project leader • **Current project phase:** Effectiveness testing using a RCT. Depending on the outcomes, the next phase will be implementation in daily care • **Professionals contributed to the project**: Researchers, clinicians (pediatric oncologists, psychologists, nurses and pain team of doctors and nurses), PhD student, IT specialists, lawyers. Educational information in the app was screened by the patient organization	· **Key stakeholders involved:** The pain team, pediatric oncologists, nurse specialists, children and their parents · **During which project phase(s) were they involved?** Children and their parents were involved throughout the entire project. The pain team was not involved in writing the grant, because there was no pain team yet. Pediatric oncologists and nurse specialists were involved in the feasibility study and will be involved in the implementation phase	Yes: Knowledge-to-Action (KTA) Framework	Key barriers · **Main: organization, sub: unsettled organization** "Our organization was new when we started the project. All procedures and pathways were not clear. This includes finding a way to collaborate with the new pain team." · **Main: intervention, sub: correctness** "A participant mentioned 'I didn't always receive the daily reminders. At one point, I didn't receive them for two days'." · **Main: organization, sub: time available** "HCP's were worried about the extra workload." Key facilitators · **Main: end-user, sub: satisfaction** "A HCP mentioned 'I think that the app will increase our knowledge on how often kids are in pain at home. And it enables us to provide them with care much quicker'." · **Main: end-user, sub: satisfaction** "A patient mentioned 'It worked perfectly: customer friendly, intuitively, simple. I didn't experience any problems'." · **Main: intervention, sub: complexity** "It was really easy and clear how to use the app."

Appendix 3. Overview outcomes semi-structured interviews (continued)

Intervention	Context research project	Stakeholder involvement	Use of implementation theory, model or framework	Identified key barriers and facilitators categorized in MIDI* main and sub-themes
Kræftværket app	· **Interviewee(s) role in project:** Project owner, project planner and head of research group · **Current project phase:** The app is implemented and disseminated throughout Denmark as a research project. Currently working on implementation in daily clinical care · **Professionals contributed to the project**: Researchers, clinicians, software developers, specialists in interface development, doctors (oncologists, pediatricians, hematologists), nurses, medical students, experts in communication, social workers, psychologists	· **Key stakeholders involved:** Patients, national network for AYA's with cancer (Danish Cancer Society) · **During which project phase(s) were they involved?** They are in the steering committee of the project (involved throughout project)	No	Key barriers · **Main: socio-political context, sub: legislation and regulations** "When you work with different hospitals and institutions they may have different juridical regulations." · **Main: organization, sub: financial resources** "It is difficult to get funding." · **Main: end-user, sub: social support** "When you developed an intervention in one institution than you might face the challenge that others are not willing to take ownership for that e-Health tool. 'How do you know that it works at our institution?'." Key facilitators · **Main: end-user, sub: cooperation** "This patient population feels the need to do something for others." · **Main: organization, sub: coordinator** "Someone who is willing to move around, who is not only in the office phoning and writing to everyone, but also goes out to other hospitals, listen to how they work there, try to work with them and help them with implementation." · **Main: organization, sub: financial resources** "When we had good financing, the project went well. At times when we had less funding, it was difficult."

Appendix 3. Overview outcomes semi-structured interviews (continued)

Intervention	Context research project	Stakeholder involvement	Use of implementation theory, model or framework	Identified key barriers and facilitators categorized in MIDI* main and sub-themes
mOST (Mobile Oncology Symptom Tracker)	· **Interviewee(s) role in project:** Co-project leader · **Current project phase:** The project has been terminated after the usability/ acceptability study, because the project leader had to decide which intervention would be developed further and decided to focus on another intervention · **Professionals contributed to the project**: Research nurses, physicians and IT specialists	· **Key stakeholders involved:** Clinicians (physicians, nurses and pharmacists) involved in care · **During which project phase(s) were they involved?** After usability/acceptability study	No	Key barriers · **Main: organization, sub: formal ratification by management** "Getting approval from our contract office, because we worked with an outside group which the university never worked with before. This took months and months and months." · **Main: intervention, sub: procedural clarity** "I struggled to make the intervention visually appealing and uniform looking when we were using different measurement tools." · **Main: organization, sub: replacement when staff leave** "The contract had been signed with the university where I was and I was leaving to another university. I could not take the project with me." Key facilitators · **Main: end-user, sub: cooperation** "Kids wanted to have an iPhone so at the start of the project this was a facilitator." · **Main: organization, sub: financial resources** "We had the financial resources to use money as incentives for the participants." · **Main: intervention, sub: complexity** "The simplicity of the intervention was a facilitator, it was very quick to answer the questions."

Appendix 3. Overview outcomes semi-structured interviews (continued)

Intervention	Context research project	Stakeholder involvement	Use of implementation theory, model or framework	Identified key barriers and facilitators categorized in MIDI* main and sub-themes
OPBG (Ospedale Pediatrico Bambino Gesu Tool)	· **Interviewee(s) role in project:** Project leader · **Current project phase:** Development phase is completed. App was used only in the research project, might be used in the future again. Open to continuing its' development · **Professionals contributed to the project**: App developer ('IT nurse'), researchers, research nurses, pediatric oncologist, medical lawyers	· **Key stakeholders involved:** The hospital, patients, committee for pain · **During which project phase(s) were they involved?** During first study	No	Key barriers · **Main: intervention, sub: compatibility** "Due to it being 2014, not everyone had a smartphone." · **Main: socio-political context, sub: legislation and regulations** "We developed an app, but now another department within the hospital deals with applications. In order to use it now, it has to go through them." · **Main: organization, sub: material resources and facilities** "Even the platforms to develop the app weren't as easy accessible as they are now. You needed more knowledge to develop an app than you need now." Key facilitators · **Main: intervention, sub: procedural clarity** "We already had certain standards for pain evaluation, we had a clear structure to base our work on." · **Main: end-user, sub: satisfaction** "We perceived a 100% satisfaction." · **Main: end-user, sub: social support** "The other nurses helped us find patients, they knew when patients would be discharged so we could contact them about participation in the study."

Appendix 3. Overview outcomes semi-structured interviews (continued)

Intervention	Context research project	Stakeholder involvement	Use of implementation theory, model or framework	Identified key barriers and facilitators categorized in MIDI* main and sub-themes
Pain Buddy	· **Interviewee(s) role in project:** Principal Investigator · **Current project phase:** Ongoing effectiveness study (RCT). Meanwhile conducting implementation interviews with children, families and HCP's to increase implementation effectiveness. Working on cultural adaptation, social support components and parent component in the app · **Professionals contributed to the project**: Clinicians (oncology nurses, nurse practitioners, bachelor and master level nurses, oncology physicians, child life specialists, anesthesiologists and psychologists), computer scientists, engineers, people with public health background	· **Key stakeholders involved:** Clinicians, children and their parents, the hospital · **During which project phase(s) were they involved?** Clinicians were involved throughout the process and have co-designed the intervention with us. Throughout each phase children and their parents were involved in the design, look and function of the intervention.	Yes: Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) Framework	Key barriers · **Main: socio-political context, sub: collaborating with external stakeholders, i.e. other disciplines/hospitals/ cultures** "As academic researchers we are used to the process evolving over time, or realizing 'Wait we need this feature', especially if you have stakeholder input. Whereas the developers want everything at the outset and then you are locked to that. The communication was challenging as well." · **Main: socio-political context, sub: collaborating with external stakeholders, i.e. other disciplines/hospitals/ cultures** "There has been a lot of hiccup's in technology that we cannot fix. Relying on other teams to make those fixes has been a challenge." · **Main: organization, sub: financial resources** "Development of a digital intervention over years is costly, mobile health apps can be difficult to fund." Key facilitators · **Main: end-user, sub: cooperation** "We used feedback from end-users to gamify the app, which helped a lot." · **Main: end-user, sub: personal benefits** "The HCP's needed to be convinced that the app would decrease their workload. It was really helpful when they saw that it actually facilitated their work." · **Main: end-user, sub: satisfaction** "Parents tell us that they really like it and that they want to be more integrated into it."

Appendix 3. Overview outcomes semi-structured interviews (continued)

Intervention	Context research project	Stakeholder involvement	Use of implementation theory, model or framework	Identified key barriers and facilitators categorized in MIDI* main and sub-themes
Pain Squad app	· **Interviewee(s) role in project:** Project leader · **Current phase of intervention:** Dissemination/scaling up · **Professionals contributed to the project**: Healthcare professionals (pediatric oncologists, nurses, physiotherapists, psychologists, pain experts, child life specialists), software developers, measurement experts	· **Key stakeholders involved:** Patients, families of patients, healthcare professionals, research funders · **During which project phase(s) were they involved?** Development, testing, and implementation	Yes: Consolidated Framework for Implementation Research (CFIR)	Key barriers · **Main: organization, sub: financial resources** "During effectiveness testing, a nurse is paid from research funding. But how will we fund this down the road, when we want to implement/scale up?" · **Main: socio-political context, sub: legislation and regulations** "Interventions like these need to tick a lot of boxes to ensure that it complies with a certain quality and (data) safety. How will we get the app certified for use in clinical care?" · **Main: organization, sub: financial resources** "Apps need constant software updates, and the look and feel of app need to be updated regularly as well. How will we be able to pay for this beyond research funding?" Key facilitators · **Main: intervention, sub: compatibility** "By repeated testing, we were able to tick all boxes and remove barriers of use of the app." · **Main: end-user, sub: cooperation** "The ultimate goal is to have staff prescribe the app to patients, and have patients use it. Therefore, their input during development and testing phases is essential to develop a compatible intervention they support." · **Main: socio-political context, sub: collaborating with external stakeholders, i.e. other disciplines/hospitals/ cultures** "Is it essential to work with software companies who speak the same language. Companies with strictly commercial interests often do not."

Appendix 3. Overview outcomes semi-structured interviews (continued)

Intervention	Context research project	Stakeholder involvement	Use of implementation theory, model or framework	Identified key barriers and facilitators categorized in MIDI* main and sub-themes
Pain Squad + app	· **Interviewee(s) role in project:** Project leader · **Current phase of intervention:** Effectiveness testing · **Professionals contributed to the project**: Healthcare professionals (pediatric oncologists, nurses, physiotherapists, psychologists, pain experts, child life specialists), software developers, measurement experts	· **Key stakeholders involved:** Patients, families of patients, healthcare professionals, research funders · **During which project phase(s) were they involved?** Development, testing, and implementation	Yes: Consolidated Framework for Implementation Research (CFIR)	Key barriers · **Main: organization, sub: financial resources** "During effectiveness testing, a nurse is paid from research funding. But how will we fund this down the road, when we want to implement/scale up?" · **Main: socio-political context, sub: legislation and regulations** "Interventions like these need to tick a lot of boxes to ensure that it complies with a certain quality and (data) safety. How will we get the app certified for use in clinical care?" · **Main: organization, sub: financial resources** "Apps need constant software updates, and the look and feel of app need to be updated regularly as well. How will we be able to pay for this beyond research funding?" Key facilitators · **Main: intervention, sub: compatibility** "By repeated testing, we were able to tick all boxes and remove barriers of use of the app." · **Main: end-user, sub: cooperation** "The ultimate goal is to have staff prescribe the app to patients, and have patients use it. Therefore, their input during development and testing phases is essential to develop a compatible intervention they support." · **Main: socio-political context, sub: collaborating with external stakeholders, i.e. other disciplines/hospitals/ cultures** "Is it essential to work with software companies who speak the same language. Companies with strictly commercial interests often do not."

Appendix 3. Overview outcomes semi-structured interviews (continued)

Intervention	Context research project	Stakeholder involvement	Use of implementation theory, model or framework	Identified key barriers and facilitators categorized in MIDI* main and sub-themes
PicPecc (Pictorial support in person-centred care for children)	• **Interviewee(s) role in project:** Principal Investigator • **Current project phase:** Previous phase: assessing needs of children, their parents and HCP's Validity testing of measurement tool (Faces Thermometer Scale), effectiveness study of tool usage during chemotherapy, study which assesses the needs of children which could be implemented into the app. Our main goal is international collaboration, but we are still applying for money to make that happen • **Professionals contributed to the project**: Physicians (pediatric oncologists), speech/language therapists, pedagogical researchers (educational sciences), applied IT specialists, nurses, physiotherapists, dentists, health economists	· **Key stakeholders involved:** Children, their parents, HCP's, childhood cancer organization · **During which project phase(s) were they involved?** Development phase	Yes: MRC (Medical Research Council) Framework for Development and Evaluation of Complex Interventions	Key barriers · **Main: organization, sub: financial resources** "We can find finding to create interventions, but it's harder to convince the clinic / funders to pay for the support and further development of an already created app. This is a management problem, because the nurses and physicians are cooperating but the funding is decided on higher levels." · **Main: end-user, sub: social support** "There is a gap between the academic and the clinic. So once you have developed an intervention in the university setting, you don't necessarily have buy-in or acceptance of the intervention at the hospital." · **Main: socio-political context, sub: collaborating with external stakeholders, i.e. other disciplines/hospitals/ cultures** "A lot of similar interventions are developed in different countries. An international network is lacking." Key facilitators · **Main: end-user, sub: satisfaction** "We have a user-centered design, so a facilitator is patient satisfaction." · **Main: socio-political context, sub: collaborating with external stakeholders, i.e. other disciplines/hospitals/ cultures** "Because HCP's from different disciplines were involved, we were able to create an app which is usable in different fields." · **Main: socio-political context, sub: collaborating with external stakeholders, i.e. other disciplines/hospitals/ cultures** "We collaborated with South Africa from the beginning. We have the international perspective as well, because we started building in eleven languages in the app from the beginning."

Appendix 3. Overview outcomes semi-structured interviews (continued)

Intervention	Context research project	Stakeholder involvement	Use of implementation theory, model or framework	Identified key barriers and facilitators categorized in MIDI* main and sub-themes
Telemonitoring System for Paediatric Oncology	• **Interviewee(s) role in project:** Supervisor of master student who developed the app and project manager • **Current project phase:** Previous phases: development phase and feasibility phase Current phase: trying to get funding in order to further develop based on feasibility study • **Professionals contributed to the project**: Researchers, IT specialists, master student, physicians, specialists in pediatric oncology, data managers, nurses	· **Key stakeholders involved:** Patients, parents, nurses, mobile team (HCP's, such as pediatric oncologists, who visit patients) · **During which project phase(s) were they involved?** Feasibility testing	No	Key barriers · **Main: socio-political context, sub: legislation and regulations** "You need a medical device certification, which is doable, but it takes a lot of time and money." · **Main: end-user, sub: social support** "You need to involve everybody who's workflows will change because otherwise the project won't work." · **Main: organization, sub: financial resources** "So far, all we did was with our own money, we have some money we can use, but at some point we have to get some funding." Key facilitators · **Main: end-user, sub: satisfaction** "Usability is extremely important. The usability was quite well and well accepted, people liked it quite lot." · **Main: organization, sub: staff capacity** "It is extremely important to have somebody who is open and able to talk to the patients, parents and physicians in the right way." · **Main: end-user, sub: social support** "You need to involve everybody who's workflows will change and get everybody involved because otherwise the project won't work."

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Availability of data

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability

SPSS version 26.0 was used for all analyses.

Author contribution

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Julia D.H.P. Simon and Isabel S. Hooijman. The first draft of the manuscript was written by Julia D. H. P. Simon, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Ethics approval

Approval for the study was obtained from the Internal Review Board of the Princess Máxima Center for Pediatric Oncology and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent to participate and for publication

Informed consent was obtained from all individual participants (i.e., project leaders) included in the study. The authors affirm that all participants consented to the publication of their data.

Conflict of interest

The authors declare no competing interests.

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6

Chapter 6

Towards Implementation of a Digital Health Tool to Reduce Pain in Children with Cancer at Home: From Knowledge to Action

Submitted.

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ABSTRACT

Background: A small percentage of evidence based innovations are successfully implemented in clinical care. A commonly used theoretical approach to guide the process of translating research into practice is the Knowledge-to-Action (KTA) framework, which consists of two parts: the knowledge creation funnel and the action cycle. Aim 1 of this paper is to describe the different phases (i.e. exploration, development, feasibility, effectiveness, implementation) of a research project with a new digital health tool for managing pain in pediatric cancer, using KTA. Aim 2 is to explore which determinants (i.e. barriers and facilitators) potentially influence future implementation outcomes, based on healthcare professional's (HCP's) attitudes.

Methods: For aim 1, KTA's knowledge creation funnel was used as guidance during the exploration and development phases, and KTA's action cycle was used during the feasibility- and effectiveness testing phases. For aim 2, HCP's completed the Acceptability (AIM), Appropriateness (IAM), and Feasibility (FIM) of Intervention Measure, as well as items of the Measurement Instrument for Determinants of Innovation (MIDI) after feasibility and effectiveness testing. Descriptive statistics were used to describe and compare assessments. To explore differences between standardized mean scale scores between time points for AIM, IAM and FIM, we used linear mixed effect regression with random intercepts to control for repeated measures.

Results: Based on the outcomes of the clinical studies, as well as the identified barriers and facilitators of implementation, we were able to make changes and detailed recommendations to facilitate successful implementation of the digital health tool in clinical care. After effectiveness testing, two barriers (HCP adherence to follow-up within set timeframe and HCP fear of increased workload) and three facilitators (all relating to the app's added value for pain care) remain, and require further attention before implementation can take place.

Conclusions: KTA has motivated us to assess determinants of future implementation consistently throughout the project, and enabled us to assess whether our efforts to remedy barriers, and maintain facilitators, were successful. But most importantly, it has increased the chance of effective use of a new digital health tool in clinical care, and thereby, improved pain management in pediatric oncology.

Keywords: Digital health, mHealth, Pediatric Oncology, KTA, Barriers, Facilitators

INTRODUCTION

Advancements in digital technology have enabled hospitals to bridge the distance with the home setting by using digital health tools such as eHealth or mHealth. eHealth refers to "the use of information technology (internet, digital games, virtual reality, and robotics) in the promotion, prevention, treatment, and maintenance of health", and mHealth refers to "mobile and wireless applications, including text messages, apps, wearable devices, remote sensing, and the use of social media such as Facebook and Twitter, in the delivery of health related services"[1]. Digital health tools have many potential benefits, among which accessibility of care to a wider public and higher cost-effectiveness[2].

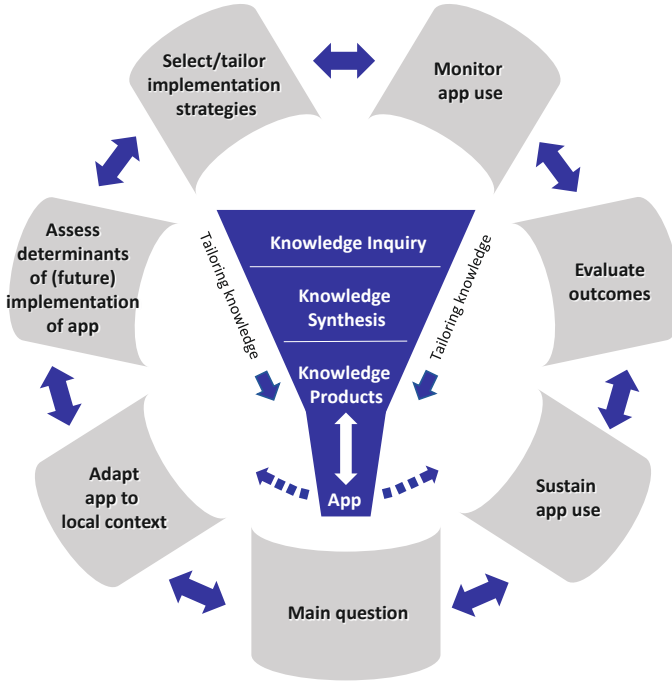
Digital health has also gained popularity in pediatric oncology, for which over the past decade many digital tools have been developed, mainly aimed at better symptom management[3-9]. One of the most common and distressing symptoms children experience during cancer treatment, is pain[10-16]. This may be caused by the cancer itself (i.e. tumor growth), by side effects of the treatment (i.e. chemotherapy or surgery), or by medical procedures (i.e. blood draws or lumbar punctures)[15,17]. A previous study has shown that the majority of children with cancer experience clinically significant pain at home during the treatment phase, yet in one third of those incidences, the pain remained untreated[14]. Parents might feel hesitant to ask the doctor for help, or are held back by long waiting times in the hospital phone queue. Another explanation for the undertreatment of pain at home are parental misconceptions about pain during cancer treatment (i.e. it is unavoidable[15]), and possible dangers of opioid-use[18]. Digital health tools may be a solution for optimizing pain management in the home setting, by making communication with healthcare professionals (HCP's) more accessible to families, and providing them with education about cancer-related pain(treatment).

Thus, digital health has the potential to improve health outcomes by making care more accessible and readily available[2]. In order to reach this goal, tools first have to go through several research phases (e.g. acceptability/feasibility/effectiveness studies) to become evidence-based. And even when tools are evidence-based, it generally takes a long time (some studies indicate up to 15-20 years[19,20]) before they are effectively implemented and used in care. As a result, only 14% of evidence based tools are successfully implemented, leaving a large amount of 'research waste'[20]. Due to this 'evidence-to-practice gap' (also defined as 'knowledge-to-practice gap' or 'know-do gap'), it takes many years before patients can benefit from effective tools[21]. There is an imbalance between the time, money and effort that is put into developing healthcare innovations on the one hand, and the amount spend on making sure these innovations are successfully used in clinical care

on the other hand[21]. Specifically for pain management in pediatric cancer, we reviewed which digital health tools had been developed over the past ten years, and found that of the fourteen identified tools, three reached the phase of effectiveness testing, and only one tool had been implemented in routine care. Other tools have yet to reach the implementation phase, often due to a lack of financial and human resources[22].

This raises the urgency of applying implementation science in research projects that strive for the uptake of tools into clinical practice[4,20,23]. There are many theoretical approaches, and for people new to the world of implementation it can be a difficult task to navigate through the available theories, models, and frameworks[24], let alone understand how these are applied to research projects. A commonly used theoretical approach to describe and guide the process of translating research into practice is the Knowledge-to-Action (KTA) framework[25]. In KTA (Figure 1), implementation of research based knowledge in practice is seen as a dynamic and iterative process. KTA consists of two components: the knowledge creation funnel and action cycle. The funnel is used during the development process of innovations, and goes from broad (i.e. gathering all information available on a subject) to narrow (i.e. the innovation that is needed

Figure 1. Knowledge-to-Action (KTA) framework



Note. Knowledge creation funnel (middle circle); action cycle (outer circle). Adapted with approval of the developer (I.D. Graham) and reproduced with permission from Wiley Publishing.

to address a certain problem). The action cycle represents which actions need to be undertaken for an innovation to be successfully implemented down the road. These actions influence each other and are iterative (not chronologic), and the action cycle can be applied several times throughout projects[26]. KTA provides users with an overview that helps guide and understand how (digital health) tools are developed based on acquired knowledge, and evaluates how these tools are then applied in clinical settings through tailoring, adapting, implementing, monitoring and sustaining[27]. KTA endorses the idea that one has to start thinking about, and planning for implementation at the start, or even before, the new projects. By doing so, researchers are able to identify potentially important determinants (barriers and facilitators) of implementation early on, which enables them to intervene and adapt the innovation and processes involved, and to monitor the effects of these efforts.

In this research project, a new digital health tool (the *KLIK Pijnmonitor app*) for managing pain at home in pediatric cancer was developed, tested, and prepared for implementation. The first aim of this paper was to describe the different phases of the project (i.e. exploration, development, feasibility, effectiveness, implementation), through an implementation lens using KTA. We selected KTA for this purpose, as it offers practical guidance in the planning and execution of implementation endeavours[28]. As a secondary aim, to explore what potentially influences future implementation outcomes, we assessed and compared determinants (i.e. barriers and facilitators) for future implementation of the tool, based on HCP's attitudes.

METHODS

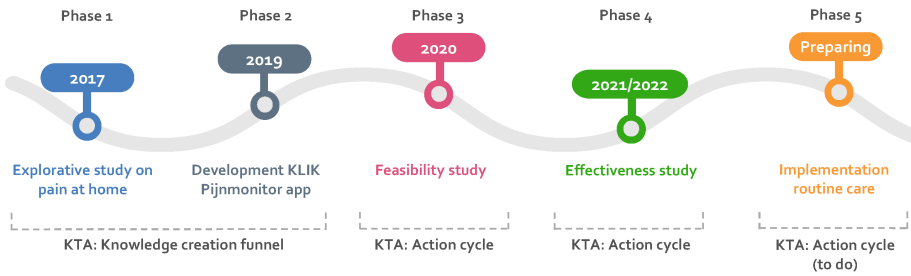
Research project

This research project entailed the development and evaluation of a digital health tool (the *KLIK Pijnmonitor app*), aimed at improving pain management of children with cancer (all diagnoses, 0-18 years old) in the home setting. The digital health tool consisted of family provision with educational information about pain(management) and real-time feedback (telephone) from HCP's on pain scores (also see figure 3). The research project was comprised of five phases: (1) exploration, (2) development, (3) feasibility testing, (4) effectiveness testing, and preparation of (5) implementation of the app into routine clinical care (see overview of phases in Figure 2).

The project was led by a core team of five professionals: senior research psychologist with expertise in psycho-oncology (MG), senior research pediatric oncologist with expertise in supportive care (WT), researcher/pediatric oncologist with expertise in palliative care and

pain (EM), researcher/psychologist with expertise in communication and implementation (SS), and a PhD student/psychologist (JS) at the Princess Máxima Center for Pediatric Oncology in Utrecht, The Netherlands. In this national center, all care for children with cancer is centralized. Approval for clinical studies carried out in the project (feasibility study, effectiveness study) was obtained from the Internal Review Board of the hospital.

Figure 2. Phases of the *KLIK Pijnmonitor app* project as guided by KTA



Design, participants and procedure

Data was collected throughout the research project from April 2016 until August 2022 (see Figure 2). During the feasibility[29] and effectiveness[30] studies, a mixed-methods design was used, including semi-structured interviews with families and HCP's (qualitative), questionnaires with families and HCP's (quantitative), and log data from the app (quantitative). The participants, methods, and outcomes of these studies are described extensively in each respective publication.

For our first aim of the current paper (to describe the different project phases through an implementation lens), an overview of results of these studies will be reviewed and discussed, using KTA. For the second aim (to explore what potentially influences future implementation outcomes), we assessed and compared determinants (i.e. barriers and facilitators) based on attitudes of HCP's who worked with the *KLIK Pijnmonitor app* during the feasibility (phase 3) and effectiveness study (phase 4). These HCP's included nurses, doctors and anaesthesiologists specialized in pediatric pain treatment. The questionnaires that were used are described below.

Measures

For our first aim (to describe the different project phases through an implementation lens), KTA was used. The knowledge creation funnel was used as guidance during phases 1 (explorative study on pain at home) and 2 (development *KLIK Pijnmonitor app*). The action cycle was used as guidance during phases 3 (feasibility study) and 4 (effectiveness study) (Figure 2).

For our second aim (to explore what potentially influences future implementation outcomes), we used two validated measures to assess determinants for (future) implementation: The Acceptability (AIM), Appropriateness (IAM), and Feasibility (FIM) of Intervention Measure, as well as the Measurement Instrument for Determinants of Innovation (MIDI). The twelve-statement AIM, IAM and FIM questionnaire was developed to monitor and evaluate the success of implementation efforts[31]. Proctor et al. (2011)[32] defined these constructs as follows: "Acceptability is the perception of stakeholders (e.g. end-users such as HCP's) that a given innovation is agreeable, palatable, or satisfactory. Appropriateness is the perceived fit, relevance, or compatibility of an innovation for a given setting. Feasibility is the extent to which an innovation can be successfully used or carried out within a given setting".

The AIM, IAM and FIM were translated to Dutch using the forward-backward method[33]. The original questionnaire by Weiner et al (2017) was translated (English-Dutch) by four independent researchers from the Psycho-Oncology research group at the Princess Máxima Center for Pediatric Oncology. In stage 2, the independent translators synthesized the translated texts into one single version. In stage 3, a native speaker in both English and Dutch (A.S. Darlington) performed back-translation (Dutch-English). In stage 4, all versions (English original, Dutch translation, English back-translation) were reviewed by a committee (J.D.H.P. Simon, M.A. Grootenhuis, A.S. Darlington). Discrepancies between versions were discussed and the committee came to a consensus on the appropriate translation. The translated version can be found in Appendix 1. Cronbach's alphas of the Dutch translation showed sufficient internal consistency, ranging between .76 and .85. HCP's in the current study rated their agreement with the 21 statements on a 5-point Likert scale (1 = completely disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, 5 = completely agree). Mean scale scores were computed (range 1-5).

Nine statements derived from the Measurement Instrument for Determinants of Innovation (MIDI)[34] were also included in the assessment of determinants of (future) implementation. The MIDI categorizes determinants into 4 main themes: the innovation itself, the end-user, the organization, and the socio-political context. In the previously published feasibility study, usefulness, general satisfaction and technical functioning of the app have been described thoroughly[29]. Therefore we only included MIDI-items to assess end-user (e.g. personal (dis)advantages of the app) and organizational factors (e.g. time consumption and workload) (see selected items in Appendix 2). The response categories for these items were answered on the same 5-point Likert scale as the AIM, IAM and FIM, but the MIDI-answers were divided into three categories: disagree [scores 1,2], undecided [score 3], and agree [scores 4,5]. For positively formulated MIDI-items

(i.e. *"Use of the KLIK Pijnmonitor app will give me better insight in pain at home"*) it was considered a barrier of implementation if ≥ 30% of HCP's disagreed [scores 1,2] with a statement. If ≥ 70% of HCP's agreed [scores 4,5] with a statement, it was considered a facilitator of implementation, and vice versa for negatively formulated items (i.e. *"Use of the KLIK Pijnmonitor app will cause an increase in workload"*).

Statistics

Analytic strategies and sample size considerations related to aim 1 (to describe the different project phases through an implementation lens) are described extensively in the feasibility[29] and effectiveness[30] papers.

For aim 2 (to explore what potentially influences future implementation outcomes), descriptive statistics were used to describe the AIM, IAM, and FIM scales (i.e. means and SDs), and the MIDI items (i.e. percentages) after feasibility (phase 3) and effectiveness testing (phase 4). To explore differences between standardized mean scale scores between time points for AIM, IAM and FIM, we used linear mixed effect regression with random intercepts to control for repeated measures. After Cohen, mean differences between two groups (i.e. the standardized regression coefficients) of .2, .5 and .8 were considered small, medium and large.[35] A two-tailed significance level of 5% was considered to be statistically significant.

For MIDI items, we compared changes between identified barriers and facilitators (descriptive statistics) after phases 3 and 4. SPSS version 26.0 was used for all analyses.

RESULTS

The section below provides a detailed description of phases 1 (exploration) to 4 (effectiveness testing) of the *KLIK Pijnmonitor app* as guided by KTA (i.e. aim 1). Furthermore, potential determinants (barriers and facilitators) for future implementation outcomes (i.e. aim 2) are described below as well. Table 1 provides a summary of the steps taken during each project phase. For an overview of the barriers and facilitators identified after phases 3 and 4, please see Table 2.

Research project phase 1: Exploration (2017)

Knowledge creation funnel: Knowledge inquiry

At the basis of the *KLIK Pijnmonitor app* project lies an explorative clinical study[14] (see Figure 2, phase 1) in which pain severity, prevalence, analgesic use, and pain interference

with daily life was assessed in children with cancer (0-18 years) receiving ambulatory chemotherapy[14]. Seventy-three children participated, and results of this study revealed that the majority experienced clinically significant pain at home (78%), and in one third of clinically significant pain incidences, no interventions were used to manage the pain. We concluded that pain was inadequately managed at home.

Knowledge creation funnel: Knowledge synthesis

After knowledge inquiry, the team concluded that a stronger focus on education and coaching of families on pain management at home setting was essential, as well as routine screening for pain at home. Thus, a systematic literature search (unpublished data) was carried out to answer the question: How can we improve pain management at home? The conclusion was to develop a digital health tool to bridge the distance between the hospital and home setting. Based on the literature and daily practice, it was clear that the tool should offer educational information on pain(treatment) for families at home, but also enable real-time feedback from HCP's. The team wrote a successful grant proposal for funding to develop a digital health tool and set up a research project (2018). In that year, the team was awarded three years of funding to develop, test and implement the *KLIK Pijnmonitor app* at the Princess Máxima Center. With the acquired funding, a PhD student was appointed to develop an app, evaluate its feasibility and effectiveness and make efforts to implement the app in clinical practice.

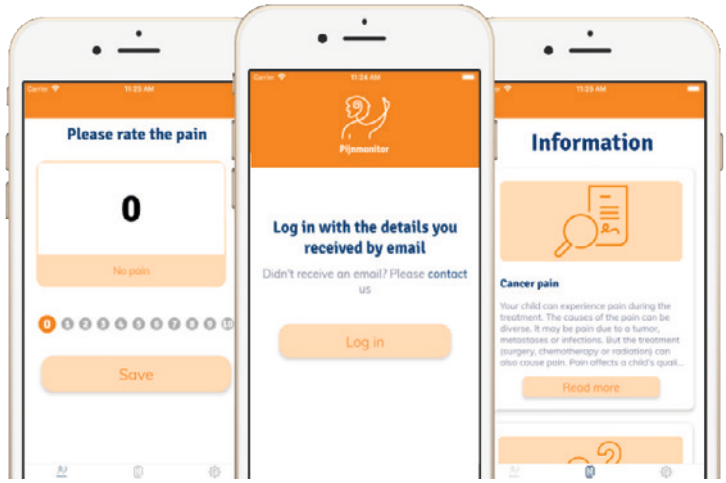
Research project phase 2: App development (2019)

Knowledge creation funnel: Knowledge products

The *KLIK Pijnmonitor app* (Figure 3) was commissioned by the Princess Máxima Center for Pediatric Oncology, and developed by an external web design company. The app was aimed at improving pain management of children with cancer (all diagnoses, 0-18 years old) in the home setting (i.e. ambulatory care), by providing families with educational information about pain(management) and real-time feedback (telephone) from HCP's on clinically significant pain scores (≥4). A more detailed description of the app and the workflow involved can be found in the feasibility paper[29]. Financial costs for the development and technical maintenance of the app throughout the entire project could not be fully covered by the acquired funding, and additional funding was necessary.

The content and design of the app was co-created by a team of pediatric oncologists, psychologists, IT-specialists, legal staff, and end-users (one representative of the patient organization and one representative of the hospital's pain service).

Figure 3. *KLIK Pijnmonitor app*



Note. The content of the app in this figure has been translated to English for the purposes of this paper. The app is currently only available in Dutch.

Research project phase 3: Feasibility study (2020)

Action cycle: Main question 'Is use of the app feasible?'

After the app was developed, the action cycle was used as guidance during feasibility testing in which we assessed whether use of the app (**V1.0**) was feasible[29]. To answer this question, a study protocol was developed, including the following outcomes: feasibility (i.e. learnability, usability, desirability), and adherence of families and HCP's to app use. During feasibility testing, twenty-seven families used the app for three weeks, and HCP's from the hospital's pain service (doctors, nurses and anaesthesiologists specialized in pediatric pain treatment) provided feedback to families when high pain scores (≥4) were reported. Approval for the study was obtained from the institutional research ethics committee.

Action cycle: Adapt app to local context

As part of the preparations for feasibility testing, the project group (researchers, psychologists, pediatric oncologists) pilot-tested the app ('debugging phase') and had brainstorming sessions with stakeholders (HCP's, families, lawyers on data security/ privacy, app developers). Outcomes were used to optimize the app (**V2.0**) and the care processes involved. Adaptations were as follows: the family version of app needed to include reminders for daily pain reporting, and the HCP version needed to include multiple (instead of one) reminders to call families following clinically significant pain scores.

Action cycle: Select/tailor implementation strategies

In order to further facilitate proper use of the app during feasibility testing, HCP's were trained in working with the app, and all app users (HCP's and families) were provided with technical support throughout the study (e.g. problems downloading app, logging in, reporting pain scores).

Action cycle: Monitor app use

To assess family adherence to the study protocol, we looked at the percentage of reported pain scores twice daily during three weeks. 37% of families reported pain twice daily during three weeks, and 63% reported pain at least once daily during the three study weeks. We assessed HCP adherence by whether they called families within the set timeframe (within 120 minutes for scores 4-6, within 30 minutes for score 7-10). In 70% of cases they did; in the remaining 30% they did contact families, but not within the specified time limit[29]. A goal was formulated to improve adherence (see sub-heading 'evaluate outcomes + select/tailor implementation strategies' below).

Action cycle: Assess determinants of future implementation of app (aim 2)

After study completion, we administered the AIM, IAM, FIM, MIDI questionnaires with HCP's who were at that point employed at the hospital's pain service (n=7). All of them completed the questionnaires. See Figures 4 and 5 for determinants (barriers and facilitators) of future implementation identified during the feasibility study (phase 3).

Action cycle: Evaluate outcomes + Select/tailor implementation strategies

With regards to feasibility of app use: questionnaires and interviews were conducted with HCP's and families after the feasibility study. Results indicated that the app was feasible (i.e. learnable, usable and desirable)[29].

Based on the outcomes of the feasibility study, and the identified barriers and facilitators of implementation, the app (**V3.0**) and care processes involved were further optimized to prepare for the effectiveness study (which included more patients and included a control arm). Adaptations consisted of: scaling up team of HCP's working with app (HCP adherence of responding within set timeframe during feasibility study was low), increasing noticeability (volume) of app notifications for HCP's, making pain reporting for families volitional (only when necessary) rather than at set times (family adherence to pain reporting twice daily during feasibility study was low), and providing families with a flyer with more specific instructions on where to use the app (only at home, not during hospitalization).

Action cycle: Sustain app use

With regards to sustainability of app use, the contract with the web design company was prolonged and updated to ensure upkeep of the app and safe data storage.

Research project phase 4: Effectiveness study (2021/2022)

Action cycle: Main question 'Is use of the app effective?'

Having demonstrated feasibility of use of the app, the team proceeded with a Randomized Controlled Trial (RCT) protocol that would assess effectiveness of the app (**V3.0**) in reducing clinically significant pain in children at home. The action cycle was again used as guidance during throughout (preparations for) this study. Study outcomes included: prevalence of clinically significant pain, interference of pain with daily life, and parental emotional wellbeing. During effectiveness testing, 158 families were randomized into two groups (intervention group: app, control group: care as usual). Throughout the study, HCP's from the hospital's pain service (doctors, nurses and anaesthesiologists specialized in pediatric pain treatment) called families when clinically significant pain scores were reported in the app. The control group received care as usual. Approval for the study was obtained from the institutional research ethics committee. This study ran between February 2021 and August 2022 (18 months).

Action cycle: Adapt app to local context

Adaptations were made to the app based on feasibility study outcomes in previous action cycle under heading 'Evaluate outcomes + Select/tailor implementation strategies' of phase 3 (also see Table 1).

Action cycle: Select/tailor implementation strategies

In order to further facilitate proper use of the app during the RCT of the app, HCP's of the Hospital's pain service were once more given an (updated) training on working with the app, and all new app users (HCP's and families) were provided with a written manual and technical support throughout the study (e.g. to solve problems downloading app, logging in, and reporting pain scores). This time, families were also provided with a flyer on app functionalities and setting (only to be used at home, not during hospitalization).

Action cycle: Monitor app use

In total, families reported fifty clinically significant pain scores using the app, of which eight were cancelled by the family before they were contacted by a HCP. They did not have to indicate a reason, but based on feedback from parents after study completion, we expect that they did not require contact with a HCP as they knew how to handle the pain. The remaining 42 clinically significant pain scores were reported by 23 different

families: 29% of the intervention group reported at least one clinically significant pain score via the app. In 52% (n=22/42), families were contacted by a HCP within the set timeframe (i.e. within 2 hours for scores 4-6 and within 30 minutes for scores 7-10); for the remaining incidences HCP's did not respond within the intended time frame. HCP adherence to contacting families within the set timeframe was lower during effectiveness testing (52%) compared to feasibility testing (70%). This is an important barrier for future implementation, and a goal was formulated to improve adherence (see sub-heading 'evaluate outcomes + select/tailor implementation strategies').

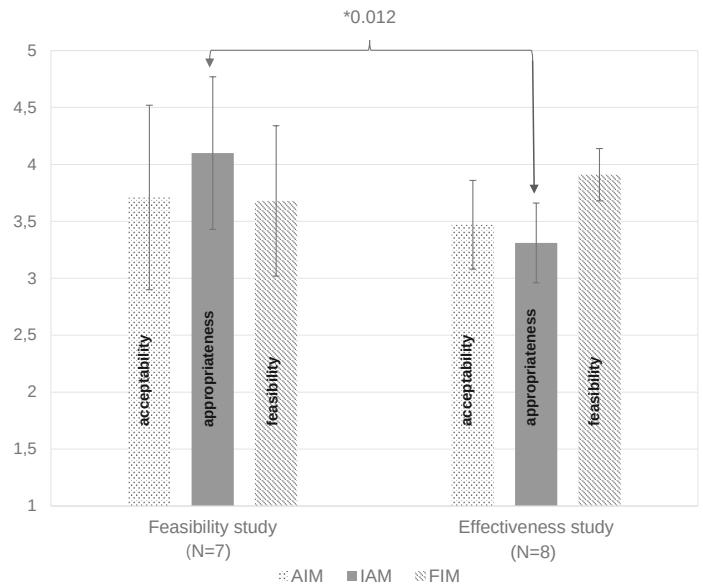
Action cycle: evaluate outcomes

With regard to effectiveness of the app in reducing pain at home: families in the intervention group reported less clinically significant pain compared to the control group (statistically significant difference)[30]. The fact that the app is evidence based, is an important facilitator for future implementation.

Action cycle: Assess determinants of future implementation of app (aim 2)

After study completion, we repeated the questionnaires (AIM, IAM, FIM, MIDI) with HCP's who were at that point employed at the hospital's pain service (n=8). Three of them were also employed at the pain service during feasibility testing and thus, completed the

Figure 4. HCP's mean group scores on acceptability, appropriateness, and feasibility of the app after feasibility (phase 3) and effectiveness (phase 4) studies



Note. AIM = Acceptability of Intervention Measure, IAM = Intervention Appropriateness Measure, FIM = Feasibility of Intervention Measure. *Significant at α = .05. Standard deviations (SD) indicated with error bars.

Figure 5. HCP's responses to MIDI-items after feasibility (phase 3) and effectiveness (phase 4) studies

Note. MIDI = Measurement Instrument for Determinants of Innovations. 'It' = *KLIK Pijnmonitor app*. If ≥30% disagreed with a statement, it was considered a barrier. If ≥70% agreed with a statement, it was considered a facilitator. Items with * are formulated negatively and therefore interpreted the opposite way.

questionnaire for the second time. So in total, determinants were assessed in 12 different HCP's. See Figures 4 and 5 for the results and a comparison between the assessments after feasibility testing (phase 3) and effectiveness testing (phase 4).

Overall, HCPs were positive about acceptability, appropriateness and feasibility of the app during phase 3 and 4 (AIM, IAM, FIM questions). No significant changes over time were found in acceptability and feasibility, but a significant difference on mean appropriateness was found between phase 3 (mean: 4.1) and phase 4 (mean: 3.3) (Beta = -1.42; 95% CI -2.47; -0.36) (p=.0012), indicating a decrease in appropriateness (large effect size).

HCP's attitudes on personal (dis)advantages of the app and organizational factors (MIDI questions) improved on 7 out of 10 items between phase 3 and 4. For two items (related to workload and sufficient staff to use app), HCP's attitudes worsened. One item (*"Working with the app will cause me to spend a lot of time responding to high pain scores"*) was still considered a barrier for implementation. In total, three facilitators (related to value for pain care) and two barriers (related to workload) were reported by HCP's at the end of effectiveness testing (phase 4).

Action cycle: Evaluate outcomes + Select/tailor implementation strategies

Based on the outcomes of the feasibility and effectiveness studies, and the identified determinants of implementation (barriers and facilitators) throughout the entire project, recommendations were made to prepare for the next steps: implementation of the app (**V4.0**) in routine clinical care at the Princess Máxima center for pediatric oncology. These recommendations are described in the discussion-section of this paper.

DISCUSSION

The current paper describes the project phases of a digital health tool to monitor pain in children with cancer through an implementation lens, using KTA (aim 1). It furthermore explores which determinants (barriers and facilitators) influence implementation outcomes (aim 2).

Using KTA has enabled us to zoom out, and continuously keep focussing on the ultimate project goal: implementation of the app into routine clinical care. It constantly focused our attention: 'What do we need to do right now, to make implementation go more smoothly in the future?' In long-term research projects consisting of multiple phases, one of the many pitfalls is having tunnel vision and forgetting about the bigger picture.

People tend to make unsubstantiated decisions, rather than decisions based on evidence. KTA is a tool that supports researchers to avoid this. Moreover, using KTA has enabled us to identify determinants (barriers and facilitators) of implementation early on, when adaptation of the app and/or care processes involved was still possible. Early identification of determinants led to detailed and focused action points. For instance, before feasibility testing, the app was adapted to the local context based on prior pilot testing ('debugging phase') with the project group; and before effectiveness testing, we adapted the app based on feasibility testing experiences. Systematic assessment of determinants of implementation provided us with a detailed overview of the existing barriers and facilitators after each study. We could then monitor the effects of our actions, and decide whether additional steps were necessary. This way, KTA prevented escalation of barriers, and strengthened facilitators. In our view, a strength of this project is that we implemented this approach in such an early stage.

Based on the results of the clinical studies, the lessons learned throughout the entire research project (aim 1), as well as the barriers and facilitators of implementation mentioned by HCP's (aim 2), we have made the following recommendations to facilitate successful implementation and sustainable use of the *KLIK Pijnmonitor app* in routine clinical care.

With regards to barriers, after feasibility testing (phase 3), issues with technical functioning of the app were mentioned. Successful actions were taken by the team to resolve the technical issues, and this barrier did not come up again after effectiveness testing (phase 4). Two important barriers that still remain after phase 4, are HCP adherence to follow-up with families within the set timeframe (70% phase 3; 52% phase 4), and HCP fear of increased workload, which will potentially hinder implementation. HCP adherence decreased over time, even though the number of patients and reported pain scores that required follow-up in the feasibility and effectiveness studies were similar (average 2-6 scores per month). With regards to fear of increased workload: the number of HCP's working with the app was scaled up after feasibility testing, and thus we expected this barrier to be remedied. The fact that both barriers still exist after phase 4 may be related to organizational change (hospital opened its doors in 2018), and an unsettled work environment (high rate of staff turnover due to COVID-19, long-term illness, maternity leaves). The decrease in HCP-reported appropriateness of the app (i.e. the app seems fitting/suitable/applicable/like a good match) between phases 3 and 4 might also be attributable to this unstable context [24].

What might ameliorate these barriers (HCP adherence, HCP fear of increased workload) is to let families indicate in the app whether they want to be called by HCP (yes/ no).

Families reported that they did not always need to be called by a HCP, as in some cases they knew what to do already. Adding this option might reduce HCP workload. Moreover, we recommend multiple interactive sessions including all relevant stakeholders (e.g. a patient and parent representative, HCP's, head of the care unit, and the researchers involved) to brainstorm for potential solutions. To achieve successful implementation, it is imperative that all stakeholders, and especially end-users of the app (i.e. families and HCP's) are involved and feel heard, as this will likely achieve buy-in, the development of novel solutions, and the identification of local champions[36]. Several reviews stress the importance of a user-centered approach, as underrepresentation of end-users might lead to innovations that do not meet their needs[3,9,22,37,38]. To promote equal representation of stakeholders during these meetings, it is advised that an external, objective party will chair these sessions. KTA's action cycle can be used to carry out the abovementioned targeted actions to improve implementation (Figure 2, phase 5). Furthermore, standardized worksheets can be used during these meetings for the prioritization of determinants[39].

It is important to recognize that our findings on barriers are in line with our previous research on determinants of implementation of a digital health tool. Barriers mentioned by HCP's mainly related to the organization (organizational change), and less frequently to users (motivation to comply) or the innovation itself (compatibility)[40,41]. Organizational barriers ('insufficient time available', 'too few financial resources') were also mentioned most frequently by project leaders in a review we carried out on digital health tools for pain in pediatric oncology worldwide[22]. This underlines the importance of addressing the issue of time and funding at an early stage, and making a realistic estimation based on previous research on the time and effort it takes to successfully implement innovations in clinical practice. There seems to be an imbalance between funding spent on developing innovations versus implementing these innovations into care. Changing the mindset of those able to make a real change (e.g. boards of directors, funding organizations) in order to decrease the knowledge-to-practice gap should be the top priority of research institutions.

HCP's mentioned three facilitators after effectiveness testing, all relating to the app's added value for pain care. Between feasibility (phase 3) and effectiveness testing (phase 4), HCP's attitudes towards working with the app improved on almost all fronts, and importantly, HCP's said that working with the app fits their job description. In addition, the app was proven evidence based: it was deemed feasible (i.e. learnable, usable and desirable) by end-users[29], and effective in reducing pain in the home setting[30]. Proven effectiveness of the app is an important facilitator for implementation in routine clinical care, as it can motivate HCP's, such as oncologists and nurses, to refer patients to the

KLIK Pijnmonitor app team. Results of the effectiveness study should therefore also be discussed during stakeholder meetings, as evidence for added value has been proven an important prerequisite for behavior change in HCP's[36].

CONCLUSIONS

We believe that the process of moving knowledge into action will come along more smoothly by using KTA to guide implementation efforts from, or even before, the start of new projects. It has motivated us to assess determinants of future implementation consistently throughout the project, and has enabled us to assess whether our efforts to remedy barriers, and maintain facilitators, were successful. As a result of this method, we were able to make detailed recommendations to facilitate successful implementation and sustainable use of the *KLIK Pijnmonitor app* in routine clinical care, and thereby, improve pain management in pediatric oncology.

LIST OF ABBREVIATIONS

AIM: Acceptability of Intervention Measure
FIM: Feasibility of Intervention Measure
HCP: Healthcare Professionals
IAM: Intervention Appropriateness Measure
KTA: Knowledge-to-Action
MIDI: Measurement Instrument for Determinants of Innovations

APPENDIX 1.

Dutch translation of the AIM, IAM and FIM scales

Dutch translation of a copyrighted version of the Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM) by Weiner et al., (2017)[1]

J.D.H.P. Simon, A.S. Darlington, and M.A. Grootenhuis

All items are rated on a 5-point Likert scale: 1 = completely disagree (*helemaal mee oneens*), 2 = disagree (*mee oneens*), 3 = neither agree nor disagree (*noch mee oneens, noch mee eens*), 4 = agree (*mee eens*), 5 = completely agree (*helemaal mee eens*).

Original	**Dutch translation**
Acceptability of Intervention Measure (AIM)	*Aanvaardbaarheid van de interventie (AIM)*
1. (insert intervention) meets my approval	1. De [interventie] krijgt mijn goedkeuring
2. (insert intervention) is appealing to me	2. De [interventie] spreekt mij aan
3. I like (insert intervention)	3. Ik ben positief over de [interventie]
4. I welcome (insert intervention)	4. Ik verwelkom de [interventie]
Intervention Appropriateness Measure (IAM)	*Geschiktheid van de [interventie] (IAM)*
1. (insert intervention) seems fitting	1. De [interventie] lijkt passend
2. (insert intervention) seems suitable	2. De [interventie] lijkt geschikt
3. (insert intervention) seems applicable	3. De [interventie] lijkt toepasbaar
4. (insert intervention) seems like a good match	4. De [interventie] lijkt een goede match
Feasibility of Intervention Measure (FIM)	*Haalbaarheid van de [interventie] (FIM)*
1. (insert intervention) seems implementable	1. De [interventie] lijkt implementeerbaar
2. (insert intervention) seems possible	2. Inzet van de [interventie] lijkt mogelijk
3. (insert intervention) seems doable	3. Inzet van [interventie] lijkt uitvoerbaar
4. (insert intervention) seems easy to use	4. De [interventie] lijkt makkelijk in gebruik

1 Weiner, B. J., Lewis, C. C., Stanick, C., Powell, B. J., Dorsey, C. N., Clary, A. S. & Halko, H. (2017). Psychometric assessment of three newly developed implementation outcome measures. *Implementation Science*, *12*(1), 108.

APPENDIX 2.

MIDI-items

All items were answered on a 5-point Likert scale (1 = completely disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, 5 = completely agree). Higher scores indicated more positive attitudes towards the intervention. Items with * are formulated negatively and therefore interpreted the opposite way: high score indicates negative attitude.

Determinants associated with the user

Personal benefits/drawbacks

Description: Degree to which using the *innovation* has advantages or disadvantages for the users themselves. Composite measure: the product of *importance* and *probability*

These questions about the importance and probability are asked for each objective separately.

Personal benefits

1. Use of the KLIK Pijnmonitor app will give me better insight in pain at home
2. Use of the KLIK Pijnmonitor app will enable me to intervene with pain at home more efficiently
3. Use of the KLIK Pijnmonitor app will ensure that pain can be tackled at an earlier stage (preventative)

Personal drawbacks

4. *****Use of the KLIK Pijnmonitor app will cause me to spend a lot of time responding to reported high pain scores
5. *****Use of the KLIK Pijnmonitor app will distract from my daily work at the hospital
6. *****Use of the KLIK Pijnmonitor app will cause an increase in workload

Professional obligation

Description: Degree to which the innovation fits in with the tasks for which the user feels responsible when doing his/her work.

7. I think working with the KLIK Pijnmonitor app fits my job description

Determinants associated with the organization

Staff capacity

Description: Adequate staffing in the department or in the organisation where the innovation is being used.

8. There is sufficient staff available to use the KLIK Pijnmonitor app as intended

Time available

Description: Amount of time available to use the innovation.

9. Our organization provides me with enough time to integrate the KLIK Pijnmonitor app in my day-to-day work.

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7

Chapter 7

Summary and General Discussion

The *RELIEF project's* main aim was to improve pain management of children with cancer at home. To achieve this, three sub-aims were formulated: first, to explore pain prevalence in children with cancer at home (chapter 2); second, to develop and test feasibility (chapter 3) and effectiveness (chapter 4) of a pain monitoring app for the home setting (the *KLIK Pijnmonitor app*), and third, to assess barriers and facilitators of implementation of digital health tools in clinical care (chapters 5 and 6).

This final chapter provides a summary of the main findings of the thesis, followed by implications for clinical practice and future research, strengths, methodological considerations and limitations of the research, and a conclusion. An overview of the studies and main findings presented in this thesis are also summarized in Table 1.

SUMMARY OF MAIN FINDINGS

Chapter 2 describes an explorative clinical study with 73 children (or one of their parents) with cancer (between 0 and 18 years old) receiving chemotherapy at the outpatient clinic. Pain severity, pain prevalence, analgesic use, and pain interference with daily life were assessed.

Results show that the prevalence of clinically significant pain in children with cancer receiving outpatient care was 78% (*main research question*), and that in roughly one third (33.6%) of clinically significant scores, no medication was used to manage the pain. We also found an association between pain interference and pain severity (the higher the pain, the more interference). We concluded that pain management at home was suboptimal [1].

Chapter 3 explores feasibility of the *KLIK Pijnmonitor app* in the home setting. In addition to feasibility, we assessed user (families' and healthcare professionals') adherence to the app, user experiences with the app, and determinants of implementation. In total, 27 children (or one of their parents) with cancer (between 0 and 18 years old) participated.

Outcomes reveal feasibility for the majority of app functions (i.e., positive evaluation by ≥ 70% families/healthcare professionals), and non-feasible aspects could be resolved (*main research question*). With regards to end-user adherence to the app: families reported their pain on a daily basis, and healthcare professionals followed-up within the set timeframe in 70% of clinically significant pain scores. During interviews with the end-users, several barriers and facilitators of implementation were identified. Barriers mainly related to time consumption and increased workload (healthcare professionals)

and to technical problems with daily reminders (families). Facilitators mainly related to experienced improved care for patients, and user friendliness of the app (healthcare professionals and families) [2].

Chapter 4 describes a Randomized Controlled Trial (RCT) to assess effectiveness of the *KLIK Pijnmonitor app* in reducing clinically significant pain at home. We also assessed whether use of the app affected different aspects of pain (duration, interference, pain management strategies), and parental emotional wellbeing. Finally, we evaluated the app with users and asked which specific app functionalities were most relevant to them. In total, 158 children with cancer between 0 and 18 years old (or one of their parents) participated. Moreover, 126 parents completed questionnaires on their own emotional wellbeing (with regard to distress, anxiety, depression, anger).

Outcomes show that use of the app in the intervention group resulted in less clinically significant pain (29%) compared to the control group (52%) (*main research question*), and that pain severity was lower in the intervention group in general. Parents in the intervention group reported significantly less distress on the emotional wellbeing questionnaire compared to the control group. No significant differences were found for pain duration, interference, and pain management strategies. Families indicated that 'healthcare professionals call when I report high pain' was the most relevant feature of the app.

Chapter 5 discusses the findings of a scoping review in which we systematically identified and characterized existing digital health tools (specifically mobile health/mHealth) for pain monitoring in children with cancer. Moreover, through semi-structured interviews with project leaders of these interventions, common barriers and facilitators of implementation were assessed.

Through the review, we identified 14 mHealth tools (apps *n*=13, wearable wristband *n*=1) (*main research question*). Most publications on these tools focused on feasibility/acceptability testing, but very few publications on the effectiveness and/or implementation were available. Results of interviews with project leaders revealed that most barriers related to the organizational context (47% of barriers), with financial resources and insufficient time available mentioned most often. Most facilitators related to end-users (56% of facilitators), with end-user cooperation and end-user satisfaction mentioned most often (*main research question*). Thus, taking into account realistic funding expectations and involving end-users during early stages of new projects, might prevent future digital health tools from ending up unused [3].

Finally, **chapter 6** uses implementation science (Knowledge-to-Action framework) to guide the process of translating research into practice. This chapter also describes barriers and facilitators that may influence future implementation of the app in the Princess Máxima Center, based on healthcare professional's attitudes.

Based on the outcomes of this study, and the identified barriers and facilitators throughout the RELIEF project, we were able to make changes and detailed recommendations to facilitate successful implementation of the *KLIK Pijnmonitor app* in clinical care. After effectiveness testing, two barriers (healthcare professionals' adherence to follow-up within set timeframe and healthcare professionals fear of increased workload) and three facilitators (all relating to the app's added value for pain care) remain, and require further attention before implementation in clinical care can take place (*main research question*). KTA has motivated us to assess determinants of future implementation consistently throughout the project, and enabled us to assess whether our efforts to remedy barriers, and maintain facilitators, were successful [4].

IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

Pain assessment: when and how?

In the past, research on pain in children with cancer has mainly focused on hospitalized children [5]. When pain was assessed at home, either the youngest population (0-4 or 0-8 year old children) was completely disregarded [5-8], or only parent proxy reporting was used to assess pain [6]. Self-reports are the preferred method of use given the highly subjective nature of pain [9]. The studies described in chapters 2, 3 and 4 of this thesis are one of the first studies to zoom in on pain in children with cancer of all ages (0-18 years old) in the home setting, while using self-reports whenever possible.

Digital health tools using patient-reported outcomes (PROs) to assess symptoms have gained popularity in pediatric oncology in recent years [10-16]. However, these tools vary in the frequency in which symptoms are assessed. For instance, the KLIK PROM method [17] prompts patients and/or parents to complete a health-related Quality of Life (HRQoL) questionnaire (includes one item on pain) every three months, so the outcomes can be discussed with a pediatric oncologist during hospital visits. Another example is the ePROtect [18] app, which assesses children's symptom burden on a daily basis. During feasibility testing of the *KLIK Pijnmonitor app* (chapter 3), we instructed families to report pain intensity twice daily at set times for which they received reminders in the mornings and evenings. However, family-adherence to follow these instructions was low (18.5%), and some families participating in that study said that they did not want to be reminded

about pain, especially when pain was not present. Studies have revealed reduced pain perception in patients being distracted from pain [19-21]. Increasing families' attention to pain by sending them daily reminders was hypothesized to have the opposite effect (i.e. increased pain perception). And thus, we decided to make pain reporting volitional (only when deemed necessary by patients) during effectiveness testing of the *KLIK Pijnmonitor app* (chapter 4). Families did have the option to activate daily reminders in the app if desired. For future iterations of the app, we recommend to maintain this approach.

One aspect that could be optimized in the future is, is the timing at which the app is provided to families. Due to organizational restrictions, we were only permitted to include patients three months after diagnosis for effectiveness testing of the app. Throughout the Randomized Controlled Trial (RCT), we received feedback from some parents that they did not always need to be contacted by a healthcare professional when their child experienced high pain, as they knew what to do themselves. Several participants in the feasibility as well as the effectiveness studies said that the app would have been more useful to them right after the diagnosis, as they knew far less about pain(management) at that stage.

We also recommend to translate the app to fit a broader range of languages (currently only available in Dutch), and cultures. Moreover, the app has the potential to monitor a broad range of symptoms. For instance, appetite loss, fatigue, nausea, cognitive impairments, decreased physical functioning and sleep quality are very common in pediatric cancer in addition to pain [8]. Many of these symptoms, and pain in particular, are also highly prevalent in other pediatric illnesses such as sickle cell disease [22], juvenile idiopathic arthritis (JIA) [23], and inflammatory bowel disease (IBD)[24]. Future studies on expansion of the app to a broader range of symptoms and patient populations are warranted. If and when such expansions are realized in the future, the implications for the involved stakeholders, and healthcare professionals in particular, should first be carefully explored and discussed.

PSYCHOEDUCATION ON PAIN(MANAGEMENT)

We did not only assess pain severity, but we looked at pain management strategies as well. The outcomes of the exploratory study on pain at home (chapter 2) show that pain was suboptimally managed by families. A previous study found a link between parental misconceptions regarding analgesic use for children and low administration of pain medication [7]. We also know there are a lot of fears and misconceptions among parents about pain(treatment) in children: many parents think children only express

pain through active, loud, and attention seeking behavior, as opposed to being quiet or withdrawn [25]. Moreover, some parents think pain is unavoidable during cancer [26], that pain medication is addictive, and works optimally when given as little as possible [27]. And thus, we believe psychoeducation on cancer-related pain (treatment), as well as routine screening for pain using PRO's [28] plays an essential role in improving pain management of children with cancer at home.

The current version of the *KLIK Pijnmonitor app* provides users with text-formatted psychoeducation on cancer-related pain (causes and consequences), pain management strategies applicable to the home setting (both pharmacologic and non-pharmacologic), and possible side effects of pharmacologic interventions. In future iterations of the app, the psychoeducational information could be complemented with images and/or explanatory videos illustrating useful pain interventions (e.g. relaxation techniques) and causes and consequences of pain. Prior research on multimedia learning has shown that text combined with visuals are more effective compared to text alone. Visuals help us make sense out of content and directs our attention, increasing the possibility that learners will remember the material [29]. It is also recommended to add this information to a broader range of (media) outlets for families such as the hospital's website, social media platforms and paper flyers.

Another element that might have a positive impact on learning and remembering psychoeducational information and applying it to in daily life, is gamification. Gamification is defined as adopting game elements to improve user experience and engagement in non-game contexts [30], and it is believed that this increases people's engagement, motivation, and the retention of learned skills [31,32]. For instance, users may receive virtual rewards (e.g. points, badges) after having watched a certain number of instructional videos. Two existing digital health tools aimed at better pain management in pediatric oncology (Pain Buddy [33] and Pain Squad +[34]) include gaming elements (reward system for adherence, use of avatars/roles users can play). However, data on these tools' effectiveness has not been published yet. Future research should assess the effectiveness of using visual- and gaming elements to increase learning of psychoeducational information via digital health tools.

And finally, we believe that including pain science education (PSE) in future iterations of the app will be a valuable addition. PSE is aimed at changing patients' understanding of the biopsychosocial aspects (biological, psychological and environmental factors) of pain [35], and it has led to decreased pain intensity and pain catastrophizing in adult cancer survivors with chronic pain [36]. Moreover, a PSE video intervention in healthy children led

to decreased recalled pain intensity compared to a control group [37]. PSE holds promise for children with cancer and survivors as well [28].

PLACEBO?

The outcomes of the RCT described in chapter 4 show that the *KLIK Pijnmonitor app* was effective in reducing clinically significant pain in the home setting. Interestingly, although clinically significant pain incidence was lower in the intervention (app) group, there was no significant difference in the use of pain management strategies (pharmacological or non-pharmacological) nor in the duration of pain between the intervention and control group when clinically significant pain did occur. And thus, one of our hypotheses is that 'placebo induced hypoalgesia' played a role here. This refers to the reduction of the pain experience as a result of cognitive modulations [38] such as the expectation of a beneficial or therapeutic outcome of an intervention [39].

Another possible explanation lies in Bowlby's attachment theory, which suggests that attachment figures (in this case the healthcare professionals) serve as a kind of safety signal ("I will be taken care of"), and their presence promotes courage, as opposed to fear in the absence of this figure [40]. As we know that fear can increase pain experience through physiological and psychological pathways [41-43], it is important to take the *KLIK Pijnmonitor app's* influence on children's and parent's levels of fear and their sense of safety into account.

A third rationale behind the lower prevalence of pain in the intervention versus control group, despite the lack of difference in the use of pain management strategies between the two groups, lies in the sense of control families experienced. Pain perceptions are modulated by cognitive and emotional variables among which controllability of pain [44]. Previous studies have shown that pain is perceived as less intense when someone can exercise some form of control over it [45-47]. It might be that simply having the app at their disposal, and knowing that help was on standby whenever they asked for it, provided families with an increased sense safety and control, thereby decreasing children's pain intensity.

PARENTAL DISTRESS

The theory of an increased sense of safety and control elicited by the app might also explain the lower levels of distress found in parents in the intervention group. It is known

that parental responses to children's pain influence the development and maintenance of pain (i.e. overly protective parents or parents critical of pain may cause higher symptom burden for their children) [48]. Thus, lower parental distress might have played a central role in the reduced pain intensity of children in the intervention group. Of course, it might also be that parents in the intervention group reported lower distress because their children reported less pain. Future studies should aim to identify the exact working mechanisms behind the effect of having a pain monitoring app at your disposal on pain intensity.

Previous research revealed that parental distress and emotional issues negatively influence the child's cancer treatment, their ability to support the child and their siblings, and threaten family stability [49-52]. And thus, assessment of parental mental health needs and providing access to appropriate interventions should continue to be an important point of focus during childhood cancer treatments in the future [53].

AUTOMATED VERSUS HEALTHCARE PROFESSIONAL FEEDBACK

Despite the relatively low healthcare professional adherence to call families within set timeframes (52% on time), use of the app still resulted in less clinically significant pain compared to the control group. This raises the question whether real-time feedback from healthcare professionals is necessary for all clinically significant pain scores. Families said that in some cases, they already knew what to do based on previous experiences or advice they received. And thus, families should be able to indicate whether they want to be called (yes or no) in future iterations of the app. This will also most likely decrease healthcare professional workload, which has been the most commonly reported barrier of (future) implementation throughout the *RELIEF project*.

Furthermore, future research should explore the possibilities of algorithm-informed feedback (i.e. automatically computed responses based on patient's data enabling personalisation of recommendations [54]). One recent publication on a remote symptom management app including algorithms to determine the level of concern and providing symptom management advice for families of children with cancer was positively evaluated (i.e. usable, acceptable) by beta testers [55]. Nonetheless, it is important to keep in mind that families rated 'healthcare professionals call when I report high pain' as the most relevant functionality of the *KLIK Pijnmonitor app*. This is also stressed by the outcomes of a review on the benefits of mobile apps for cancer pain management (mostly for adults) which revealed that apps with an 'instant messaging module' (i.e. a channel for real-time communication between patients and medical staff) significantly reduced

patient's pain scores, as opposed to apps without such modules [15]. Moreover, patients using apps with instant messaging modules saw a greater increase in QoL and decrease in pain catastrophizing [15]. And thus, the *KLIK Pijnmonitor app* should always maintain a certain level of 'human-ness' in future iterations. A blended-care approach will likely result in the most optimal outcome for all end-users: a real-time communication option with healthcare professionals for critical pain scores will remain, but should be made optional to families. For lower, less critical scores, algorithm-informed feedback might provide families with sufficient information to manage the pain themselves.

With regards to algorithm-informed feedback, there might also be a role for artificial intelligence (AI) technology in the future. A preliminary study assessed medical knowledge of a language based AI (ChatGPT) in comparison to that of expert human clinicians, and found promising results indicating that this technology has the potential to assist in clinical decision-making in the future [56]. However, these technologies are not ready to provide reliable medical advice yet, and should be handled with extreme caution. Nonetheless, use of AI in healthcare will undoubtedly become a widely studied field of research, as it holds great potential to make healthcare more efficient and cost-effective[56].

COST EFFECTIVENESS

Cost-effectiveness of digital health tools like the *KLIK Pijnmonitor app* should also be closely monitored. Cancer-related pain can be a big financial burden to families [57] as well as healthcare systems [58]. For instance: pain is the most common symptom seen by emergency health services in adult cancer patients, for whom over half of the ER visits result in hospital admission [59]. As a result of improved survival rates in pediatric cancer [60], the care expenses are expected to rise due to an increased need for prolonged treatment of symptoms such as pain [61-63]. Thus, not only curing cancer, but proper management of cancer-related adverse effects is an important goal for public health as well as the economy. A growing body of evidence in adult cancer patients suggests that timely monitoring of symptom burden can improve survival rates and the QoL of patients [64-66], and thereby benefit the health economy [61]. And thus, widespread use of digital symptom monitoring tools that enable care at a distance, have a strong focus on symptom (worsening) prevention, and educate and empower families, may decrease hospital admissions and public health expenses in the future.

AND NOW..

Results of the RCT has provided us with evidence that the *KLIK Pijnmonitor app* can reduce pain at home [67]. However, in order for the app to reach its full potential, it first needs to be successfully implemented in clinical care. This final step is often neglected: previous studies revealed that the majority of digital health tools are not available to patients in the real-world setting (i.e. research-to-practice gap) [68,69]. A key pillar of implementation science lies is the assessment of barriers and facilitators of implementation. Thus, throughout the *RELIEF project* key stakeholders (families and healthcare professionals working with the app) (chapter 6), as well as project leaders of similar digital health tools aimed at pain management in pediatric oncology (chapter 5), were inquired about their experiences in order to identify and act on existing barriers and facilitators.

After effectiveness testing was completed, two barriers (healthcare professionals' adherence to follow-up within set timeframe and healthcare professionals fear of increased workload) and three facilitators (all relating to the app's added value for pain care) remain. Chapter 6 includes detailed recommendations to guide further steps towards successful implementation of the *KLIK Pijnmonitor app* in clinical practice based on the Knowledge-to-Action (KTA) implementation framework [70]. In addition, it is important to keep the following aspects in mind:

When implementing and/or scaling up the use of innovations, the following five domains described by the Consolidated Framework for Implementation Research (CFIR) [71] should be taken into account: 1) inner setting (e.g. organizational readiness for implementation), 2) outer setting (e.g. competitive pressure to develop innovations versus implementing existing ones), 3) intervention characteristics (e.g. legitimacy of who developed the intervention), 4) process (e.g. attracting and involving appropriate individuals in the implementation and use of the intervention), and 5) the characteristics of individuals (e.g. stakeholders' attitudes toward and value placed on the intervention). In order to address all of these domains and to carry out the required alterations to the app and processes involved (see recommendations, chapter 6), designated personnel is required to carry out all practical actions that come with use of the *KLIK Pijnmonitor app* in clinical care (e.g. serving as a main point of contact for internal and external questions regarding the app, training healthcare professionals, creating user accounts, transferring knowledge, handling data).

As PhD-trajectories often do not provide sufficient time to implement interventions in clinical care, many interventions are at risk of ending up unused. In order to reduce research waste in the future, changes to academic and funding structures are required.

We strongly advise research groups to apply for implementation-specific grants, and to make implementation science a key component of healthcare institutions.

STRENGTHS, METHODOLOGICAL CONSIDERATIONS AND LIMITATIONS OF THE RESEARCH

Strengths

Firstly, the results described in chapter 4 of this thesis are the first definitive results on effectiveness of a digital health tool for pain monitoring using an RCT.

Another unique feature of this thesis lies in the application of an implementation framework (Knowledge-to-Action [KTA]), with help of the model's original developer (Ian Graham), to guide the *RELIEF project* from start to finish. As became evident in chapter 5 of this thesis (scoping review mHealth interventions for pain in pediatric oncology and interviews with project leaders), only one third of project leaders reported using a theoretical model for implementation in their projects. And even if they reported using a model, this does not mean they applied it in a meaningful way. To demonstrate, a systematic review on use of KTA in practice showed that 146 papers attributed use of the framework (i.e. referenced or informed by), however upon close examination, only 10 studies used KTA in an integrated way [72].

A strength also lies in the use of a mixed-methods design in most of the studies, including quantitative measures (questionnaires, app log-data, scoping literature review) as well qualitative measures (interviews with families, healthcare professionals and co-project leaders worldwide). This has yielded to more depth and breadth of data. For instance, the use of a scoping literature review to inform readers on the state of the field, combined with project leaders' personal experiences (interviews on common barriers and facilitators) has created rich, useful data providing valuable lessons for future researchers and clinicians.

Methodological considerations and limitations

There are some methodological considerations worth mentioning. Firstly, there is a discrepancy between the cut-off points we used for self-reporting versus proxy-reporting pain intensity (NRS-11) in chapter 2 (exploratory study pain at home) and chapters 3 and 4 (feasibility and effectiveness study). In chapter 2, pain intensity scores were provided by a parent/caregiver (for children aged 0-4), jointly (for children aged 5-8) or by the children themselves (aged 9-18). Whereas in chapters 3 and 4, a parent/caregiver provided pain intensity scores for children aged 0-7, and children aged 8-18 were asked

to self-report pain intensity. Parents were still allowed to help, but the focus for this age group lay on self-reports. The rationale behind our decision to start self-reporting at age 8 rather than 9, is the strong evidence supporting the reliability and validity of the NRS-11 as a self-report scale for pain intensity of children 8 years and up [73]. It is important to keep in mind that because these cut-offs were different, the outcomes of chapter 2 cannot be compared to the outcomes of chapters 3 and 4.

Another methodological consideration lies in the choice of instruments. We used the Brief Pain Inventory Short Form (BPI-SF), which has been validated for adults and been previously used in children. The Dutch language version was not formally validated in children. For the purposes of the *RELIEF project*, the Dutch language version was slightly adapted to children: instead of asking to what degree the pain has interfered with normal work (original BPI-SF), we asked how the pain interfered with school/playtime/hobbies.

We also used the Acceptability (AIM), Appropriateness (IAM), and Feasibility (FIM) of Intervention Measures [74] to assess healthcare professionals attitudes towards the *KLIK Pijnmonitor app*. Although the Dutch translation showed sufficient internal consistency (range between .76 and .85), some healthcare professionals said that some questions were difficult to interpret and make a distinction between questions as they seemed very similar.

With regards to the representativeness of participants, caution is warranted regarding the generalizability of these results to children and parents of other nationalities since the app was only available in Dutch at this stage. In the future, translations are planned. Furthermore, no sociodemographic data of participating families was available (migration background, educational level, parents' marital status), and thus, no conclusions can be drawn on the possible impact of these factors on the outcomes. For instance, for children of divorced parents who had to alternate between houses, it might have been more difficult to adhere to using the app.

And finally, it is important to take into account the context in which the *RELIEF project* took place: during centralization of pediatric cancer care to one pediatric hospital in The Netherlands. For this reason, the exploratory study on pain prevalence in the home setting (chapter 2) was carried out at the Sophia Children's Hospital in Rotterdam, while all other phases of the *RELIEF project* were carried out at the Princess Máxima Center in Utrecht. This big organizational change caused an unsettled work environment, which might have influenced the outcomes of the project, especially those relating to barriers and facilitators of implementation. For instance, organizational barriers (e.g. staff capacity, coordinator, time available) will have likely played a more prominent

Table 1. Overview of studies and main findings presented in this thesis

Chapter	Short title	Aim(s)	Participant characteristics	Outcome measures/Method	Main findings	Conclusion/take home
Sub-aim 1. To explore pain prevalence in children with cancer at home						
2	**Explorative study** on pain at home	To assess pain severity, prevalence of (clinically significant*) pain, analgesic use, and pain interference with daily life	N=73 children with cancer (all diagnoses, 1-18 years) receiving chemotherapy at the outpatient clinic	Brief Pain Inventory-Short Form (BPI-SF)	78% of children experienced clinically significant pain at least once*. In 33.6% of clinically significant scores, no medication was used. There was an association between pain interference and pain severity (the higher the pain, the more interference)	There is a high prevalence of clinically significant pain* at home, and pain management is suboptimal
Sub-aim 2. To develop and test feasibility and effectiveness of a pain monitoring app for the home setting (the KLIK Pijnmonitor app)						
3	**Feasibility study** of the *KLIK Pijnmonitor app*	To assess adherence to, feasibility of, and barriers and facilitators of implementation of the KLIK Pijnmonitor app	N=27 children with cancer (all diagnoses, 0-18 years); N=7 HCP's	Mixed-method design: feasibility questionnaire and log data from app (quantitative); qualitative semi-structured interviews with end-users (families, HCP's) on barriers and facilitators	18.5% Of families reported pain twice daily (family adherence). In 70% of high pain scores, HCP's followed-up within set timeframe (HCP adherence). The majority of app functions are feasible. Facilitators related to user friendliness, and barriers related to technical problems with daily reminders	App is user friendly, works well technically and use seems feasible in a clinical setting. Alterations to app and processes involved were needed to increase family and HCP adherence

Table 1. Overview of studies and main findings presented in this thesis (continued)

Chapter	Short title	Aim(s)	Participant characteristics	Outcome measures/Method	Main findings	Conclusion/take home
4	**Effectiveness study** of a pain monitoring app	To assess effectiveness of the KLIK Pijnmonitor app to reduce the amount of children experiencing clinically significant pain* at home	N=159 children with cancer (all diagnoses, 0-18 years) of which: n=79 intervention group n=79 in control group; N=126 parents; N=8 HCP's	Brief Pain Inventory Short Form (BPI-SF), Emotion Thermometer for parental distress (ET), Evaluation questionnaire app	The intervention group reported fewer clinically significant pain* scores compared to the control group, and pain severity was lower in the intervention group in general. Parents in the intervention group also reported significantly less stress	App is an effective tool for reducing clinically significant pain* at home during treatment, and it has a positive impact on parental stress
Sub-aim 3. To assess barriers and facilitators of implementation of digital health tools in clinical care						
5	**Scoping review** of digital health tools and barriers and facilitators of implementation	To identify and characterize existing digital tools for pain monitoring in children with cancer, and to assess common barriers and facilitators of implementation	N=13 project leaders of digital health tools	Mixed-method design: scoping review (quantitative), semi-structured interviews (qualitative)	14 tools identified (apps *n*=13, wearable wristband *n*=1). Most barriers of implementation related to the organization (financial resources, insufficient time available). Most facilitators related to end-users (cooperation, satisfaction)	Very few publications on effectiveness and/or implementation of digital health tools are available
6	**Implementation study** of a digital health tool	To describe the use of implementation science (KTA framework) to guide the process of translating research into practice, and to assess barriers and facilitators in HCP's after feasibility and effectiveness testing	N=12 HCP's (7 after feasibility testing and 8 after effectiveness testing, of which 3 overlap)	Acceptability (AIM), Appropriateness (IAM), and Feasibility (FIM) of Intervention Measure, and Measurement Instrument for Determinants of Innovation (MIDI)	KTA motivated us to assess barriers and facilitators throughout the project, and monitor whether our efforts to remedy barriers, and maintain facilitators, worked. Two barriers (HCP adherence and HCP fear of increased workload) and three facilitators (app's added value for pain care) remain at the end of effectiveness testing	KTA increases the chance of successful implementation and effective use of innovations in clinical care

Note. *Clinically significant pain defined as score of ≥ 4 on an 11-point NRS-scale (0-10). HCP's = healthcare professionals. KTA = Knowledge-to-Action

role than in hospitals that are up and running, and this may have negatively influenced healthcare professionals attitudes towards getting used to yet work-related innovation.

CONCLUSION

This thesis demonstrates that use of the *KLIK Pijnmonitor app* is feasible in children with cancer and their families, and proves that it is effective in reducing children's pain at home. These findings are of great value for daily clinical practice, as pain is one of the most common and distressing adverse effects that children may experience during cancer treatment [6-8,26,62,75]. Unmanaged pain not only negatively impacts the QoL of children [76,77], but that of their parents as well [77-80]. Thus - when implemented properly - the *KLIK Pijnmonitor app* not only decreases pain, but it can also positively influence the QoL of children and their families. The *RELIEF project* has opened up a wide range of opportunities for the development and use of digital symptom monitoring tools in the future, not only in pediatric oncology, but in a wide range of pediatric and adult illnesses as well.

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Chapter 8

Nederlandse Samenvatting

In **hoofdstuk 1**, de algemene inleiding, worden de achtergrond, de opzet en de doelen van het *RELIEF project* beschreven. Het project is vernoemd naar de Engelse vertaling van pijnvermindering (pain relief). Pijn is een van de meest gerapporteerde en stressvolle symptomen bij kinderen die worden behandeld voor kanker. Pijn die wordt ervaren tijdens de behandeling kan worden gecategoriseerd in 1) behandeling-gerelateerde pijn als gevolg van chemotherapie, bestraling of chirurgie, 2) pijn gerelateerd aan medische ingrepen, zoals lumbaalpuncties of beenmergaspiraties, en 3) ziekte-gerelateerde pijn als gevolg van de tumor zelf of de uitzaaiingen.

Omdat onderzoek naar pijn bij kinderen met kanker zich tot nu toe vooral heeft gefocust op de ziekenhuis-setting, is er nog maar weinig bekend over pijn in de thuissituatie. Wat wel bekend is, is dat ondanks het bestaan van wetenschappelijk bewezen interventies tegen pijn (zowel medicatie als alternatieven), de pijn thuis vaak nog niet goed wordt behandeld. Wat hierin onder andere meespeelt is gebrekkige kennis bij ouders over pijn(behandeling) en angsten over bijwerkingen van pijnmedicatie. Het op tijd aanbieden van ondersteunende (psycho)oncologische zorg, waaronder informatie over de oorzaken van en het omgaan met pijn, vergroot de kans op een betere kwaliteit van leven van kinderen en hun ouders.

Digitale zorg (zoals het gebruik van apps) kan de afstand tussen het ziekenhuis en het thuisfront overbruggen en zo pijnmanagement thuis verbeteren. Met behulp van digitale zorg kunnen symptomen thuis namelijk beter gemonitord worden en kan er sneller worden ingegrepen als dat nodig is. In de afgelopen jaren zijn er veel digitale zorg-interventies voor beter pijnmanagement ontwikkeld. Helaas wordt het merendeel van deze interventies niet gebruikt in de klinische praktijk. Dit wordt ook wel de wetenschap-praktijk-kloof ('research-to-practice gap') genoemd. Implementatie-wetenschap richt zich op het verkleinen van deze kloof en gebruikt methoden en theorieën om de vertaalslag van onderzoek naar gebruik in de klinische praktijk te verbeteren.

Het *RELIEF project* is opgezet om pijnmanagement van kinderen met kanker in de thuisomgeving te verbeteren. Om dit doel te bereiken, zijn drie subdoelen geformuleerd: ten eerste, het onderzoeken van de aanwezigheid van pijn in de thuissituatie bij kinderen met kanker (hoofdstuk 2), ten tweede, het ontwikkelen en testen van de haalbaarheid (hoofdstuk 3) en effectiviteit (hoofdstuk 4) van een pijnmonitoring-app voor thuis (de *KLIK Pijnmonitor app*), en ten derde, het beoordelen van de helpende en niet helpende factoren voor de implementatie van digitale zorg-interventies in de klinische zorg (hoofdstukken 5, 6). Het onderstaande figuur geeft de tijdlijn van het *RELIEF project* weer met bijbehorende hoofdstukken uit dit proefschrift.

In hoofdstuk 2 beschrijven we een exploratieve klinische studie naar de aanwezigheid van pijn in de thuissituatie bij kinderen met kanker. 73 Kinderen (of een van hun ouders) met kanker (tussen 0 en 18 jaar oud) die chemotherapie kregen op de dagbehandeling en verder thuis verbleven, deden mee aan het onderzoek. Naast het meten van de aanwezige pijn, hebben we gekeken naar de ernst van de pijn, medicatiegebruik en de invloed van pijn op het dagelijks leven.

Uit de resultaten kwam naar voren dat 78% van de kinderen wel eens klinisch significante ('ernstige') pijn had, en dat bij ongeveer een derde van alle ernstige pijnscores geen medicatie werd gebruikt om de pijn te verminderen. We vonden ook dat de intensiteit van pijn van invloed was op het dagelijks leven van kinderen met kanker: hoe hoger de pijn, hoe groter de invloed op hun dagelijks leven en daarmee hun kwaliteit van leven. We concludeerden dat pijnmanagement thuis niet optimaal was.

In hoofdstuk 3 wordt gekeken naar de haalbaarheid van het gebruik van een digitale zorg-interventie (de *KLIK Pijnmonitor app*), ontwikkeld om pijnmanagement bij kinderen met kanker (0-18 jaar) in de thuisomgeving te verbeteren. Naast haalbaarheid is er gekeken of gebruikers (gezinnen en zorgverleners) de app gebruikten zoals bedoeld ('adherence'), en onderzochten we niet helpende ('barriers') en helpende ('facilitators') factoren voor het slagen van toekomstig gebruik van de app in de klinische praktijk. In totaal deden 27 kinderen (of een van hun ouders) met kanker (tussen 0 en 18 jaar oud) mee aan het haalbaarheidsonderzoek.

Resultaten toonden de haalbaarheid voor de meerderheid van de app-functies aan (d.w.z. een positieve evaluatie door ≥ 70% van de families/zorgverleners). Daarnaast konden niet-haalbare app-functies worden opgelost. Met betrekking tot juist gebruik van de app: 18,5% van de deelnemende gezinnen rapporteerde twee keer per dag een pijnscore (tussen de 0 en 10) zoals gevraagd, en in 70% van de gerapporteerde ernstige pijnscores belden zorgverleners de gezinnen binnen de van tevoren vastgestelde tijdslimiet op. Niet helpende factoren voor toekomstige implementatie van de app hadden vooral te maken

met vrees van zorgverleners dat het reageren op pijnscores hen teveel tijd zou kosten en dat het zou leiden tot een verhoogde werkdruk. Een andere niet helpende factor waren de technische problemen met dagelijkse herinneringen die gezinnen ervoeren. Helpende factoren hadden vooral betrekking op verbeterde pijnzorg voor patiënten en gebruiksvriendelijkheid van de app (genoemd door zowel zorgverleners als gezinnen).

In **hoofdstuk 4** wordt een gerandomiseerd onderzoek (RCT) beschreven naar de effectiviteit van de *KLIK Pijnmonitor app* in het verminderen van ernstige pijn in de thuissituatie. Het onderzoek bestond uit twee groepen: een groep kreeg toegang tot de app (de interventiegroep) en de andere groep niet (controlegroep). Daarnaast is er ook gekeken naar het effect van de app op verschillende aspecten van pijn (hoelang de pijn duurde, de invloed op het dagelijks leven, pijnmanagement-strategieën) en het emotionele welzijn (waaronder angst en stress) van ouders. Ten slotte hebben we de app geëvalueerd met gebruikers (wat waren de nuttigste functies van de app?). In totaal deden 158 kinderen (of een van hun ouders) met kanker (tussen 0 en 18 jaar oud) mee aan het onderzoek. Daarnaast vulden 126 ouders vragenlijsten in over hun eigen emotionele welzijn.

De resultaten toonden aan dat gebruik van de app (door de interventiegroep) leidde tot minder ernstige pijnscores (29%) in vergelijking met de controlegroep (52%) en dat de intensiteit van pijn in het algemeen lager was in de interventiegroep. Ouders in de interventiegroep gaven daarnaast minder stress (‘distress’) aan in vergelijking met de controlegroep. Er werden geen verschillen gevonden tussen de twee groepen (interventiegroep/controlegroep) voor duur van de pijn, de invloed van pijn op het dagelijks leven en pijnmanagement-strategieën. Gezinnen vonden het feit dat zorgverleners hen belden nadat zij hoge pijnscores hadden gerapporteerd de meest nuttige functie van de app.

In hoofdstuk 5 wordt een verkennende review beschreven naar bestaande digitale zorg-interventies (specifiek: mobiele interventies zoals apps) voor pijnmonitoring bij kinderen met kanker. Daarnaast zijn projectleiders van bestaande tools bevraagd over de meest voorkomende niet helpende en helpende factoren voor implementatie van digitale zorg-interventies in de klinische praktijk.

Uit de review komen 14 mobiele zorg-interventies naar voren (apps n=13, draagbare polsband n=1). De meeste publicaties over deze interventies beschrijven haalbaarheids- of aanvaardbaarheidsstudies. Er waren zeer weinig publicaties over effectiviteit en/of implementatiesucces. Resultaten van interviews met projectleiders toonden aan dat de meeste niet helpende factoren gerelateerd waren aan de organisatorische context (47%

van de niet-helpende factoren). “Onvoldoende financiële middelen’ en “onvoldoende beschikbare tijd’ werden daarbij het vaakst genoemd. De meeste helpende factoren hadden betrekking op eindgebruikers (zorgverleners en/of gezinnen) (56% van de helpende factoren). Daarbij werden ‘medewerking van eindgebruikers’ en ‘tevredenheid van eindgebruikers’ het vaakst genoemd.

Hoofdstuk 6 beschrijft een implementatiestudie van de *KLIK Pijnmonitor app* waarin het Knowledge-to-Action (KTA) Framework wordt gebruikt om de vertaalslag van onderzoek naar gebruik in de klinische praktijk te begeleiden. Dit hoofdstuk beschrijft ook niet helpende en helpende factoren die van invloed kunnen zijn op toekomstige implementatie van de app in het Princess Máxima Centrum, gebaseerd op de attitudes van zorgverleners die met de app hebben gewerkt.

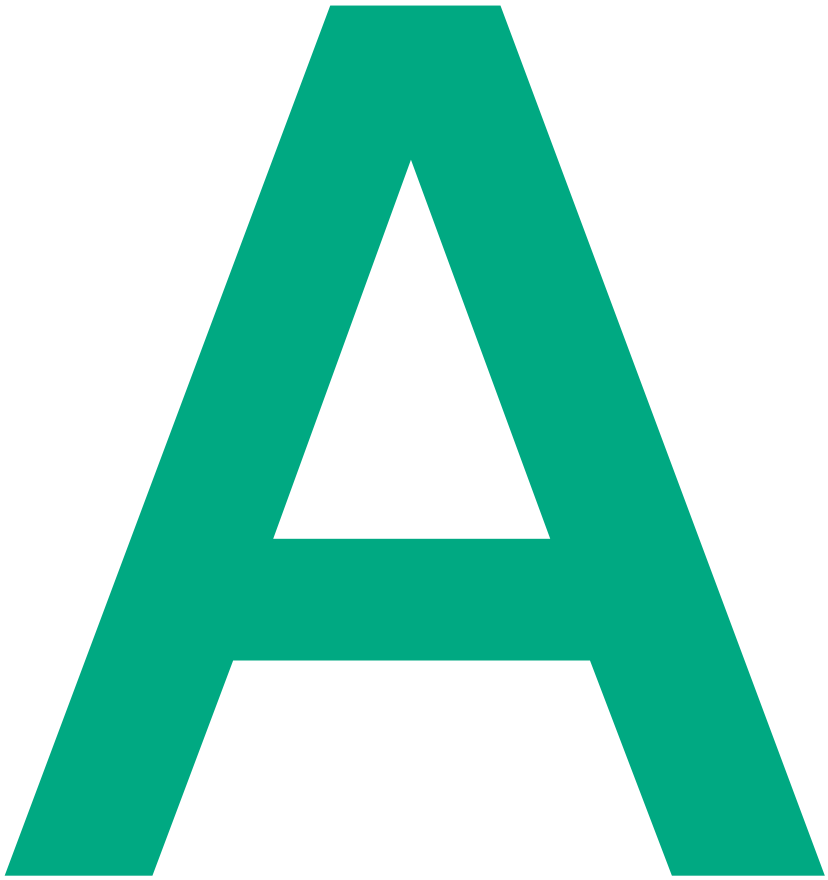
De resultaten van de klinische studies uit dit proefschrift, en daarnaast de geïdentificeerde niet helpende en helpende factoren, hebben ons in staat gesteld om al tijdens het project op een wetenschappelijk verantwoorde manier aanpassingen te doen en suggesties te doen om implementatie van de *KLIK Pijnmonitor app* in de klinische praktijk te laten slagen. Na afloop van de RCT (effectiviteitsonderzoek, hoofdstuk 4) waren er nog twee niet helpende factoren (naleving van zorgverleners voor terugbellen binnen de vooraf vastgestelde termijn en vrees van zorgverleners voor verhoogde werkdruk) over. De drie helpende factoren die overbleven na de RCT waren allemaal gerelateerd aan de toegevoegde waarde van de app voor pijnzorg. Hier moet aandacht aan worden besteed voordat implementatie in klinische praktijk kan plaatsvinden.

In hoofdstuk 7 worden de belangrijkste bevindingen van dit proefschrift samengevat. Daarnaast nemen we de implicaties voor de klinische praktijk en toekomstig onderzoek onder de loep, en worden zowel de beperkingen als de sterke kanten van dit onderzoek belicht. Een overzicht van de studies en de belangrijkste bevindingen is tevens te vinden in tabel 1 van hoofdstuk 7.

CONCLUSIE

Dit proefschrift toont aan dat het gebruik van de *KLIK Pijnmonitor app* haalbaar is bij kinderen met kanker, hun families en zorgverleners, en dat de app effectief is in het verminderen van ernstige pijn bij kinderen in de thuisomgeving. Daarnaast zorgt de app voor vermindering van distress bij ouders. Dit zijn erg betekenisvolle uitkomsten voor de dagelijkse klinische praktijk, aangezien pijn een van de meest voorkomende en stressvolle symptomen is die kinderen tijdens de kankerbehandeling ervaren.

Onbehandelde pijn heeft niet alleen een negatieve invloed op de kwaliteit van leven van kinderen, maar ook op die van hun ouders. En dus - als deze op de juiste manier geïmplementeerd wordt - heeft de *KLIK Pijnmonitor app* niet alleen de mogelijkheid om pijn bij kinderen te verminderen, maar vergroot de app ook de kans op een betere kwaliteit van leven van kinderen en hun ouders. Met deze bevindingen heeft het *RELIEF project* een scala aan mogelijkheden geopend voor de ontwikkeling van, het onderzoek naar en het gebruik van digitale zorg-interventies in de kinderoncologische klinische praktijk. De bevindingen uit dit proefschrift kunnen daarnaast dienen als leidraad voor de ontwikkeling en het gebruik van digitale zorg-interventies in de kinder- en volwassengeneeskunde in brede zin.



Appendices

PHD PORTFOLIO

Courses and workshops	Year
Writing in English for Publication	2018
Bijscholing 'Professionals in de Kinderoncologie'	2018
BROK course EMWO	2018
Introduction to hypnotherapy	2019
The Art of Presenting Science	2019
Research Planning and Time Management	2021
Giving Effective Presentations	2021
CTO Introduction Course	2021
Supervising research of master students	2021
Basic Methods and Reasoning in Biostatistics	2021
Multilevel Modelling and Longitudinal Data Analysis	2022
Presentations	**Year**
Oral, European Paediatric Psychology Conference 2021 (EPPC)	2021
Oral, Congress of the International Society of Paediatric Oncology (SIOP)	2021
Oral, Congress of the International Society of Paediatric Oncology (SIOP)	2022
Oral, Princess Máxima Center Research Meeting	2019
Oral, Princess Máxima Center Research Meeting	2022
Oral, Webinar Digital Health Interventions European Paediatric Psychology Network (EPPN)	2022
Poster, Quality of Life Symposium Princess Máxima Center	2020
Poster, Congress of the International Society of Paediatric Oncology (SIOP)	2021
Poster, SKION day Princess Máxima Center	2022
(Inter)national conferences and research retreats	**Year**
Global Implementation Conference (GIC), Glasgow	2019
Research retreat Princess Máxima Center	2019
CTO PhD Retreat 2019	2019
CTO PhD Retreat 2020	2020
European Paediatric Psychology Conference 2021 (EPPC)	2021
Congress of the International Society of Paediatric Oncology (SIOP)	2021
Research retreat Princess Máxima Center	2021
Congress of the International Society of Paediatric Oncology (SIOP)	2022
Supervising	**Year**
Isabel Hooijman, Master student Clinical Neuropsychology	2022

CURRICULUM VITAE

WERKERVARING

Promovendus
Prinses Máxima Centrum voor Kinderoncologie | augustus 2018 - februari 2023
Promotieonderzoek naar de ontwikkeling, evaluatie en zorgimplementatie van een mHealth interventie (KLIK Pijnmonitor app) gericht op de verbetering van pijnmanagement bij kinderen met kanker in de thuissituatie

Basispsycholoog i.o.
Prinses Máxima Centrum voor Kinderoncologie
Intakes en kortdurende behandeling van psychologische effecten na behandeling van kinderkanker bij 'survivors' (18+) op de LATER-poli onder supervisie van Alied van der Aa, GZ-psycholoog | *april 2022 - januari 2023*

Nevenfunctie: redacteur psycho-oncologisch vakblad
Nederlandse Vereniging Psychosociale Oncologie (NVPO) | november 2018 - november 2021
Interviews voor rubriek 'Vanuit de patiënt' over ervaringen en coping van mensen met kanker

OPLEIDING EN NASCHOLING

Basiscursus Cognitieve Gedragstherapie (CGT)
King Nascholing | januari 2023 – heden

Training Upcoming Leaders in Pediatric Science (TULIPS)
PhD curriculum 2020 - 2022

Master Medische en Gezondheidspsychologie
Universiteit van Leiden | 2017 - 2018
- Focus: de diagnose en behandeling van de psychologische aspecten van chronische ziekte, en de preventie van ziekte en promotie van gezondheid
- Klinische praktijkstage: *Leids Universitair Medisch Centrum (LUMC), Medische psychologie afdeling*
- Cursusleider online cursus ('Grip op Pijn') met CBT-focus voor reumapatiënten met chronische pijn en diagnostiek
- Reguliere behandeling van hartpatiënten met angst, chronische vermoeidheid en aanpassings- en acceptatieproblematiek onder supervisie van GZ-psycholoog
- Master thesis: De Hoogstraat Revalidatie. Supervisors: Dr. E. Scholten en Prof. Dr. M. W. M. Post *Publicatie: Scholten E.W.M., Simon J.D.H.P., Van Diemen T., Hillebregt C.F., Ketelaar M., Woldendorp K.H., Osterthun R., Visser-Meily J.M.A., Post M.W.M. Appraisals and coping mediate the relationship between resilience and distress among significant others of persons with spinal cord injury or acquired brain injury: a cross-sectional study. BMC Psychol. (2020) doi: 10.1186/s40359-020-00419-z.*

Bachelor Psychologie
Universiteit van Utrecht | 2014 - 2017
Focus: klinische en gezondheidspsychologie
Minor: Health Psychology at Ottawa University, Canada (2016 - 2017)

Bachelor Journalistiek
School voor Journalistiek Utrecht | 2010 – 2014

Hoger Algemeen Voortgezet Onderwijs Profiel: Economie en Maatschappij
Stella Maris College Meerssen | 2004 - 2009

DANKWOORD

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Maar die woorden zeg ik jullie liever persoonlijk.

From research to relief