Long-term follow-up of childhood cancer survivors: clinical decision support and research participation

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CHAPTER 1

General introduction and outline of the thesis
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Childhood cancer incidence and survival
In the Netherlands, about 550 children under the age of 19 are diagnosed with cancer annually [1], with leukemia (27%), tumors of the central nervous system (20%) and lymphoma (10%) occurring most frequently. Although a relatively rare disease, cancer is the second most common cause of death, and the leading medical cause of death, in children under 15 years of age [2]. Since the 1970s, pediatric oncologists have been developing effective multi-modality treatment protocols, combining chemotherapy, radiotherapy, surgery and other therapies to treat childhood cancer [3]. Due to these improvements in the treatment of childhood cancer, the average 5-year survival rate has increased to over 80% over the past decades (figure 1) [2, 4-7]. As a result, the group of childhood cancer survivors (CCS) is increasing in size and attained age. In the Netherlands, the current estimated number of 5-year CCS is 7500. Due to the increased survival of children with cancer, it has become clear that the treatment used to cure the cancer can, unfortunately, also cause long-term health problems [8-11]. Frequently occurring health problems after treatment with chemotherapy include, amongst others, cardiotoxicity, neurotoxicity, and hearing loss, while treatment with radiotherapy can lead to a wide spectrum of problems among which cardiovascular disease, pulmonary disease, secondary malignancies, and fertility problems [8-10, 12-14]. These so-called late effects may not become evident until many years after treatment and can significantly impair CCS’ quality of life. Many CCS have to cope with an increased morbidity and, in some cases, a reduced life expectancy [15-18]. It is estimated that 88% of survivors will develop a chronic health condition by age 49, and 48% will develop a serious, life-threatening, or disabling condition [19]. Thus, in many cases, dealing with health-related concerns is not something which ends after having been cured from childhood cancer.

Follow-up care for childhood cancer survivors
The need for structured long-term follow-up of CCS has been uniformly recognized [20]. Therefore, the Late Effects of Childhood Cancer task force of the Dutch Childhood Oncology Group (DCOG LATER) was established in the Netherlands. DCOG LATER aims to 1) provide structured long-term follow-up care for CCS in order to detect and treat late effects in an early stage, improve quality of life, and reduce the risk of premature mortality, 2) inform CCS about
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their prior treatments, current health risks and need for long-term follow-up, and 3) conduct research on childhood cancer survivorship [1]. DCOG LATER is a nationwide multidisciplinary collaboration between clinicians, researchers, and representatives of the Dutch Childhood Cancer Parents Organization (in Dutch: Vereniging Ouders, Kinderen en Kanker, VOKK). Seven outpatient clinics for long-term follow-up care (LATER outpatient clinics) have been set up in the university hospitals (five pediatric oncology clinics and two stem cell transplant clinics) responsible for the treatment of childhood cancer patients [21]. At these outpatient clinics, survivors are seen regularly by a pediatric oncologist or an adult physician, who perform a medical assessment including an anamnesis, physical examination and additional screening procedures, which depend on the previous childhood cancer diagnosis and treatment.

In order to standardize follow-up care in the outpatient clinics, DCOG LATER has developed and implemented an evidence-based guideline for screening CCS in 2010 [22]. The DCOG LATER guideline provides information about which late effects can be experienced by survivors, recommendations about which survivors are in need for screening, what types of screening procedures should be used, and at what frequency these procedures need to be performed (i.e. once every two years, or once every five years). Since its introduction in 2010, the DCOG LATER guideline has been communicated to healthcare practitioners involved in follow-up care of CSS in a paper-based format. The DCOG LATER guideline consists of three parts, in which different research questions are addressed. The first part provides recommendations about possible late effects, diagnostic screening procedures and therapeutic interventions. The recommendations contained in this part of the guideline are structured according to 24 organ/clinical domains, such as heart, kidneys, lungs and neurology. The second part of the guideline provides recommendations aimed at improving CCS’ employment and social functioning. Finally, the third part of the guideline provides recommendations on the structure of follow-up care.

It has been demonstrated that paper-based guidelines often do not suit healthcare professionals’ information retrieval strategies [23, 24]. Furthermore, variability in CCS’s medical history and the high volume of recommendations within the DCOG LATER guideline complicates the ability of healthcare practitioners to
use the guideline in daily practice. A possible solution for improving the usability of paper-based clinical guidelines is to implement them in a Clinical Decision Support System (CDSS) which is linked to an Electronic Medical Record (EMR). Guideline-based CDSS may overcome problems with the use of paper-based guidelines by offering patient-specific overviews of guideline recommendations for the end users. It has indeed been shown that CDSS for guidelines can improve guideline adherence by increasing the knowledge of preferred practice, by reducing inertia to previous practice, and by reducing guideline complexity [25]. In addition, guideline-based CDSS offer support to healthcare practitioners at the time and location where decision making actually takes place [26].

However, despite the proven benefits of CDSS [27], developing systems for the highly complex and dynamic domain of clinical medicine remains a serious challenge [28], and the uptake of these systems therefore still remains limited [29]. Insight into factors that impede or contribute to the optimal design and implementation of CDSS can enhance their development and deployment. One of the major barriers to acceptance and uptake of these systems is poor usability. Therefore, designing a CDSS that fits end users’ preferences and work patterns requires a detailed analysis. Using Human Factors Engineering (HFE), detailed insights into end user work patterns can be acquired. This knowledge can subsequently be used to design, develop and deploy computer systems with high usability. Within healthcare, methods from HFE can be applied to explore healthcare practitioners’ information processing and handling of complex medical decisions [30]. This thesis focuses on using such methods to design a CDSS that guides healthcare practitioners in screening individual CCS using a CDSS which is aligned to daily clinical practice to guarantee high usability.

**Research on late effects after childhood cancer treatment**

Clinical guidelines need to be regularly updated to remain in concordance with changing scientific knowledge [31]. To inform the development of long-term follow-up guidelines, continuous monitoring of CCS is necessary to obtain insight into 1) late effects not yet recognized, 2) risk groups for developing late effects, 3) accurate detection of late effects, and 4) strategies to prevent late effects [3, 20, 32, 33]. Therefore, DCOG LATER also aims to conduct research on childhood cancer survivorship. In general, research over the past decades has
mainly focused on the identification of late effects and characterization of groups of survivors at risk for developing late effects [3, 32, 34]. These late effects studies have led to adjustments in some of the treatment protocols for childhood cancer. Moreover, pediatric treatment modalities which have demonstrated to induce long-term toxicity have been eliminated where possible [3, 6]. In order to further increase the knowledge about late effects, DCOG LATER has set up a nationwide study investigating late effects after childhood cancer. This DCOG LATER study involves a cross-sectional study of the entire Dutch cohort of 5-year childhood cancer survivors. The goal of the DCOG LATER study is to gain knowledge about earlier and more accurate detection of late effects, to identify late effects not yet recognized, and to further define high risk groups of survivors.

Within the DCOG LATER study all 5-year CCS known to be alive are invited to fill out a general health and lifestyle questionnaire and participate in medical assessments at one of the outpatient follow-up clinics. Unfortunately, participation rates in cohort studies in general, and in CCS specifically, have been declining over the past decades, raising a specific concern related to selection bias due to low participation rates among this group of subjects [35, 36]. Furthermore, participation rates of subjects who are invited to participate in medical research are often influenced by several sociodemographic characteristics [36, 37]. As a result, selection bias can occur when participants and non-participants differ with respect to demographic factors and/or exposure variables (e.g. childhood cancer treatment) which affect the outcome under study. Previous research has shown that CCS who visit long-term follow-up clinics for medical care are more likely to suffer from late adverse effects [38]. Thus, low participation rates among CCS who have never visited a follow-up clinic or who visited the clinic a long time ago, would most certainly lead to an overestimation of the prevalence of late effects. For the DCOG LATER study, it may well be that CCS already engaged in regular medical follow-up at one of the LATER outpatient clinics are more likely to participate. Unfortunately, direct assessment of selection bias is often not possible, since information about study outcomes are rarely available for non-participants. However, when general characteristics about the eligible study population are available, it is possible to assess whether these characteristics are represented equally in the participant group compared to the eligible population.
As for every other research study in which subjects are invited to participate, it is very important for the DCOG LATER study to achieve high participation rates to achieve generalizability of study results (external validity). It has been demonstrated that certain invitation strategies and choice of data collection tools can favourably influence subjects’ participation rates [39]. However, studies investigating the effect of invitation strategies and subject characteristics on participation rates of CCS are scarce. One study by van den Berg found comparable participation rates between CCS who received an invitation to complete a web-based questionnaire only and CCS who received an invitation to either complete a paper-based questionnaire or a web-based questionnaire [40]. For the DCOG LATER study, evaluating strategies to improve participation rates is imperative to increase the validity and generalizability of study results. Therefore, in this thesis, we focus on evaluating invitation strategies to increase CCS participation rates and measuring external validity in the DCOG LATER study.

Aim and outline of this thesis
The aim of this thesis is to 1) improve the usability and use of the DCOG LATER guideline for follow-up care of CCS through the development of a CDSS and 2) to evaluate strategies aimed at achieving optimal participation rates in questionnaire studies involving CCS. The thesis is divided into two parts reflecting the two aims.

Part 1. Improving the use of a guideline for follow-up care of childhood cancer survivors
The objectives of part 1 of this thesis are (1) to investigate factors contributing or impeding a successful implementation of guideline-based CDSS, (2) to investigate whether the use of a HFE method can guide the design of a prototype CDSS user interface, (3) to assess whether this prototype CDSS better supports healthcare practitioners in defining screening recommendations for CCS compared to a paper-based guideline. Building on these insights, recommendations for the design of guideline-based CDSS in order to enhance the usability and acceptance of these CDSS are provided.

Insight into factors that impede or contribute to a successful implementation of
guideline-based CDSS is necessary to enhance their development and deployment. Therefore, in chapter 2 we describe the results of a systematic literature review of factors impeding or contributing to a successful implementation of guideline-based CDSS used by physicians. Chapter 3 reports on a study assessing whether a prototype CDSS better supports healthcare practitioners in the retrieval of childhood cancer survivor’s follow-up recommendations compared to the paper-based guideline. Finally, in chapter 4 a new method used to develop a prototype CDSS (implementing the DCOG LATER guideline) based on healthcare practitioners’ information retrieval strategies is described.

Part 2. Optimizing childhood cancer survivor participation in a nationwide questionnaire study

Part 2 of this thesis focuses on the general health and lifestyle questionnaire that is part of the DCOG LATER. To produce valid and generalizable results obtained for the DCOG LATER patient cohort through the DCOG LATER questionnaire study, it is crucial that participation rates are high and free of selection bias as much as possible, ensuring a study population that is representative of the general childhood cancer survivor population as a whole. The objectives of this part of the thesis are (1) to assess which study design and subject characteristics influence CCS participation rates in questionnaire studies, (2) to assess the impact of different questionnaire modes (web-based/paper) and reminders on participation rates, (3) to assess differences between participants and eligible CCS in the DCOG LATER questionnaire study.

In chapter 5, a systematic literature review is described in which participation rates of CCS invited to fill out a health-related questionnaire are assessed. Furthermore, the effect of several study and CCS characteristics on participation is examined. Chapter 6 describes a pilot study we conducted to assess the effect of different invitation strategies on participation rates. Chapter 7 reports on differences between CCS that participate in the questionnaire study and CCS who do not participate in order to evaluate external validity.

Part 3. Discussion

Finally, in chapter 8, the main study findings are summarized and placed into perspective. Recommendations for clinical practice and future studies in the field
of childhood cancer survivorship care and research are further provided. This thesis concludes with a summary in the Dutch language.

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