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

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General discussion
The general aim of the research in this thesis was twofold: 1) to improve the usability and use of the DCOG LATER guideline for follow-up care of childhood cancer survivors (CCS) through the development of a Clinical Decision Support System (CDSS), 2) to evaluate strategies aimed at achieving optimal participation rates in questionnaire studies involving CCS. In this chapter the main findings will be discussed, followed by an overview of the strengths and limitations of the studies presented in this thesis. Finally, recommendations for future research and clinical practice are described.

Main findings
Part 1. Improving the use of a guideline for follow-up care of childhood cancer survivors
In 2010 the DCOG LATER group developed and implemented a paper-based guideline in order to provide structured long-term follow-up care for CCS. Paper-based guidelines, however, often appear difficult to use in clinical practice because they fail to provide patient-specific recommendations and contain complicated document structures [1]. As a consequence, these guidelines often do not meet healthcare practitioners’ practical information needs [2]. Computerized CDSS have the ability to overcome these problems by offering patient-specific overviews of guideline recommendations. However, many CDSS are yet unsuccessful because they do not match with the cognitive and work patterns of healthcare providers using these systems as these patterns are not considered during the design and implementation of these systems [3]. To optimally design CDSSs, a detailed analysis of these cognitive and work patterns is required. Human Factors Engineering (HFE), is a scientific discipline focusing on designing healthcare systems and processes while accounting for cognitive reasoning, physical limitations and work patterns of system users [3, 4]. Previous reports from the Institute of Medicine and the National Academy of Engineering (NAE) have identified HFE approaches as one of the key factors in developing and delivering better healthcare systems [5, 6]. Part 1 of this thesis described the results regarding the development of a user-friendly guideline-based CDSS providing patient-tailored screening recommendations for medical follow-up of childhood cancer survivors by using methods from HFE to align the CDSS with healthcare practitioners’ cognitive work patterns. However, before this guideline-based CDSS can be successfully implemented in clinical practice, insight into
factors impeding or facilitating a successful implementation is necessary.

A literature review was conducted (chapter 2) providing an in-depth exploration of factors facilitating or impeding a successful implementation of guideline-based CDSS. After an extensive search process, 35 publications were included. Factors were identified thematically by textual analysis of the included publications and were individually mapped to the human, organization and technology-fit (so-called HOT-fit) framework for evaluating health information technology implementations. The synthesis of evidence revealed 421 factors which mainly focused on technological and human issues. Main factors facilitating guideline-based CDSS implementation included: 1) systems providing patient-specific recommendations, 2) evidence supporting the recommendations, 3) CDSS that are intuitive and user-friendly, and 4) the availability of hands-on and tailored training of physicians in using a CDSS. Main impeding factors included: 1) physicians’ believe that use of guideline-based CDSS will hamper the patient-physician relationship, 2) physicians’ worries for a loss of autonomy, 3) physicians’ lack of time to use a system, and 4) a lack of fit between the physicians’ workflow and the guideline-based CDSS. Furthermore, the literature review showed a clear gap in research on organizational factors associated with a successful implementation of guideline-based CDSS.

The results of the systematic literature review revealed that a lack of fit between physicians’ workflow and the guideline-based CDSS is an important barrier for a successful implementation of these systems. How to fit a CDSS seamlessly into the particular clinical process at hand needs to be the first objective of a CDSS implementation project. Methods from cognitive psychology can be used to gain insight into these clinical processes. These insights can subsequently be used in the design of CDSS matching these clinical processes. Therefore, in this thesis, the think-aloud method in combination with propositional analysis was used to gain insight into healthcare practitioners’ information processing while using the paper-based guideline for long-term follow-up of CCS (chapter 4). From these insights, a model of healthcare practitioners’ information processing was constructed and this model was subsequently used as input for the design of a prototype CDSS. This approach resulted in a prototype CDSS design with increased effectiveness (completeness of retrieved guideline recommendations)
and efficiency (time to retrieve screening recommendations) compared to its paper-based counterpart (chapter 3). Furthermore, we have shown that usability problems experienced by healthcare practitioners when using the paper-based guideline were overcome with the prototype CDSS. Our study has thus shown that, by using methods from HFE, insight into healthcare practitioners’ information processing can be gained, which can be used to design an efficient and user-friendly CDSS.

Part 2. Optimizing childhood cancer survivor participation in a nationwide questionnaire study
DCOG LATER has set up a nationwide study among CCS which aims to gain knowledge about an earlier and more accurate detection of well-known late effects, to identify late effects not yet recognized, and to further define high risk groups of survivors. In the first phase of this study, all CCS in the DCOG LATER study cohort were invited to complete a questionnaire about general health and lifestyle risk factors for late adverse events. For the questionnaire survey to produce valid results, it is crucial that the participating CCS are representative of the CCS population as a whole. If the study participants differ from the total group of eligible CCS with respect to demographic characteristics and treatment variables that affect the outcome under study, the study’s generalizability and external validity may be compromised. Thus, obtaining high response rates for the questionnaire survey is of utmost importance. Unfortunately, participation rates in research studies have been declining over the past decades [7-9]. Investigating invitation strategies leading to the highest participation rates is becoming more and more important for questionnaire-based studies. Furthermore, insight into which subject characteristics influence participation rates can help other researchers in setting up a questionnaire study and choosing appropriate recruitment strategies. In part 2 of this thesis we therefore reported on the results of studies investigating invitation strategies and subject characteristic influencing participation rates in questionnaire studies involving CCS.

First, in order to gain insight into aspects of invitation strategies and characteristics of CCS which might influence participation rates in questionnaire-based studies, a systematic literature review was conducted (chapter 5). From a systematic literature review including 35 publications, five characteristics of invitation
strategies that appeared to influence participation rates of CCS were identified: the use of reminders, the use of incentives, the possibility to answer a shortened version of the questionnaire (on paper or by telephone), the invitation being sent through CCS' GPs, and a prenotification before sending out the questionnaire. By using one or more of these strategies, researchers can improve participation rates and thereby the quality of their questionnaire-based studies among CCS.

In addition, higher participation rates were achieved in studies which, besides CCS, also surveyed GPs or parents (with CCS being aware that their GPs or parents had received a questionnaire as well). Thus, when conducting a study in which both CCS and parents or GPs are invited to complete a questionnaire, researchers are advised to send these questionnaires simultaneously. The literature review also revealed that participation in questionnaire-based studies is higher for certain subgroups of CCS. Female CCS, Caucasians, and CCS with a higher educational level are more likely to complete and return a questionnaire compared to male CCS, CCS of ethnic minorities and CCS with a lower educational level, respectively. Unfortunately, although this review identified several aspects of invitation strategies and CCS characteristics that seem to influence participation rates, it was difficult to assess their exact influence due to underreporting of methodological and study details in the included publications.

In a pilot study (chapter 6), we assessed the impact of three different invitation strategies (to which 750 CCS in total were randomly assigned) on participation rates of CCS, combining different questionnaire modes (web-based and paper-based) and reminders. After the initial invitation, CCS in the first and second strategy received two postal reminders followed by a telephone reminder, while CCS in the third strategy only received one postal reminder followed by a telephone reminder. Furthermore, CCS were offered a paper-based questionnaire at different contact moments (at initial invitation, first postal reminder, or second postal reminder, respectively). At each of the several contact moments (initial invitation or reminders), CCS had the possibility to complete the web-based questionnaire. The second invitation strategy (two postal and one telephone reminder, and the paper-based questionnaire added to the first postal reminder) yielded the highest participation rate (60.6%, compared to 57.4% and 56.4% in the first and third strategy, respectively), although differences were not statistically different. The results thus show that an invitation strategy offering a web-based
questionnaire without a paper-based questionnaire at initial contact can be used without compromising participation rates among CCS. However, CCS with a higher socioeconomic status more often completed the web-based questionnaires compared to CCS with a lower socioeconomic status. To reduce the risk of selection bias, we thus advise to always offer potential participants the choice to either complete a paper-based questionnaire or a web-based questionnaire. For this reason, the third strategy (paper-based questionnaire added to the initial invitation, and with one postal and one telephone reminder) was chosen for the nationwide DCOG LATER questionnaire study which was conducted after the pilot study.

Generalizability of the study results from the nationwide DCOG LATER questionnaire study was assessed by comparing sociodemographic, disease and treatment characteristics of participating CCS with the entire eligible group of CCS (chapter 7). The results showed that these characteristics are not equally distributed between the participant group (N=3171) and the eligible group of CCS (N=5330). In line with the literature review as described in chapter 5, the results show that female CCS and CCS living in areas with a larger proportion of individuals with high socioeconomic status were more likely to participate. Furthermore, characteristics such as age, having recently visited the LATER outpatient clinic for medical care (within 2 years prior to the study), and living in less urban areas were found to influence participation. With respect to age, an interesting finding was that teenage CCS (11 to 17 years of age) were more likely to participate compared to CCS between 18 and 35 years of age. The higher participation rate among teenage CCS may be explained by the fact that these CCS were diagnosed with cancer more recently and thus still are in regular follow-up. However, this might also be due to the fact that their parents were invited to complete a part of the questionnaire as well. As the literature review in chapter 5 already suggested, involving parents in questionnaire studies simultaneously with teenage CCS increases the chance of participation among this group of CCS.
Strengths and limitations of the studies described in this thesis
Part 1. Improving the use of a guideline for follow-up care of childhood
cancer survivors
The main strength of the literature review of guideline-based CDSSs presented in
chapter 2 was that results from a variety of qualitative, quantitative, and mixed
methods studies were combined, and that a systematic and extensive search
strategy was used in order to limit the chance of missing relevant publications.
Another important strength is that two independent researchers systematically
determined the inclusion of all relevant publications. Furthermore, they
independently extracted data from the included publication using a standardized
data collection form and mapped the resulting list of factors to an evaluation
framework, the so-called HOT-fit framework [10]. However, there are also some
limitations to the study. Although the above mentioned mapping of factors was
done independently, it remains a subjective activity potentially leading to biased
results. In addition, some bias might have occurred during the inclusion process
since only publications between 2004 and 2015 were included. This timeframe
was chosen on purpose so that only evaluation studies on newer generation
guideline-based CDSSs would be included. Furthermore, the inclusion process
could have been biased because CDSSs were subjectively classified as being a
guideline-based CDSS, since there is no universal standard to classify CDSS
type, and also because studies were included that assessed the same CDSS in the
same clinical setting (although from different perspectives).

The major strength of the usability studies presented in chapter 3 and 4 is the
HFE approach we applied to develop a prototype CDSS embedding the DCOG
LATER guideline for screening CCS. By involving potential end users in the
development and evaluation of the prototype CDSS we were able to design a
user-friendly CDSS providing patient-tailored guideline recommendations.
Since there are only a few physicians and physician assistants involved in CCS
long-term follow-up care (about 2 to 4 persons per LATER outpatient clinic), the
number of potential end users that participated (13 participants in total) can be
considered as being representative of the entire eligible user group. Furthermore,
this number of participants suffices to gain a thorough understanding of users’
information processing and to identify at least 80% of usability problems
[11]. However, participation in the study was voluntary, potentially leading to
biased results. Furthermore, the proportion of participating physician assistants and physicians throughout the different participating clinics was not equally distributed. This difference was caused by the fact that patient visits are prepared in different ways across the clinics. Preparation of a patient visit consists of reviewing a CCS’ previous cancer diagnosis and treatment information, and determining the screening procedures for CCS as recommended by the DCOG LATER guideline. In some of the clinics, patient visits are prepared solely by a physician, while in other clinics the preparation is done solely by a physician assistant or in collaboration with a physician.

The analysis of the paper-based guideline, the development of the prototype CDSS, and the evaluation of the prototype CDSS were performed by the same researchers. We consider this to be both a strength and a weakness. It allowed the developers of the prototype CDSS to elaborate on relevant design comments from the healthcare practitioners and it helped them to ensure that in future redesigns of the prototype, these comments would be addressed. However, responses of participants during the think aloud sessions may have been biased by this lack of independence from the researchers, thereby potentially discouraging reporting of concerns with the CDSS by participants.

Participants did not receive any training or explanation prior to using the prototype CDSS. As a consequence, participants might have needed more time to retrieve patient-specific screening procedures with the prototype CDSS compared to the situation in which they had previously already explored the CDSS. In addition, usability problems that were found could have been overcome by providing training. Although this could limit our findings, we were specifically interested in gaining insight into the ease of learning to use the prototype CDSS, and therefore chose not provide any training or explanation about the prototype CDSS.

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

The main strength of the literature review presented in chapter 5 is our meticulous attempt to include all relevant articles and data, by performing an extensive and systematic literature search, using two independent researchers
as well as a standardized data collection form. Based on the conclusion of the review, we formulated multiple strategies for including CCS in questionnaire-based studies. However, due to the underreporting of methodological details of studies, a quantitative analysis could not be conducted and the review thus mainly included descriptive results. Because of these reasons, the results of this review should be interpreted with caution.

The strength of the study described in chapter 6 lies in its practical applicability in clinical research. The study describes the pros and cons of a pilot study in which CCS were randomly assigned to one of three different invitation strategies that can be used by researchers conducting questionnaire surveys among CCS. Because there was a difference in CCS’ questionnaire mode preferences (CCS with a lower socioeconomic status preferred a paper-based questionnaire), we chose to implement the invitation strategy with the option for CCS to choose between either a paper-based or a web-based questionnaire, together with one postal reminder and one telephone reminder, in the nationwide questionnaire survey of the DCOG LATER study as described in chapter 7. In order to evaluate the effectiveness of a combination of follow-up strategies and paper-vs. web-based questionnaires, a sequential multiple assignment randomized trial would have been the most ideal study design [12]. By using this study design, participants could have been randomly assigned to an intervention at each of the invitation and reminder stages. By randomizing participants multiple times, it is possible to assess the effectiveness of the interventions at each stage. Since our study was set up as a pilot for the nationwide questionnaire survey, we chose to use a standard stratified randomized trial because of higher practical applicability. For a sequential multiple assignment randomized trial, more study arms and a larger study group would have been needed, which was too complex for this pilot study aimed to select the most appropriate strategy for a questionnaire study in the entire Dutch cohort.

The main strength of the study presented in chapter 7 is the extensive dataset that was available to compare CCS participating in the DCOG LATER study with all eligible CCS. Besides data on childhood cancer diagnosis and treatment, neighbourhood-level socio-demographic data from the Statistics Netherlands (CBS) were collected as an indicator of CCS’ socio-demographic
status. However, it is possible that these average neighbourhood values do not fully represent the CCS’ socio-demographic status. For example, if a CCS with a high socioeconomic status lives in a neighbourhood with many inhabitants with a low socioeconomic status, it would be (incorrectly) assumed that this particular CCS also has a low socioeconomic status. Another limitation of this study is the inability to compare differences in health outcomes between participating and non-participating CCS. In case participation is related to both health status and treatment or lifestyle exposures, selection bias will affect associations between exposure and specific outcomes in CCS. Ideally, in order to assess the presence of selection bias, participants and non-participants should be compared with respect to health status outcomes as assessed by the LATER questionnaire. Possible differences between participants and non-participants will be investigated in the near future by comparing outcome data obtained from the LATER questionnaire or medical record abstraction from the GPs and LATER outpatient clinics. However, outcome data from the LATER questionnaire have to be validated first, a process which is currently being undertaken within the DCOG LATER study.

**Directions for future research and clinical practice**

**Part 1. Improving the use of a guideline for follow-up care of childhood cancer survivors**

The insights resulting from the studies in part 1 of this thesis can aid project teams during the design and implementation of guideline-based CDSS systems. These studies add to the growing realization that the HFE approach is essential in the design, evaluation, and implementation of health information systems aimed at quality improvement in clinical practice [3]. By using methods from HFE, we have shown that it is possible to design a first prototype CDSS with high usability. Therefore, we expect that only a few design iterations will be necessary before the CDSS will be fully implemented in clinical practice of all participating LATER outpatient clinics, because usability problems could be revealed and addressed in an early stage of system design.

Currently, the prototype CDSS has not yet been implemented within the LATER outpatient clinics. Although the prototype CDSS has shown to be effective in a simulated setting, its effectiveness in daily clinical practice remains to be assessed.
An actual implementation of the system would require a detailed understanding of the sociotechnical environment within the DCOG LATER outpatient clinics. Many conceptual models can be used for this purpose. However, there has been limited attention on approaches that consider a multidimensional approach to health information technology implementations [4, 13]. Most of these models focus mainly on human (individual healthcare practitioners) and technological issues [14-16]. Our systematic literature confirms this finding. Moreover, a clear gap was seen in research focusing on the organizational structure in which a guideline-based CDSS is introduced. Recently, there has been a push towards the use of socio-technical models [3, 15]. These models, such as the SEIPS (Systems Engineering Initiative for Patient Safety) model, [17] the healthcare professional performance model by Karsh et al. [18], and the 8-dimensional model of Sittig et al. [13], consider an entire system, the interaction between its individual components, and its interactions with other systems [3]. One of these models can be used to gain a holistic view of the people and processes within the LATER outpatient clinics. By using these models, barriers and facilitators to a successful implementation of the CDSS can be identified beforehand in each of the clinics. Tailored strategies can then be defined to prevent these barriers from occurring and exploit the facilitators to increase the success of CDSS implementations.

The prototype guideline-based CDSS embedding the DCOG LATER guideline was built as a stand-alone application, with the possibility to integrate the system with the existing DCOG LATER registry. The DCOG LATER registry contains data about a CCS’ childhood cancer diagnosis, possible recurrences or subsequent neoplasms, and treatment that was given. Furthermore, the registry is currently being expanded with the possibility to enter questionnaires and other data that are collected during the nationwide DCOG LATER study. In order to provide decision support based on the entire DCOG LATER guideline, the registry would have to be expanded with data collected during follow-up care of CCS, since the guideline also provides recommendations about the consequences of certain diagnostic screening procedures. Such an expansion would either require an increased registration burden for the LATER outpatient clinics, or a linkage of the DCOG LATER registry with the local Electronic Medical Records (EMRs) in each of the clinics. A third option would be to completely integrate the CDSS in the local EMRs, which would then require that all historical diagnosis and
treatment data concerning the childhood cancer is available within those EMRs.

In an ideal situation, data registered during childhood cancer care (including long-term follow-up) is integrated in an IT infrastructure facilitating re-use of these data for secondary purposes such as clinical research and quality management. Within such an infrastructure, CCS data are collected and registered once in the EMR during the treatment of childhood cancer or follow-up care and then made available (after anonymization) for secondary purposes such as evaluation of care and clinical research. Additional data collected for clinical research (such as the data from the questionnaires collected for the nationwide DCOG LATER study) should be integrated with data extracted from the EMR (independent of the system through which these additional data are collected). This requires that data are collected in a clear and structured manner, according to standards and a uniform data model in a similar manner in all EMRs of all clinics. As an additional advantage, a standardized registration of data within EMRs will make it possible to integrate the CDSS with each EMR, thereby enabling the provision of patient-specific recommendations based on evidence-based guidelines, and to monitor guideline adherence. To achieve the ambition of integrated care and research for childhood cancer patients and CCS a commitment from all healthcare practitioners involved in pediatric oncology is necessary. In the near future, such an opportunity is provided by the opening of a new hospital specialized in pediatric oncology. As of 2018, the Princess Máxima Center for pediatric oncology will be responsible for the treatment of all childhood cancer patients in the Netherlands. The center aims to improve survival rates and quality of life for children with cancer by combining health care, research, education and training [19]. Currently, efforts are being made by the center to build an IT infrastructure which enables data collected during patient care to be re-used for secondary purposes.

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

In view of the general decline in participation rates of research studies [7-9], investigating invitation strategies leading to the highest participation rates is becoming more and more important for future questionnaire-based studies. Therefore, the studies as described in part 2 of this thesis has increased our
knowledge as to which strategy would lead to the highest participation rate in the nationwide DCOG LATER questionnaire study. Moreover, based on the results from these studies, a number of strategies are recommended for researchers interested in designing and using questionnaire surveys aimed at CCS. Researchers are advised to send a prenotification to the CCS before sending out the questionnaire, to use a combination of postal and telephone reminders, and to include the possibility for CCS to answer a shortened version of the questionnaire. Unfortunately, the literature review in chapter 5 also showed that details of the study methodology used are often underreported in research publications. In addition, results showed that invitation strategies are often not compared in randomized trials. Further research into the effects of various invitation strategies should focus on comparing different strategies. Furthermore, when reporting about questionnaire studies, researchers should provide (as supplementary data) detailed information on the recruitment strategy, study population, participation rates, and differences between participants and non-participants.

Besides the previously recommended invitation strategies, this thesis showed that involving CCS’ GP and parents seems to increase participation rates in questionnaire-based studies. Recent evidence by Gorman et al. already showed that study recruitment can benefit from collaborative relationships that are formed with, not only healthcare providers, but also with CCS advocacy groups’ members [20]. In the Netherlands, such a collaborative effort has already been formalized by the establishment of the so-called VOX, which is the sub-division of the Dutch Childhood Cancer Parent Organization (in Dutch: VOKK), and in which fellow survivors are united. A representative of VOX has been included in the DCOG LATER board. Over the past years, VOX has increased their efforts in increasing CCS’ knowledge about the existence of the DCOG LATER follow-up clinics and scientific studies, probably leading to increased recruitment of CCS in DCOG LATER studies.

In our nationwide DCOG LATER questionnaire study, CCS visiting the LATER outpatient clinic in the 2 years preceding the questionnaire were more likely to participate. By increasing CCS’ commitment to the long-term follow-up clinics, participation rates in scientific research studies might also
increase. Unfortunately, recent studies show that clinic attendance among CCS is relatively low (with attendance rates between 30% and 50%), even though specialized follow-up clinics have become well-established [21-24]. Barriers to engaging in survivorship care include limited insurance, lack of time, major life changes, anxiety, and barriers transitioning from pediatric to adult care [24]. Furthermore, recruitment of CCS in research studies is also often hampered by CCS who became lost to follow-up after they switched from pediatric to adult care [21, 24]. These barriers are similar to the barriers seen in recruiting CCS for research studies. In the pilot study presented in this thesis, two major reasons for declining participation in the questionnaire study were lack of time, and CCS expressing that they no longer wanted to be confronted with their childhood cancer past. Targeted interventions aimed at empowering CCS to engage in both life-long survivorship care and scientific research are needed. These interventions should be aimed at addressing the previously mentioned barriers, and could include interventions focusing on a seamless transition from pediatric to adult care, the provision of a survivorship passport to increase CCS’ knowledge about their health risks, and providing social support to overcome anxiety.

References
General discussion

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