Rebecca Josephine
van Kalsbeek-Grootendorst

Improving quality of survival after childhood cancer by developing, implementing and evaluating care

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Colofon

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Verbeteren van de kwaliteit van overleving na kinderkanker door het ontwikkelen, implementeren en evalueren van zorg

(met een samenvatting in het Nederlands)

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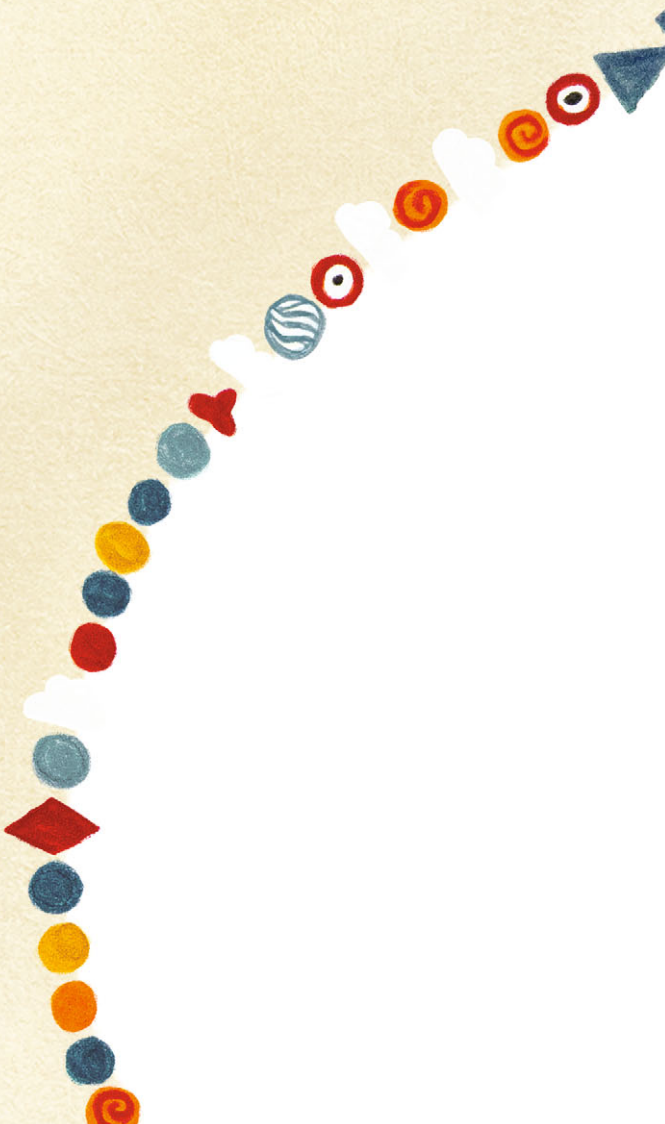

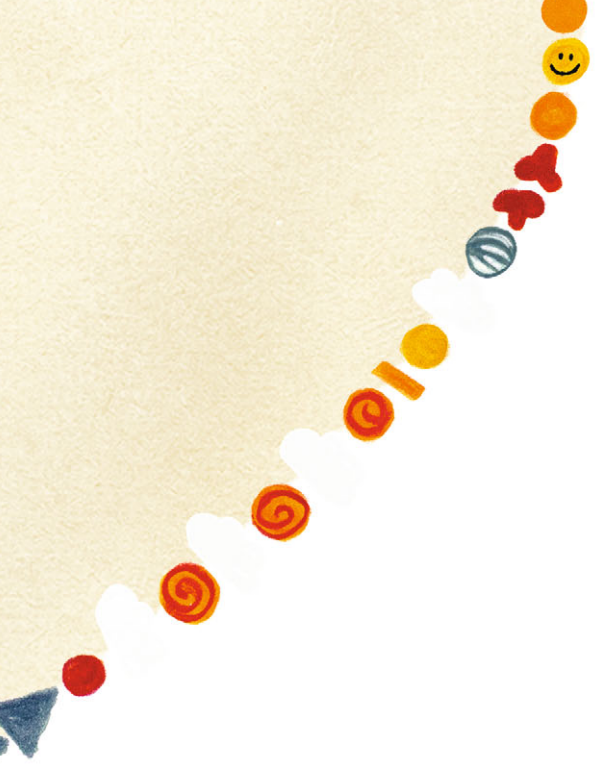

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General introduction and thesis outline

CHILDHOOD CANCER

Cancer and its consequences date back to the earliest traces of our history, and continue to be a part of our lives today (1). The origin of cancer is intertwined with our nature as human beings. It can be summarized as a loss of control on the inhibitory or stimulatory impulses our bodies use to live, repair and grow – albeit with devastating consequences. The unruly and unrestrained growth of cancer cells disturbs the normal functioning of our healthy cells, organs and tissues. As such, it leads to illness and death.

Despite these basic characteristics shared between all malignancies, childhood cancer is not simply an adult cancer presenting at a younger age. The spectrum of childhood cancer is different, with leukemias, lymphomas, low grade gliomas, and neuroblastomas occurring relatively frequently in children, compared to breast, prostate, skin, lung and colon cancer in adults (2, 3). Moreover, whereas adult cancers are often related to lifestyle and environmental risk factors, the cause of many pediatric cancers is yet to be discovered (4).

The earliest treatment of cancer was mostly limited to surgery. Other treatment options that are relatively common nowadays, such as chemotherapy, radiotherapy, targeted therapy, immunotherapy, and stem cell transplantation are still quite new to the arsenal to combat cancer (5). The history of treating children with cancer, compared to adults, is even more recent. Only in the 1950s, children with cancer first received anti-tumor therapies, and it was not until the 1960s that pediatric oncology became more successful, with acute lymphoblastic leukemia as the hallmark disease for which cure could be achieved (6).

In the Netherlands, approximately 600 children are diagnosed with cancer each year (7). Up to recently, these children would have been treated at one of the seven pediatric oncology hospitals around the country (8). In 2018, a unique initiative driven by parents and healthcare professionals resulted in the centralization of research and care in one single center: the Princess Máxima Center for pediatric oncology in Utrecht. Essential diagnostics, care and follow-up are performed at this institution, whereas less complex parts of treatment are, if possible, given at shared care centers that are located more closely to a child's home. The concentration of knowledge, expertise and resources in one place is an important step toward the mission of the Princess Máxima Center: to cure every child with cancer with optimal quality of life.

SURVIVING CHILDHOOD CANCER

Nowadays, more than 80% of all children diagnosed with cancer in high-resource settings will survive five years after their diagnosis (7). The European population of childhood cancer survivors is currently estimated to include 500,000 individuals, and will grow continuously (9). A vast majority will reach adulthood and experience similar milestones as healthy peers, such as completing their education, having a job, moving out, being in a relationship, or starting a family (10).

Unfortunately, curing childhood cancer often comes at a cost. Up to 75% of childhood cancer survivors experiences at least one therapy- or disease-related late effect (11). These may manifest as physical, psychological, social or neurocognitive consequences of

treatment, sometimes occurring years to decades after the initial diagnosis, and contribute to early mortality (12, 13). Prevalent late effects include subsequent neoplasms, organ dysfunction such as heart failure or pulmonary dysfunction, endocrine disorders, cognitive impairment, and psychosocial challenges (14-17). As the average 50-year old survivor is reported to have twice as many chronic health conditions as sibling or community controls, the burden of surviving childhood cancer can be substantial (18, 19). It is even further increased for those treated during earlier decades, or exposed to higher doses of radiation and chemotherapy. Over the past few decades, the expanding body of knowledge has led to a better understanding of the spectrum of late effects, treatment-related risk factors that may increase their incidence, and their impact on quality of life (20).

SURVIVORSHIP CARE AND INTERNATIONAL GUIDELINE DEVELOPMENT

Lifelong follow-up care is essential to improve the health and quality of life of childhood cancer survivors through the prevention, early detection and management of late effects (21-23). In the Netherlands, the first outpatient clinics dedicated to providing long-term follow-up were initiated in the 1990s. In 2018, most were centralized in the late effects clinic ("LATER poli") at the Princess Máxima Center. More than 3,000 survivors visit this outpatient clinic each year. In comparison, access to long-term follow-up care is much more fragmented across Europe, especially after childhood cancer survivors transition from pediatric to adult healthcare settings (24). In a survey in 2012, only one out of three pediatric oncology centers reported having established services for adult survivors of childhood cancer (25). Common barriers for the implementation of a late effects clinic included a lack of dedicated time, personnel, knowledge and financial resources, in addition to other local challenges.

Although the model of care might vary, it is generally agreed that surveillance for specific late effects should be stratified by cancer diagnosis- and treatment-related risk (20, 26). In addition to performing surveillance, late effects clinics fulfill an important role as an expert center. They create awareness about late effects among healthcare providers, give survivors age-appropriate education about their treatment history and potential late effects, and provide guidance regarding lifestyle, health or life insurance, education, and employment (27).

Evidence-based guidelines translate research findings to clinical care by describing which survivors may be at risk for a certain late effect and recommending surveillance strategies to identify and treat these health conditions (28, 29). A survey among European clinicians illustrated the value of evidence-based guidance in providing long-term follow-up care across different care models (30).

Initially, several national guideline groups, including the Dutch Childhood Oncology Group, worked separately to perform systematic reviews of published studies, use available evidence and expert opinion to define risk groups, and describe appropriate diagnostic tests, intervals of screening, and further management (31-34). A wider collaboration would avoid of duplicate work, allow optimal use of expertise, and enhance research opportunities. Increasing recognition of these benefits resulted in the initiation of the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) in 2010 (29). Since then, 20 guidelines have been developed by multidisciplinary

IGHG panels, covering topics from fertility preservation, heart failure, and subsequent neoplasms to cancer-related fatigue and mental health problems (35-41). Despite the international collaboration, guideline development remains a challenging and time-consuming task, often spanning two or more years from initiation to completion. To prioritize their efforts, the IGHG performed a Delphi survey shortly after its initiation, which resulted in a focus on dedicated guidelines for heart failure, subsequent breast cancer, central nervous system malignancies, coronary artery disease, gonadal dysfunction, and growth hormone deficiency among childhood cancer survivors. Nevertheless, guidelines for many other clinically relevant topics are still under development and urgently awaited by those providing survivorship care.

In Europe, the PanCare Guidelines Group, a working group within the Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer (PanCare), contributes to the development, implementation and dissemination of long-term follow-up guidelines. Equity of access to optimal long-term follow-up care is PanCare's main aim (42). The organization was founded in 2008 to unite professionals, survivors and their families in their efforts to create awareness about childhood cancer survivorship, promote collaborative research, sustain a knowledge base, and support best practices of long-term follow-up care.

Since its initiation, the PanCare network has participated in several European research projects. Among those is the PanCareFollowUp project, initiated in 2019 by a group of researchers, clinicians and survivors. The aim of PanCareFollowUp is to improve access to long-term follow-up care for adult survivors of childhood cancer. In this project, fourteen institutions from ten countries will collaborate to develop a person-centered care model (the PanCareFollowUp Care Intervention) and an eHealth intervention (the PanCareFollowUp Lifestyle Intervention). Moreover, the PanCareFollowUp Consortium will evaluate the feasibility of the implementation of these interventions and assess their effectiveness in empowering survivors and improving their quality of life.

SURVIVORSHIP RESEARCH AND THE DCCSS-LATER 1 AND 2 STUDY

Although various questions regarding late effects have been studied, for example the identification and impact of certain risk factors or the cost-effectiveness of certain types of surveillance (43-46), there are still many knowledge gaps. Examples include the potential long-term adverse effects of novel therapies (47, 48), how to balance survival and late effects in shared decision-making about cancer treatment (49), and the effectiveness of lifestyle interventions to improve symptom burden or reduce the impact of modifiable cardiovascular risk factors (50). Continued research focusing on relevant clinical questions is important to fill these gaps and to strengthen the recommendations in the surveillance guidelines.

Several childhood cancer survivor cohorts have been established worldwide (51). In the Netherlands, the population-based Dutch Childhood Cancer Survivor Study (DCCSS)-LATER cohort (1963-2001) provides a unique source to identify the risk factors for certain late effects and to validate the findings from other cohorts (52, 53). It includes all patients with a histologically verified diagnosis of malignancy covered by the International Classification of Childhood Cancer, third version, including selected low-grade brain tumors and Langerhans Cell Histiocytosis treated with chemotherapy and/

or radiotherapy; diagnosed at an age of <18 years; treated in one of the seven pediatric oncology centers in the Netherlands between 1963-2001; treated with chemotherapy and/or radiotherapy; and with ≥5 year survival after diagnosis. The DCCSS-LATER cohort (1963-2001) consists of 6,165 childhood cancer survivors, both living and deceased. The cohort was recently expanded to include a total of over 12,000 five-year survivors diagnosed up to 2018. Detailed information on cancer diagnosis and treatment, including therapy for recurrences, is available in a central database.

The DCCSS-LATER (1963-2001) cohort has given rise to two large cross-sectional cohort studies: the DCCSS-LATER study part 1: questionnaire and linkage study (2010-2017) and the DCCSS-LATER study part 2: clinic visit and questionnaire study (2014-2020) (52, 53). The DCCSS-LATER 1 study examined the prevalence and risk factors of a variety of health outcomes using a questionnaire among survivors and their siblings and linkages with medical registries. Among others, the resulting publications provide more insight on heart failure, reproductive and obstetric outcomes, fatigue, subsequent neoplasms, and mortality among childhood cancer survivors (54-61). The DCCSS-LATER 2 study was designed to address knowledge gaps identified during guideline development, by formulating clinical research questions to structure 16 outcome-specific projects. Participants were invited for a questionnaire and clinic visit, with specific additional tests depending on their eligibility and consent for one of the 16 sub-studies, for example focusing on kidney failure, hypertension, oral health and psychosocial wellbeing (62-65).

Similarly, there are still some unanswered questions regarding the long-term impact of childhood cancer treatment on the lungs (66). Pulmonary diseases constitute an important part of the excess cumulative burden of disease that survivors experience, and are associated with increased hospitalization rates and premature death (67, 68). Although the majority of survivors remains asymptomatic even in the presence of pulmonary dysfunction, some report symptoms such as chronic cough, shortness of breath, sharp chest pain, or exercise intolerance, or may require supplemental oxygen (69-71). Treatment-related pulmonary dysfunction most often presents as restrictive or diffusion impairment, which are associated with a lower functional exercise capacity (72-74). Moreover, some survivors treated with stem cell transplantation may experience obstructive dysfunction due to bronchiolitis obliterans (75).

Previous studies have identified risk factors for long-term pulmonary dysfunction, which include certain types of chemotherapy (bleomycin, busulfan, carmustine, and lomustine), radiotherapy to a field exposing the lungs (including total body irradiation), and pulmonary or chest wall surgery (72, 73, 76-80). However, the role of cyclophosphamide as a potential pulmonary toxic agent has been debated since this finding was first reported in the 1970s (81). Cyclophosphamide is an alkylating agent that is used in many childhood and adult cancer treatment protocols, and which is often administered in combination with known pulmonary toxic treatments (82). Established long-term consequences of cyclophosphamide treatment include subfertility and premature ovarian insufficiency (83, 84). In contrast, the evidence for pulmonary dysfunction as a late effect of cyclophosphamide is inconsistent. The few studies that reported on long-term pulmonary consequences were limited by small cohort sizes, potential confounding by established pulmonary toxic treatment, comorbidities or lifestyle factors, and differences in outcome definitions and assessment (73, 78, 85-87). A representative cohort and

rigorous methodology are needed to answer the question whether cyclophosphamide in itself is related to long-term pulmonary dysfunction, in order to develop strong recommendations regarding the necessity of pulmonary surveillance in these survivors.

QUALITY OF SURVIVAL

One of the key elements to achieving the mission of the Princess Máxima Center, to cure every child with cancer with optimal quality of life, is providing care with the highest quality (88). Since Porter's seminal paper on value-based healthcare in 2010, the benefits of measuring outcomes to evaluate and improve the quality of care have received increasing attention (89, 90). Measurement of outcomes, including both survival and adverse consequences faced by patients and survivors, is essential to determine the success in reaching the mission of the Princess Máxima Center.

Over the past decade, core outcome sets have been defined for a wide spectrum of health conditions and patient populations (91-95). However, a core set containing the most important outcomes for quality of survival in pediatric oncology was still lacking. Fundamental aspects of such a core set should include the participation of patients and survivors, to ensure it represents outcomes of value to them, and international collaboration, to harmonize the development, implementation and evaluation of the core outcome set globally and facilitate benchmarking with other centers (96).

AIMS AND OUTLINE OF THIS THESIS

Aims

This thesis aims to contribute to the quality of survival experienced by childhood cancer survivors by facilitating the implementation of person-centered survivorship care, addressing the knowledge gap regarding cyclophosphamide and long-term pulmonary dysfunction, and developing a core outcome set for childhood cancer to monitor the occurrence of important outcomes and identify opportunities for improvement of the quality of care.

Specific objectives are to: 1) develop a person-centered care model for survivorship care, including surveillance recommendations and tools required for implementation; 2) establish a study protocol to evaluate the feasibility, effectiveness and costs of implementing this person-centered survivorship care model in different centers across Europe; 3) study the association between cyclophosphamide and long-term pulmonary dysfunction in a population-based cohort of Dutch childhood cancer survivors, and; 4) develop a core outcome set for 17 types of childhood cancer including harmonized outcome definitions and measurement instruments.

Part 1: Life after childhood cancer and the importance of survivorship care

An outline of the concept of cancer survivorship and different care models that are currently used to organize and provide long-term follow-up care is presented in **Chapter 2**. In **Chapter 3**, we describe the European PanCareFollowUp project which was initiated to improve the health and quality of life of childhood cancer survivors by facilitating the implementation of person-centered survivorship care. Main components of this project are the development and evaluation of the PanCareFollowUp Care and Lifestyle

Intervention. The chapter includes an overview of the aims and objectives of the project, as well as the tasks and expected output of each of the eight work packages. In **Chapter 4**, we describe the PanCareFollowUp Care Intervention in more detail. This person-centered care model was co-developed with childhood cancer survivors and consists of three steps: 1) completion of a Survivor Questionnaire (by the survivor) and Treatment Summary (by the healthcare provider) before the clinic visit; 2) a clinic visit including education and shared decision-making about surveillance for specific late effects, and; 3) a follow-up call to finalize the individualized Survivorship Care Plan. Tools that are used in the PanCareFollowUp Care Intervention, such as the Survivor Questionnaire, Treatment Summary template, Survivorship Care Plan template, and educational materials, are also provided here. Surveillance guidelines are an essential part of long-term follow-up. For those topics which were not yet covered by the IGHG, we developed European consensus-based recommendations in **Chapter 5**. The protocol for the PanCareFollowUp Care Study, which aims to study the feasibility, effectiveness and costs of implementing the PanCareFollowUp Care Intervention, is presented in **Chapter 6**. The Care Study enrolled participants at four sites (in Belgium, the Czech Republic, Italy and Sweden) from 2020 to 2022. Its results can be used to inform healthcare providers, management staff and policy makers about the importance and feasibility of providing lifelong long-term follow-up care for adult survivors of childhood cancer. Finally, in **Chapter 7**, we explore the potential pulmonary toxicity of cyclophosphamide in the DCCSS-LATER 2 PULM sub-study. Using a questionnaire, clinic visit and pulmonary function test, we aim to examine the prevalence of long-term pulmonary dysfunction among survivors and the association with cyclophosphamide as a potential independent risk factor.

Part 2: Evaluating the quality of care for childhood cancer patients and survivors

An introduction to the role of clinical practice guidelines and quality indicators in pediatric oncology is given in **Chapter 8**. In **Chapter 9**, we describe the initiation of the International Childhood Cancer Outcome Project. This worldwide effort resulted in the development of a concise core outcome set for 17 types of childhood cancer: the International Childhood Cancer Core Outcome Set. In collaboration with childhood cancer survivors and 17 types of healthcare providers, we present a core set including harmonized outcome definitions and measurement instruments, that can be used to evaluate institutional progress on key outcomes and benchmark with other centers.

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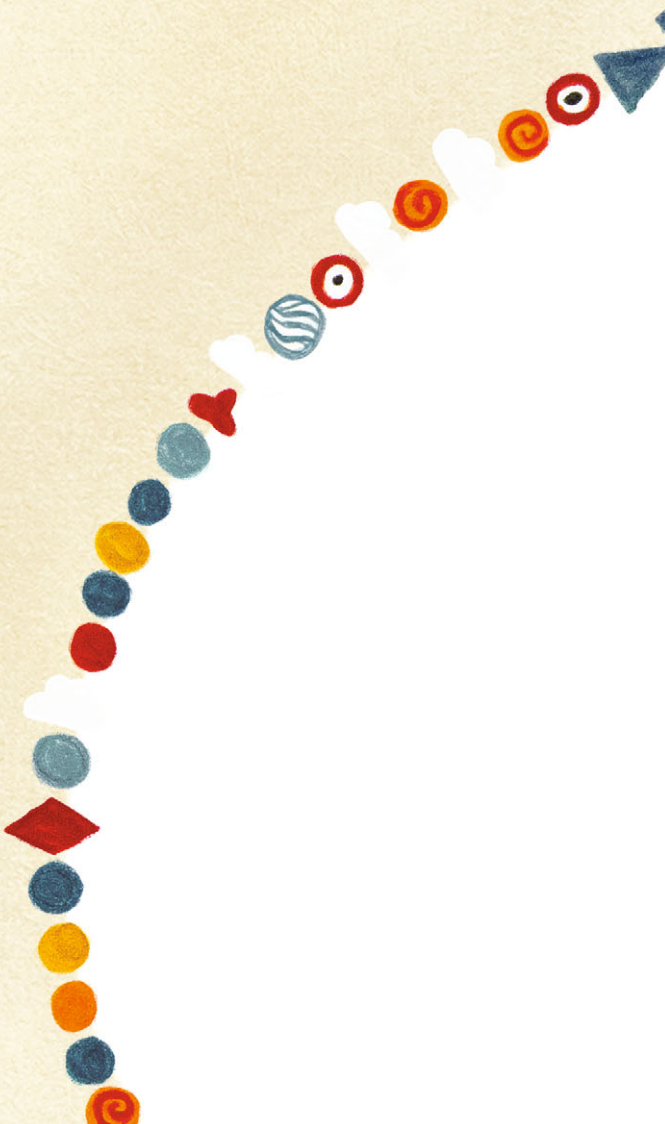
Part 1

Life after childhood cancer and the importance of survivorship care



2

The concept of cancer survivorship and models for long-term follow-up

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ABSTRACT

With improved survival of childhood, adolescent and young adult (CAYA) cancer, the European survivor population of 300,000-500,000 continues to expand. Most survivors will experience at least one and often multiple cancer- and treatment-related late effects throughout their lives, including endocrine toxicities. Besides affecting their physical and psychosocial health status, these might reduce life expectancy and quality of life. Prevalent endocrine complications include hypothalamic-pituitary dysfunction, central precocious puberty, primary thyroid, male or female gonadal dysfunction, metabolic syndrome and low bone mineral density. Long-term follow-up (LTFU) care, including education, risk-based prevention and surveillance strategies, is essential to reduce the burden of endocrine complications and to allow for timely interventions. To integrate scientific expert knowledge, evidence-based clinical practice guidelines have been developed by the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) and PanCare. These guide LTFU care by describing risk populations and preferred surveillance modalities. Moreover, consensus-based recommendations have been developed by PanCareFollowUp where evidence-based guidance is still awaited. The PanCareSurFup models of care guidelines recommend multidisciplinary team care at or under guidance of a cancer survivorship expert center, so CAYA cancer survivors receive appropriate care and support to optimize health.

INTRODUCTION

Survival of children diagnosed with cancer has improved significantly over the last few decades. Transforming from a population with little chance of achieving remission in the 1960s, most childhood cancer patients will now live beyond adolescence or even adulthood (1, 2). Conceptually, survivorship is considered to begin from diagnosis, continuing through treatment and beyond, whether or not the patient is free of disease or experiencing recurrent or advanced disease (3). Survival is considered long-term if extending beyond five years after diagnosis. As a result of the increased cure rates, but also a reduction in late mortality, the current European population of five-year childhood, adolescent and young adult (CAYA) cancer survivors is estimated at 300,000-500,000 and expected to increase by 12,000 each year (4, 5).

Unfortunately, these survivors are often burdened by late cancer-related effects such as organ dysfunction, subsequent neoplasms, psychosocial and cognitive issues, difficulties in education and employment, and a reduced quality of life (QoL) (6-9). These include persisting effects after treatment, but new complications may also develop years or decades after the initial treatment. At an average age of 25 years, 75% of CAYA cancer survivors have at least one such adverse health outcome, considered severe, disabling or life-threatening in 40% (7). This increases to an average of 17 chronic health conditions of which five are severe at the age of 50 years, twice as many as reported in community controls (6). In addition to the primary diagnosis and subsequent treatment, the occurrence and severity of late effects is often determined by a myriad of factors including genetic susceptibility, premorbid and comorbid conditions, health behavior and demographic determinants such as current age and gender (6, 10-13). Overall, the physical and psychosocial burden of cancer-related disease negatively impacts the health status and QoL of survivors (12, 14).

SPECTRUM OF ENDOCRINE LATE EFFECTS

Endocrine toxicities are a substantial contributor to the total cumulative burden of disease among CAYA cancer survivors, alongside cardiovascular, pulmonary, renal, auditory, neurocognitive and musculoskeletal complications, and subsequent neoplasms (6, 15). They include long-lasting complications that have arisen during treatment, but adverse outcome may also emerge years to decades later, adding up to almost three chronic endocrine conditions in the average 50-year CAYA cancer survivor (6). Importantly, diagnosis and treatment of these late complications is often delayed with potential health implications (15, 16). Frequently occurring endocrine late effects comprise hypothalamic-pituitary (HP) dysfunction, primary thyroid dysfunction, primary gonadal injury, metabolic syndrome, obesity, diabetes mellitus, and decreased bone mineral density (Figure 1) (17). Each of these will be briefly introduced in this chapter and described in more detail in the other chapters.

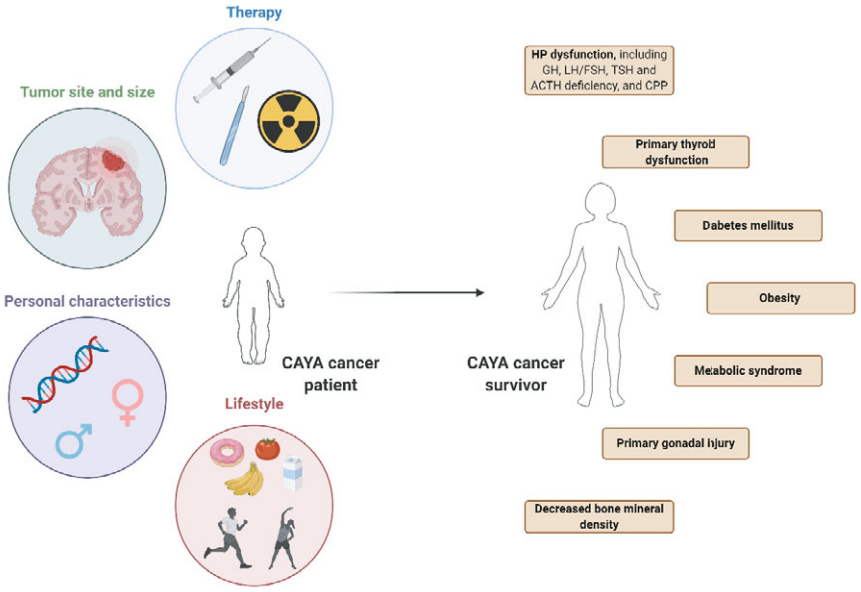

Figure 1. Risk factors for and spectrum of endocrine late effects in survivors of childhood, adolescent and young adult cancer

Figure created with BioRender.com. ACTH, adrenocorticotropic hormone; CAYA, childhood, adolescent and young adult; CPP, central precocious puberty; GH, growth hormone; HP, hypothalamic-pituitary; LH/FSH, luteinizing hormone/follicle-stimulating hormone; TSH, thyroid stimulating hormone.

Hypothalamic-pituitary dysfunction

Damage to the HP structures may cause deficiencies in the HP hormones, including growth hormone (GH), luteinizing hormone/follicle-stimulating hormone (LH/FSH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), and can induce central precocious puberty (CPP) (18). Central diabetes insipidus, although resulting from direct HP injury by tumor growth-related mass effects or surgical resection, is generally not considered a late endocrine effect, as it typically occurs within weeks after treatment (19). Whereas tumor size and brain surgery drive most of the early-occurring HP dysfunction, late HP effects are often dose-dependently related to radiotherapy and occur months, years or even decades after the initial treatment (16, 18, 19). All three factors are major causes of the late endocrine burden of survivors (18). The contribution of chemotherapy to late endocrine burden is still being debated (20).

Half of all survivors who have received cranial radiotherapy will develop at least one HP-related hormonal deficiency, with prevalences among those with tumor HP involvement around 80, 55, 50 and 30-50% for GH, TSH, LH/FSH and ACTH deficiency respectively (16, 18). These observations have driven protocol changes, including the reduction of harmful and potentially avoidable exposures such as prophylactic central nervous system irradiation in acute lymphoblastic leukemia (21), and minimization of scatter radiation by using protons instead of photons (22). Some novel agents, including tyrosine kinase and immune checkpoint inhibitors, have been reported to cause endocrine

adverse effects, but potential reversibility after discontinuation and long-term endocrine outcomes still have to be elucidated (23, 24). Notably, HP dysfunction may have an impact on physical, psychosocial and neurocognitive outcomes in CAYA cancer survivors, depending on the type of hormone deficiency observed (18).

Primary thyroid dysfunction

Thyroid conditions after childhood cancer treatment include hypothyroidism and hyperthyroidism, as well as thyroid nodules and malignancies. For hypothyroidism, a variety of risk factors have been described including radiotherapy to a volume exposing the thyroid gland, 131-I-metaiodobenzylguanidine (MIBG) treatment, conventional chemotherapeutic agents such as busulphan and cyclophosphamide, the more novel tyrosine kinase inhibitors and immune system modulators, or hematopoietic stem cell transplant (HSCT)-induced immune-mediated thyroiditis (23-26). In contrast, hyperthyroidism, thyroid nodules and thyroid cancer are most often caused by radiation to volumes exposing the thyroid gland and therapeutic 131-I-MIBG (27-29).

Primary gonadal injury

Male and female gonadotoxicity are important side-effects of treatment, and their repercussions may vary over the course of life. Male gonadal failure encompasses impaired spermatogenesis, testosterone insufficiency and physical sexual dysfunction, and may result in emotional distress, impaired pubertal development and subfertility among male CAYA cancer survivors (30). Contributors to the male gonadotoxicity risk include radiotherapeutic (total body irradiation or radiotherapy to a volume exposing the testes or pelvis), chemotherapeutic (especially alkylating agents including cyclophosphamide, chlormethine, procarbazine, ifosfamide, busulfan/cyclophosphamide or fludarabine/melphalan HSCT conditioning), and surgical exposures (surgery to the spinal cord, sympathetic nerves or pelvis) (31). Female impairment of gonadal function results in primary ovarian insufficiency which may present with primary or secondary amenorrhea, impaired pubertal development, or premature menopause, with risk determinants including alkylating agents (especially cyclophosphamide and procarbazine) and radiotherapy to a volume potentially exposing the ovaries (32).

Metabolic syndrome, obesity and diabetes mellitus

Metabolic syndrome is defined by the World Health Organization as the co-occurrence of diabetes mellitus or impaired glucose tolerance with at least two out of four conditions including obesity, hypertension, dyslipidemia and microalbuminuria. Its relevance derives from its association with cardiovascular adverse health outcomes (33). Metabolic syndrome occurs at significantly higher rates in CAYA cancer survivors than in the general population. Part of this excess prevalence may be experienced due to treatment-related exposures such as abdominal or total body irradiation or prolonged systemic glucocorticoid usage (34). At particular risk for obesity are those with hypothalamic damage due to a tumor or surgery involving the HP region (35). Fortunately, improvement in survivors' lifestyles has been shown to improve their cardiometabolic risk profile, enabling survivors to influence their own health outcomes despite their potentially heightened risk (36).

Low bone mineral density

Low bone mineral density is present in 9-18% of five-year CAYA cancer survivors (6, 15). Resulting from an imbalance between bone acquisition and resorption, multiple cancer-related factors can be distinguished that may contribute to its etiology in any individual survivor. These may be related to the primary diagnosis (e.g., the impact of leukemia on bone structure), treatment (prolonged glucocorticoid use or craniospinal or total body irradiation, or HSCT), comorbidities (GH deficiency or hypogonadism), and lifestyle (lower levels of weight bearing physical activity, nutritional factors such as vitamin D and calcium intake) (37, 38). More recently, the adverse impact of retinoid derivatives and tyrosine kinase inhibitors has been reported (23, 39).

IMPORTANCE OF LONG-TERM FOLLOW-UP TO REDUCE BURDEN OF MORBIDITY AND IMPROVE QUALITY OF LIFE

The ultimate goal of treating a child, adolescent or young adult with cancer is that he or she "becomes a resilient and autonomous adult with optimal health-related quality of life, accepted in society at the same level as his/her age peers" (40). This underscores the universally recognized importance of adequate long-term follow-up (LTFU) care for CAYA cancer survivors (41). LTFU care facilitates strategies for prevention and early detection of late effects, timely initiation of treatment, education of the survivor about their health and treatment history and risks, and empowerment in adopting a healthy lifestyle. Reducing the occurrence and severity of late complications becomes increasingly important as individual survivors and the overall survivor population age, leading to a further increase in the burden of late chronic conditions and putting a strain on healthcare resources. Moreover, LTFU care includes psychosocial support and guidance in topics such as education, employment, or insurance. Optimally, survivors are also supported in their transition from acute care to LTFU and from pediatric to adult care services, which require higher levels of self-management (41).

Core components of LTFU comprise a summary of cancer treatment and a personalized survivorship care plan based on clinical practice guidelines (CPGs) and shared-decision making. Altogether, the multi-faceted structure of LTFU care helps to mitigate potential late effects in the physical, psychological, and social domains of a survivor's life and thereby aims to improve their quality of life. Several reports have indicated that LTFU care creates awareness about late effects, contributes to higher detection rates of important late effects and reduces emergency care visits (42, 43). However, more rigorous studies on the effects of LTFU care on survivors' medical and psychosocial, as well as health economic, outcomes remain to be conducted.

CLINICAL PRACTICE GUIDELINES

In the 1990s and early 2000s, as a pressing need for guidance in LTFU surveillance and care emerged, several experts groups developed CPGs describing the content of LTFU care for specific survivor populations (44). These included the North American Children's Oncology Group (COG), the Dutch Childhood Oncology Group (DCOG), the United Kingdom Children's Cancer and Leukaemia Group (CCLG), and the Scottish Intercollegiate Guidelines Network (SIGN) (45-48). Although each group used evidence-

based methodologies, they reached different conclusions regarding risk groups, surveillance tests, and follow-up initiation and frequency. In addition to uncertainty about the optimum approach for an individual survivor, this also translated into suboptimal use of financial and staff resources and duplication of work.

Therefore, the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) was established in 2010, as an international collaboration to harmonize and formulate CPG recommendations according to a common vision (44). In addition to recommending risk-based prevention and surveillance, particular attention is also directed at reducing unnecessary or even harmful procedures. Working groups represent a geographical spread of continents and multitude of professional backgrounds, including survivor representatives, but also experts in pediatric oncology and hematology, radiology, radiation oncology, pharmaco-oncology, epidemiology, survivorship care, psychology and other fields relevant to the guideline topic.

Thus far, eight evidence-based IGHG guidelines have been published in peer-reviewed journals, describing optimum surveillance and management strategies for asymptomatic cardiomyopathy, fatigue, obstetric care, ototoxicity, male gonadotoxicity, premature ovarian insufficiency, thyroid cancer, and female breast cancer (34, 36, 37, 55-59). Based on the level of evidence, each included recommendation is classified as strong (green), moderate (yellow) or weak (orange) or as a recommendation not to do (red). CPGs for various other late effects, including endocrine toxicities such as HP dysfunction, CPP, thyroid dysfunction, bone toxicity and metabolic syndrome, are being developed or nearing completion. In parallel, the European CAYA cancer survivorship organization PanCare is creating evidence-based CPGs describing optimum approaches to LTFU care organization and implementation, as well as transition from acute to LTFU care and from pediatric to adult care settings (41, 49).

Despite the remarkable progress achieved in developing harmonized CPGs to guide LTFU care, it has also become clear that development of these evidence-based guidelines is time- and resource-consuming. As a result, many late effects are still awaiting harmonized recommendations for prevention and surveillance. Hence, the partners in the European PanCareFollowUp project which is focused on implementation of person-centered LTFU care across Europe have formulated surveillance recommendations for those late effects currently lacking CPGs. This has resulted in the development of 28 consensus-based recommendations by a multinational team representing a total of 19 European countries. These will be used in the novel PanCareFollowUp Care Intervention and will be published in a peer-reviewed journal soon.

The PanCareFollowUp recommendations include, among other topics, strategies for surveillance of endocrine late effects such as diabetes mellitus, dyslipidemia, overweight and obesity, hypertension, bone problems and thyroid function abnormalities to bridge the gap until publication of the corresponding IGHG guidelines. As the consensus-based recommendations only address the topics where evidence-based guidelines are lacking, the green, yellow and red, but not the orange recommendations in the existing IGHG guidelines have been adopted in the PanCareFollowUp Care Intervention. Preliminary recommendations from the IGHG working groups for HP dysfunction and CPP have been included as well. Future updates to the consensus-based recommendations will be performed by the PanCare Guidelines Group. An overview of existing recommendations for endocrine late effects is presented in Table 1.

Table 1. Existing recommendations for surveillance of endocrine late effects

Recommendation for surveillance of …	**Who is at risk?** CAYA cancer survivors treated with or with a history of …
Premature ovarian insufficiency (IGHG[b])	- Alkylating agents - Radiotherapy to a volume exposing the ovaries, including TBI Note: only female survivors with the exposures mentioned above are considered at risk.
Male gonadotoxicity (including impaired spermatogenesis, testosterone deficiency and physical sexual dysfunction) (IGHG[c])	- Alkylating agents - Radiotherapy to a volume exposing the testes, including TBI - Surgery to the spinal cord, sympathetic nerves or pelvis - Hypogonadism Note: only male survivors with the exposures mentioned above are considered at risk.
Thyroid cancer (IGHG[d])	- Radiotherapy to a volume exposing the thyroid gland, including TBI - Therapeutic 131-I-MIBG
HP dysfunction, including GHD, TSHD, LH/FSHD and ACTHD (preliminary IGHG[e])	- Radiotherapy to a volume exposing the HP region, including TBI *(if ≥ 30 Gy, refer directly to (pediatric) endocrinologist or see in multidisciplinary team)* - Surgery near or within the HP region *(refer directly to (pediatric) endocrinologist or see in multidisciplinary team)* - CNS tumors near or within the HP region *(refer directly to (pediatric) endocrinologist or see in multidisciplinary team)* - Hydrocephalus or cerebrospinal fluid shunt *(at risk for GHD)*

What surveillance modality should be used and at what frequency?[a]
Pre- and peri-pubertal survivors at risk: - FSH and estradiol in case of failure to initiate or progress through puberty at least for girls ≥ 11 years of age, and for girls with primary amenorrhea (16 years of age) *Post-pubertal survivors at risk:* - FSH and estradiol in case of menstrual cycle dysfunction suggesting premature ovarian insufficiency, or if assessment of potential for future fertility is desired *Not recommended:* Measurement of AMH as the primary surveillance modality
Post-pubertal survivors treated with radiotherapy ≥ 12 Gy to a volume exposing the testes, including TBI: - Early morning testosterone at clinically appropriate time intervals - LH in addition to (early morning) testosterone if clinical signs of hypogonadism, previous low or borderline testosterone concentrations, or if an early morning testosterone sample cannot be obtained, at least every 2-3 years *Post-pubertal survivors at risk that desire assessment of potential for future fertility:* - Semen analysis
All survivors at risk: - Counselling regarding options for differentiated thyroid carcinoma surveillance, at least every 5 years *If the decision to commence surveillance is made, a shared decision should be made for one of these two surveillance modalities:* - Neck palpation, every 1-2 years, starting 5 years after radiotherapy, or - Thyroid ultrasonography, every 3-5 years, starting 5 years after radiotherapy
Pre-pubertal and peri-pubertal survivors at risk: - Height velocity in relation to parental height, and Tanner stage, every 6 months - fT4, TSH, 8 AM cortisol every year *Post-pubertal survivors at risk:* - fT4, TSH, 8 AM cortisol, IGF-1 every year *Post-pubertal female survivors at risk:* - Estradiol, LH and FSH every year *Post-pubertal male survivors at risk:* - Morning testosterone, or free testosterone in survivors with overweight, and LH every year Note: Surveillance should be initiated at ≥ 6 months from the end of radiotherapy, or from diagnosis or occurrence of hydrocephalus or cerebrospinal fluid shunt for non-radiated at-risk survivors. Continue surveillance at least 15 years from exposure. Continuation of surveillance should be a shared decision between survivor and HCP considering available healthcare resources. If surveillance is terminated, the survivor should be educated about possible signs and symptoms of HP axis problems.

Table 1. Existing recommendations for surveillance of endocrine late effects (continued)

Recommendation for surveillance of …	**Who is at risk?** CAYA cancer survivors treated with or with a history of …
Central precocious puberty (preliminary IGHG[f])	- Radiotherapy to a volume exposing the HP region - Surgery near or within the HP region - CNS tumors near or within the HP region - Hydrocephalus or cerebrospinal fluid shunt
Thyroid function problems (PCFU[g])	- Radiotherapy to a volume exposing the thyroid gland, including TBI - Allogeneic HSCT - I-131 MIBG therapy - Radioiodine therapy (I-131 ablation therapy)[h] - Total thyroidectomy[i]
Reduced bone mineral density (PCFU[g])	- Prolonged corticosteroids as anti-cancer treatment, at least 4 weeks continuously - Methotrexate - HSCT, especially with any history of cGvHD - TBI - Cranial and/or spinal radiotherapy - Gonadal failure - GHD
Metabolic syndrome (PCFU[g]) (continued)	
Diabetes mellitus and impaired glucose metabolism	- Radiotherapy to a volume exposing the pancreas, including TBI
Dyslipidemia	- TBI - HSCT
Overweight and obesity	- CNS tumors near or within the HP region - Radiotherapy to a volume exposing the HP region, including TBI - Surgery near or within the HP region

	What surveillance modality should be used and at what frequency?[a]
	All survivors at risk: - Height velocity in relation to parental height, and Tanner stage, every 6 months *Male survivors at risk exposed to gonadotoxic treatment:* - Morning testosterone if puberty is suspected as testicular volume measurements may not be reliable Note: Surveillance should be initiated at ≥ 6 months from the end of radiotherapy, or from diagnosis or occurrence of hydrocephalus or cerebrospinal fluid shunt for non-radiated at-risk survivors. Surveillance should be continued until the age of 8 years (girls) or 9 years (boys).
	Survivors at risk ≤ 18 year of ages: - TSH and fT4 measurement, every year *Survivors at risk > 18 years of age:* - TSH and fT4 measurement, every 2-3 years *Female survivors at risk:* - TSH and fT4 measurement prior to attempting pregnancy and periodically during pregnancy
	All survivors at risk: - A DXA scan once, if possible, and thereafter as clinically indicated
	All survivors at risk: - Fasting blood glucose with or without HbA1c at least every 5 years - Fasting lipid profile starting no later than at the age of 40 years, and at least every 5 years subsequently - Height, weight and BMI at least every 2 years and at every LTFU visit

Table 1. Existing recommendations for surveillance of endocrine late effects (continued)

Recommendation for surveillance of …	**Who is at risk?** CAYA cancer survivors treated with or with a history of …
Metabolic syndrome (PCFU[g]) (continued)	
Hypertension	- Radiotherapy to a volume exposing the kidneys, or to a volume exposing the heart and associated large vessels, including TBI - Nephrectomy - Ifosfamide - Platinum based chemotherapy - Nitrosoureas - Immunosuppressives

ACTHD, adrenocorticotropic hormone deficiency; BMI, body mass index; CAYA, childhood, adolescent and young adult; cGvHD, chronic graft-versus-host disease; CNS, central nervous system; FSH, follicle-stimulating hormone; fT4, free thyroxine; GHD, growth hormone deficiency; HCP, healthcare provider; HP, hypothalamic-pituitary; HSCT, hematopoietic stem cell transplant; I-131-MIBG, I-131-metaiodobenzylguanidine; IGHG, International Late Effects of Childhood Cancer Harmonization Group; LH, luteinizing hormone, LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiency; LTFU, long-term follow-up; MIBG, metaiodobenzylguanidine; PCFU, PanCareFollowUp; TBI, total body irradiation; TSH, thyroid stimulating hormone; TSHD, thyroid stimulating hormone deficiency.

[a] Surveillance should be initiated no later than five years after treatment or five years from diagnosis, depending on the individual healthcare systems, and surveillance should be continued life-long, unless specified otherwise.

[b] This recommendation reflects the content of the IGHG Premature Ovarian Insufficiency guideline (reference 32; accessible through www.ighg.org/guidelines/topics/premature-ovarian-insufficiency/).

[c] This recommendation reflects the content of the IGHG Male Gonadotoxicity guideline (reference 31; accessible through www.ighg.org/guidelines/topics/male-gonadotoxicity/).

[d] This recommendation reflects the content of the IGHG Thyroid Cancer guideline (reference 29; accessible through www.ighg.org/guidelines/topics/thyroid-cancer/).

[e] This recommendation reflects the recommendations of the preliminary evidence-based IGHG Hypothalamic-Pituitary Dysfunction guideline. The guideline will be published in a peer-reviewed journal soon.

[f] This recommendation reflects the recommendations of the preliminary evidence-based IGHG Central Precocious Puberty guideline. The guideline will be published in a peer-reviewed journal soon.

[g] The PanCareFollowUp Recommendations will be submitted for publication in a peer-reviewed journal soon.

[h] CAYA cancer survivors treated with radioiodine treatment should receive follow-up by an endocrinologist starting directly after exposure.

[i] CAYA cancer survivors treated with a total thyroidectomy should receive follow-up by an endocrinologist starting directly after surgery. These survivors and their HCPs should be aware of the risk of primary hypoparathyroidism.

What surveillance modality should be used and at what frequency?[a]
All survivors at risk: - Blood pressure measurement at least every 2 years and at every LTFU visit

An important consideration with regard to any CPG is the pace at which new evidence emerges, thereby quickly outdating the evidence summaries that support its conclusions. In the field of CAYA cancer survivorship, almost 3,300 papers were published on CAYA cancer survivorship in 2019 alone, compared to 1,200 publications a decade before, translating to approximately 10 potentially relevant papers being published every day. The next step forwards may be introduced by enabling real-time evidence summaries to be created based on regular database searches. For example, an automated monthly update on relevant publications could facilitate CPG working groups to provide updates on a six-monthly or annual basis. The PanCareFollowUp Consortium is therefore also developing such a living guideline tool to support the ongoing creation of high-quality CPGs in LTFU care.

MODELS OF CARE

The organization and delivery of LTFU care varies widely between countries and even institutions within countries, reflecting the diversity of healthcare systems, resources and cultural preferences that surround patients and survivors of CAYA cancer (41). The PanCareSurFup guideline for the organization of long-term follow-up care recommends that LTFU care should be provided in or under the guidance of a cancer survivorship expert service or cancer center (Table 2). It should include an individualized survivorship care plan, including a treatment summary and recommendations based on the international CPGs (41).

Current examples of care organization include cancer center-delivered, shared, general practitioner-led or supported self-management care models, the first of which is most commonly implemented (41). The preferred alternative should result from a joint decision between the survivor and the healthcare provider, taking into consideration the survivor's treatment history, cancer-related and overall health risks, personal preferences, as well as the healthcare infrastructure. Regardless of the care model, it is strongly recommended that care decisions are guided by a multidisciplinary team under guidance of a survivorship expert center (41). At minimum, a key worker, physician with late effects

Table 2. PanCareSurFup recommendations for the organization of long-term follow-up care of childhood, adolescent and young adult survivors

General recommendation
We recommend that LTFU care should be available and accessible for all childhood, adolescent and young adult cancer survivors throughout their lifespan
Organization of LTFU care
We recommend that LTFU care for survivors of childhood, adolescent and young adult cancer should: Be provided in or under the guidance of a cancer survivorship expert service or cancer center Provide multidisciplinary care
We recommend that the survivor and healthcare provider make a joint decision for the optimal model of LTFU care[a], based on previous cancer treatment, health conditions, survivor preferences, and the healthcare system
To provide LTFU care for survivors of childhood, adolescent and young adult cancer we recommend: To have commitment of the (national and local) healthcare providers (systems) and insurers To have sufficient time for consultation
Personnel involved in LTFU care
We recommend that each survivor can make their own informed choice for a healthcare provider after informed discussion with the survivorship team
We recommend that the cancer survivorship expert center that will organize LTFU care includes: Key worker/coordinator Lead doctor specialized in late effects Nurse practitioner Multidisciplinary expert team of specialists[b] The possibility of consulting specific specialists[c]
Components of LTFU care
We recommend that LTFU care for survivors of childhood, adolescent and young adult cancer includes: Surveillance and preventive strategies based on published evidence based guidelines Coordination of care (particularly in shared care models) Education for professionals Education of survivors, families & carers Coordination of scientific research
We recommend that the cancer survivorship expert center provides: An individualized survivorship care plan Including a treatment summary with risk stratification care plan Patient/survivor and parent education to support effective self-management A plan for transition of care: From active treatment to LTFU From survivorship expert center to primary care (for low risk survivors) From pediatric to adult health services

Table 2. PanCareSurFup recommendations for the organization of long-term follow-up care of childhood, adolescent and young adult survivors (continued)

Start of LTFU care
We recommend that LTFU care should start no later than 5 years after treatment or 5 years from diagnosis, depending on the individual healthcare systems

From Michel et al. (reference 41). Reprinted by permission from Springer Nature Customer Service Center GmbH. LTFU, long-term follow-up.

[a] Self-management with primary care support for adult survivors; follow-up at primary care level or by a nurse experienced in management of late effects, followed by supported self-management; follow-up at cancer survivorship expert center; or shared care between survivorship expert center and primary care or pediatric centers.

[b] Pediatric oncologist/hematologist, (neuro-)psychologist, cardiologist, endocrinologist, medical oncologist, hematologist, rehabilitation physician, occupational worker, radiotherapist, social worker.

[c] Pulmonologist, nephrologist, neurologist, neurosurgeon, ear nose and throat specialist, ophthalmologist, gynecologist, dermatologist, insurance worker, urologist, general internal medicine.

expertise, nurse practitioner, multidisciplinary team representing pediatric and adult oncology, (neuro)psychology, endocrinology, cardiology, radiotherapy, physical rehabilitation therapy, occupational and social work should be at hand, with consultation of other experts available if needed.

Especially for CAYA cancer survivors at risk for endocrine conditions, specific expertise is important. Moreover, LTFU care should be initiated no longer than five years after diagnosis or treatment but may need to be initiated at an earlier stage in those with or at risk of early-onset chronic morbidities including many endocrinopathies. Care is suggested to continue lifelong at regular intervals, based on the most recent risk-based recommendations. Current challenges include the shift from expert- to survivor-centered care, with possible implications for the current care structures, but the potential to better address survivor's current unmet needs (50).

CONCLUSION

Survivors of CAYA cancer are at risk for long-term adverse chronic health problems, some of which may arise years to decades after initial therapy. Endocrine complications represent a significant proportion of the late effects burden, and survivors at risk should receive person-centered guideline-based surveillance to maintain and improve their health and QoL through timely management. Harmonized evidence-based CPGs are essential to guide multidisciplinary LTFU teams in providing the care that is needed. Consensus-based recommendations have been developed by the PanCareFollowUp project to address late effects still awaiting evidence-based guidelines. Although the structure of LTFU may vary from center to center, it is recommenced strongly that care should be provided by a multidisciplinary team at or under guidance of a survivorship expert center.

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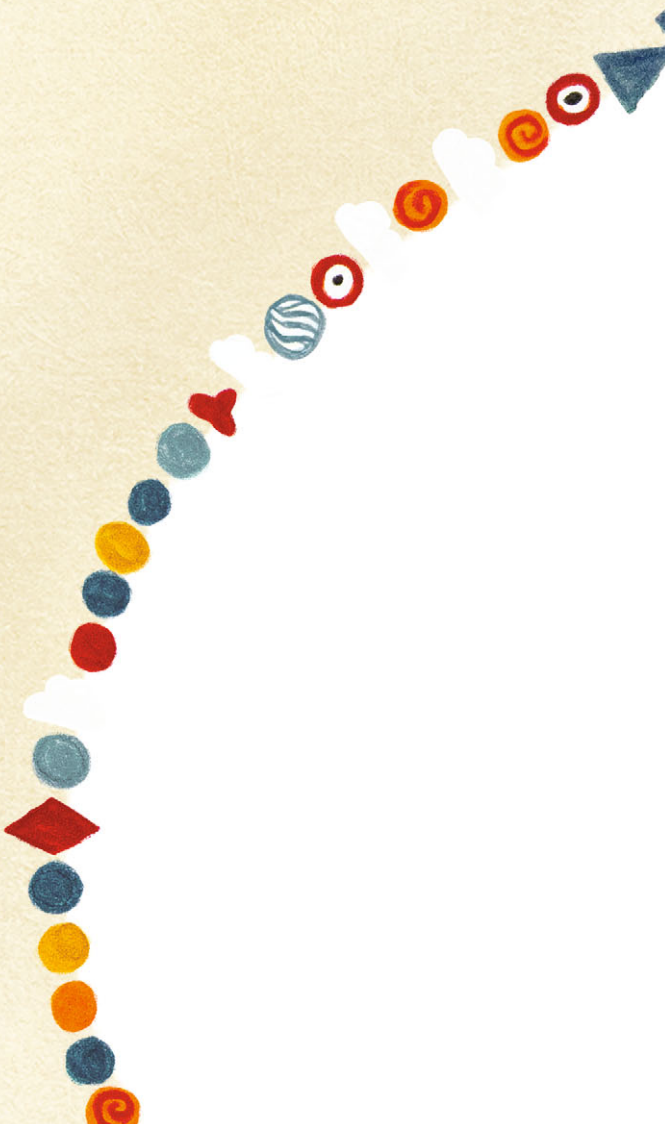

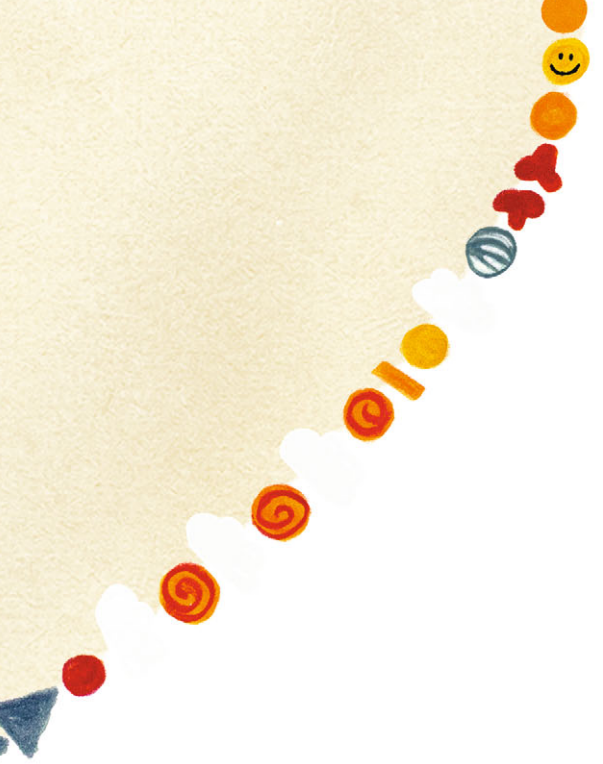

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The European multistakeholder PanCareFollowUp project: novel, person-centered survivorship care to improve care quality, effectiveness, cost-effectiveness and accessibility for cancer survivors and caregivers

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ABSTRACT

Background The majority of childhood cancer survivors are at risk for treatment-related adverse health outcomes. Survivorship care to mitigate these late effects is endorsed, but it is not available for many adult survivors of childhood cancer in Europe. The PanCareFollowUp project was initiated to improve their health and quality of life (QoL) by facilitating person-centered survivorship care.

Methods The PanCareFollowUp Consortium was established in 2018, consisting of 14 project partners from ten European countries, including survivor representatives. The consortium will develop two PanCareFollowUp Interventions, including a person-centered guideline-based model of care (Care Intervention) and eHealth lifestyle coaching (Lifestyle Intervention). Their development will be informed by several qualitative studies and systematic reviews on barriers and facilitators for implementation and needs and preferences of healthcare providers (HCPs) and survivors. Implementation of the PanCareFollowUp Care Intervention as usual care will be evaluated prospectively among 800 survivors from Belgium, Czech Republic, Italy and Sweden for survivor empowerment, detection of adverse health conditions, satisfaction among survivors and HCPs, cost-effectiveness and feasibility. The feasibility of the PanCareFollowUp Lifestyle Intervention will be evaluated in the Netherlands among 60 survivors.

Results Replication Manuals, allowing for replication of the PanCareFollowUp Care and Lifestyle Intervention, will be published and made freely available after the project. Moreover, results of the corresponding studies are expected within the next five years.

Conclusions The PanCareFollowUp project is a novel European collaboration aiming to improve the health and QoL of all survivors across Europe by developing and prospectively evaluating the person-centered PanCareFollowUp Care and Lifestyle Interventions.

INTRODUCTION

Each year, 35,000 European children, adolescents and young adults are diagnosed with cancer (1). Fortunately, as treatments have improved, so have five-year survival rates. In Western European countries, survival has surged from 40% to more than 80% since the 1970s, with similar trends but lower survival rates in Eastern European countries (2). As a result, the current population of European childhood cancer survivors has increased to around 500,000 and expands each year (1). Cancer therapeutic regimens, such as chemotherapy, radiotherapy, and surgery, are crucial for achieving survival, but are likely to have adverse effects on physical and mental health as well as psychosocial wellbeing later in life such as a risk of subsequent neoplasms, organ dysfunction, fatigue or educational and employment difficulties (3-7).

Person-centered and guideline-based survivorship care can mitigate the negative impact on quality of life (QoL) of survivors and their families (8). Survivorship care has a strong focus on education, prevention or early detection of late effects, and timely intervention when problems occur (9). In addition to risk-based surveillance, a healthy lifestyle is a powerful tool to reduce survivors' elevated risk of chronic health conditions. Survivorship care may include person-centered lifestyle advice with consideration of their medical history, physical limitations, psychosocial functioning, or other barriers and facilitators that survivors may experience in adapting to and maintaining a healthy lifestyle (10, 11). Considering limited healthcare resources, provision of follow-up care also needs to be sustainable and cost-effective (12). Person-centered strategies that engage patients, allow shared decisions and support empowerment have been shown to produce more satisfaction, better health, higher QoL, and lower costs (13). Person-centered care facilitates shared decision-making between the survivor and healthcare provider (HCP) through three key elements: initiating, working, and safeguarding the partner relationship (14-16). It may support survivors as they transition from treatment to follow-up, from childhood to adolescence, and from pediatric to adult healthcare settings. Thus, they may be able to navigate the complexity of various specialists being involved in adult healthcare and take responsibility for their own health (17).

Implementation of survivorship care, however, has proven challenging across the globe (18). Only 38% of European hospitals offer a survivorship care program for survivors that have left pediatric oncology services, with availability and level of person-centered care varying considerably (19). Although HCPs generally agree on the importance of person-centered survivorship care, multiple barriers exist that prevent proper implementation, including lack of personnel, time required by HCPs and funding (19). Furthermore, the absence of optimal survivorship care for most survivors might also be explained by the fact that it is complex. Although different care models have been suggested over the years, improvement in long-term follow-up care is still urgently needed (20).

To meet this request, the Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer (PanCare) established the Horizon 2020-funded PanCareFollowUp project (**www.pancarefollowup.eu**) to improve current care and get more insight into the feasibility and effectiveness of delivering optimal person-centered survivorship care. The multidisciplinary PanCare network (**www.pancare.eu**) unites professionals, childhood cancer survivors and their families with the aim of reducing the

frequency, severity and impact of late adverse effects by establishing high quality and sustainable survivorship care for all survivors in Europe (21). PanCare has initiated and/or contributed to multiple European-funded projects to improve survivors' health and QoL, such as PanCareSurFup (22), PanCareLIFE (23), the European Network for Cancer Research in Children and Adolescents (ENCCA), the Joint Action on Rare Cancers (JARC) and the European Expert Pediatric Oncology Reference Network for Diagnostics and Treatment (ExPO-r-Net). The PanCareFollowUp Consortium was established in 2018, consisting of 14 project partners from ten European countries. As a project partner, Childhood Cancer International Europe ensures that survivors contribute to all stages of the project, from development and assessment to implementation.

The PanCareFollowUp project includes the development and evaluation of two person-centered interventions: the PanCareFollowUp Care and Lifestyle Interventions (Figure 1).

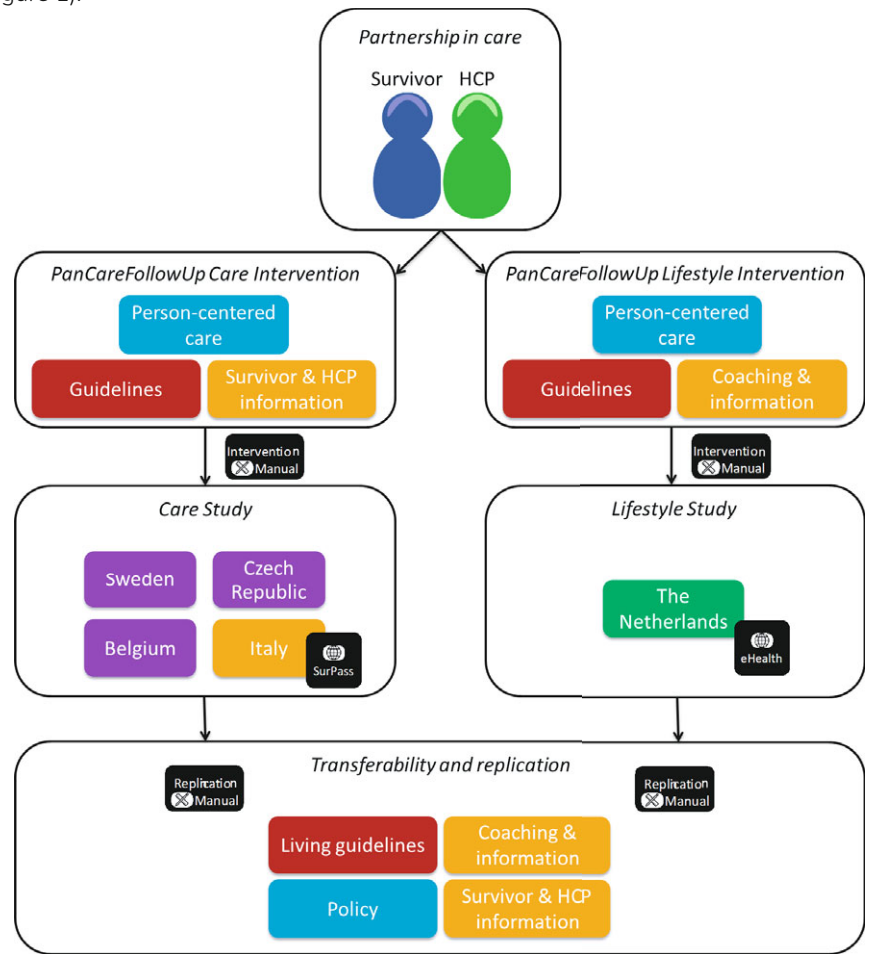

Figure 1. Overview of the PanCareFollowUp project, including the PanCareFollowUp Care and Lifestyle Inbterventions and the corresponding Care and Lifestyle Studies
HCP, healthcare provider; SurPass, Survivorship Passport.

The Care Intervention consists of a person-centered, guideline-based care model that can be tailored to the survivor's needs and preferences within the local healthcare context. The Lifestyle Intervention innovatively builds upon current survivorship care through an eHealth intervention with personalized lifestyle coaching. Experiences of Dutch survivorship clinics that have already implemented person-centered care successfully (24, 25) will be used to govern the development of both Interventions.

METHODS

Aims and objectives of the PanCareFollowUp project

The overall aim of the PanCareFollowUp project is to empower childhood cancer survivors across Europe and improve their health and QoL by facilitating a high standard of person-centered survivorship care. This research has three main objectives: (1) development and evaluation of the person-centered PanCareFollowUp Care Intervention using a prospective cohort study (Care Study) (Figure 2), (2) development and evaluation of the PanCareFollowUp Lifestyle Intervention using a feasibility study (Lifestyle Study) (Figure 2), and (3) sustainable replication, including free distribution of a Care and Lifestyle Replication Manual after the project.

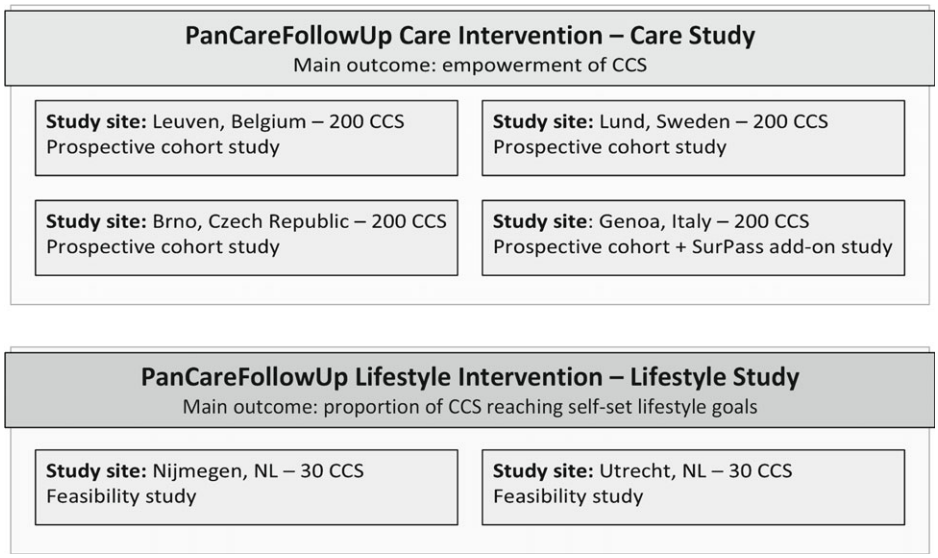

Figure 2. Study cohorts in the PanCareFollowUp Care and Lifestyle Studies
CCS, childhood cancer survivors; NL, the Netherlands.

Organizational structure of the PanCareFollowUp project

The project consists of eight Work Packages (WPs): WP1-4 to develop and conduct the Care Study, WP5 to develop and conduct the Lifestyle Study, and WP6-8 to cover dissemination, management and ethics, respectively (Table 1).

Table 1. Overview of tasks and Work Package leads involved in the eight Work Packages comprising the PanCareFollowUp project

Work Package 1: Person-centered PanCareFollowUp Care Intervention *Work package lead:* PMC
Develop the PanCareFollowUp Care Intervention, including PanCareFollowUp Recommendations, Survivor Questionnaire, Treatment Summary template, Survivorship Care Plan template and information materials for survivors and HCPs
Perform preimplementation study and develop tailored implementation strategies
Deliver workshop on person-centered care
Develop system to update current guidelines when new evidence is published
Develop a Replication Manual for future implementation of the PanCareFollowUp Care Intervention after the end of the project
Work Package 2: Conduct of PanCareFollowUp Care prospective cohort study *Work package lead:* ULUND
Develop the PanCareFollowUp Care Study Protocol
Develop and test the PanCareFollowUp Care Study Handbook and SOPs
Prepare study sites, including establishment of local working groups and securing local ethics approval
Conduct and manage PanCareFollowUp Care prospective cohort study, including data collection
Work Package 3: Measures and analyses of PanCareFollowUp Care prospective cohort study *Work package lead:* DCS
Select outcome measures and data collection instruments and develop data dictionary
Design and build database of PanCareFollowUp Care prospective cohort study
Data management and statistical analysis of PanCareFollowUp Care prospective cohort study
Work Package 4: Survivorship Passport *Work package lead:* SIOP-E
Feasibility study of SurPass web-based delivery of PanCareFollowUp Care Intervention, including exploration of a SurPass mobile app
Develop plain language brochures for survivors for all PanCareFollowUp Recommendations
Work Package 5: PanCareFollowUp eHealth Lifestyle Intervention *Work package lead:* RUMC and PMC
Perform two systematic reviews on 1) effectiveness and effective components of eHealth lifestyle interventions, and 2) barriers and facilitators for survivors in adapting to and maintaining a lifestyle with regular physical activity and/or a healthy dietary intake
Qualitative interviews and focus group discussions with survivors and HCPs on barriers and facilitators in adopting a healthy lifestyle and delivering lifestyle advice to survivors
Develop the PanCareFollowUp eHealth Lifestyle Intervention and evaluate with a feasibility study
Develop a Replication Manual for future implementation of the PanCareFollowUp eHealth Lifestyle Intervention after the end of the project

Table 1. Overview of tasks and Work Package leads involved in the eight Work Packages comprising the PanCareFollowUp project (continued)

Work Package 6: Communication and dissemination *Work package lead:* PanCare
Develop and execute tailored communication and dissemination strategies Support future replication and legacy
Work Package 7: Management *Project Coordinator:* PMC *Project Administrator:* PT
Coordination and scientific leadership Project management support
Work Package 8: Ethics requirements *Work package lead:* ICRC
Ensure compliance with ethical requirements

DCS, Danish Cancer Society, Denmark; HCP, healthcare provider; ICRC, International Clinical Research Center at St. Anne's University Hospital, Czech Republic; PMC, Princess Máxima Center for Pediatric Oncology, the Netherlands; RUMC, Radboud University Medical Center, the Netherlands; SIOP-E, European Society for Pediatric Oncology, Belgium; SOP, Standard Operating Procedure; SurPass, Survivorship Passport; ULUND, Lund University, Lund, Sweden.

Work Package 1: Development of the person-centered PanCareFollowUp Care Intervention

Clinical practice guidelines

To ensure consistent high-quality care in daily practice, evidence-based clinical practice guidelines (CPGs) that inform on effective preventative measures and surveillance methods are essential (9). CPGs describe the risk-based surveillance that is recommended and discussed with the survivor in a shared decision-making process. Recognition of the advantages of international collaboration in CPG development led to the initiation of the International Late Effects of Childhood Cancer Guideline Harmonisation Group (IGHG) by several guideline groups in 2010 (25-28). So far, eight widely accepted IGHG guidelines have been published in peer-reviewed journals, several with major contributions from PanCareSurFup, with further ones in development (29-36). PanCareSurFup has published recommendations for models of long-term follow-up care, and a guideline for transition from pediatric to adult healthcare settings is close to completion (17, 37).

WP1 will contribute to the completion of ongoing evidence-based IGHG efforts by developing recommendations for several topics for which no evidence-based recommendations exist yet, using a pragmatic methodology. Further, the PanCareFollowUp project will develop a "living guideline tool" that regularly searches for new literature and automatically informs specified guideline groups. Novel findings can thus be promptly discussed and guidelines can be updated in a timely manner, advancing CPG development and state-of-the art care provision (36).

PanCareFollowUp Care Intervention

The novel person-centered guideline-based PanCareFollowUp Care Intervention consists of three steps: (1) a pre-visit Survivor Questionnaire to identify the survivor's health needs and preferences; (2) a clinic visit during which survivors receive a personalized Treatment Summary summarizing their childhood cancer treatment, engage in shared decisions about appropriate surveillance strategies, receive or are scheduled for additional tests and receive a draft Survivorship Care Plan; and (3) a follow-up call to discuss diagnostic test results and refine the Survivorship Care Plan based on the test results.

WP1 will develop the PanCareFollowUp Care Intervention, including the PanCareFollowUp Recommendations, Survivor Questionnaire, Treatment Summary and Survivorship Care Plan template as well as online education materials for survivors and HCPs. A preimplementation study will be conducted at the four study sites to qualitatively identify barriers and facilitators for implementing person-centered survivorship care from both survivors' and HCPs' perspectives. WP1 will also train participating HCPs in person-centered care. The resulting implementation strategies and intervention materials will be evaluated throughout the project and summarized in a postproject Replication Manual.

Work Package 2: Conduct of the Care study

WP2 is responsible for the preparation and conduct of the Care Study at four sites in Belgium, the Czech Republic, Italy and Sweden. The PanCareFollowUp Care Intervention will be implemented as usual care and evaluated in a prospective cohort study among 800 survivors aged ≥16 years with six months follow-up. WP2 will facilitate identification and recruitment of participants and local data collection. The benefits of the Care Intervention for survivors, as well as experiences of HCPs, and costs for the system will be examined through questionnaires and clinical data. The four study sites have been selected to represent different healthcare systems with various levels of pre-existing survivorship care implementation.

Work Package 3: Measures and analyses of the Care Study

WP3 will select appropriate outcome measures and develop the study questionnaires for the Care Study. The main outcome is survivor empowerment, which contributes to self-management and becomes increasingly important when transitioning from pediatric to adult healthcare settings (38). Other patient-reported outcomes include health-related QoL, mental health, resilience, shared decision-making, and satisfaction. In addition, prevalent adverse health conditions and detection of new clinical conditions as well as cost-effectiveness and feasibility of the PanCareFollowUp Care Intervention will be evaluated.

WP3 also constitutes the PanCareFollowUp data coordination center. This center will be responsible for building and maintaining the database in the cloud-based Castor Electronic Data Capture system, managing data collection from survivors and HCPs, monitoring of data quality and the study recruitment process, and conducting study analyses.

Work Package 4: Survivorship Passport

WP4 will update the existing Survivorship Passport (SurPass) developed within the ENCCA and PanCareSurFup projects with the PanCareFollowUp Recommendations, and

will evaluate the feasibility of providing web-based delivery of the PanCareFollowUp Care Intervention at the Italian study site (Figure 2). The SurPass is an online tool that details a survivor's diagnosis, treatment history and personalized guideline-based care plan in plain language (39). The platform is hosted in the Cineca data center in Casalecchio di Reno, Italy, which is compliant with the highest security standards and data quality procedures, as per ISO 270001 and 9001 certifications. Personal data are encrypted, and privacy is enforced with role-based user security (survivor, healthcare professional, data manager), authentication, identification and authorization mechanisms to share and store data.

WP4 will also collaborate with the PanCare PLAIN group that aims to write plain language summaries of the surveillance guidelines, which will be available online and as recommendation brochures for each recommendation generated in WP1.

Work Package 5: Development and feasibility study of the PanCareFollowUp eHealth Lifestyle Intervention

WP5 will focus on the development and pilot testing of the person-centered PanCareFollowUp eHealth Lifestyle Intervention, which aims to improve survivors' dietary intake and physical activity. It will consist of individual coaching sessions with an eHealth lifestyle coach delivered via secured video conferencing software. Two approaches (motivational interviewing and person-centered care) will be used to help survivors set their personal goals. The REVIVER study will be used as a background for developing the Lifestyle Intervention (40). Further evidence-based strategies to inform the Lifestyle Intervention include two systematic reviews regarding (1) effectiveness and effective components of eHealth lifestyle interventions and (2) barriers and facilitators for survivors in adapting to and maintaining a healthy lifestyle with regular physical activity and/or a healthy dietary intake. In addition, qualitative interviews and focus group discussions with survivors and HCPs, together with the reviews, give a more comprehensive view on barriers and facilitators to adopt and support a healthy lifestyle.

The feasibility of the PanCareFollowUp Lifestyle Intervention will be evaluated in a prospective study including 60 survivors affiliated with two survivorship clinics in the Netherlands, where person-centered survivorship care is already implemented (24). The main outcome is the proportion of survivors who reach their personal goals for lifestyle change set with their eHealth lifestyle coach. Using an effect and process evaluation, a Replication Manual will be developed at the end of the project to disseminate the PanCareFollowUp Lifestyle Intervention across other survivorship care clinics.

Work Package 6: Communication and dissemination

A key objective of the PanCareFollowUp project is to communicate the importance of survivorship care, including support to adopt a healthy lifestyle, to relevant stakeholders. The audiences include survivors and parents, HCPs, advocacy groups, healthcare policy makers, researchers, the general public and media. The activities include a project website (**www.pancarefollowup.eu**), social media and email updates, scientific publications of the project's protocols and results, evidence-based policy recommendations, conference presentations, seminars, and workshops. After the end of the project, the materials will be hosted online through PanCare.

Work Package 7: Management
The leadership of the PanCareFollowUp project is divided among the project management team, the project board and WP leaders. Overall responsibility is assigned to the project management team, which includes the project coordinator and project administrator. They are responsible for coordination and scientific leadership, and for project management support, respectively. The project board governing the PanCareFollowUp project consists of one representative of each project partner and is chaired by the project coordinator. Main tasks include managing progress and risks.

Work Package 8: Ethics requirements
The role of WP8 is to oversee that PanCareFollowUp is conducted in compliance with relevant ethical requirements in clinical research, personal data protection and study participants' privacy. Under the oversight of WP8, participants will be informed of their rights: each center collecting data will seek approval via relevant ethics committees, and the study participants' signed informed consents will be secured. An external, independent ethics advisor will provide advice on ethical issues raised during the project.

RESULTS AND DISCUSSION

Access to survivorship care is necessary across Europe and constitutes the main aim of the PanCareFollowUp project. A sustainable and cost-effective strategy is required, considering the limited healthcare resources available. This may be realized through CPG-based care with a focus on prevention, early detection and timely management of late effects, and a person-centered approach with high involvement of survivors to manage their needs. The PanCareFollowUp Consortium will develop and evaluate the person-centered PanCareFollowUp Care and Lifestyle Interventions including Replication Manuals to empower survivors to achieve better health and QoL. These Replication Manuals are especially important to inform and support institutions with incomplete or without follow-up care to mitigate barriers and identify facilitators for the implementation of person-centered survivorship care within their healthcare system, and as such, to improve its availability across Europe.

Several positive impacts are anticipated. The first is a reduced burden on survivors and their caregivers through education, awareness and shared decisions about adequate health management. Empowered survivors will be better equipped to take charge of their own care, with a care plan developed together with their HCP. Second, the PanCareFollowUp project will generate surveillance recommendations for topics currently lacking CPGs, initiate development of a living guideline tool, and provide policy recommendations for survivorship care which will be distributed across Europe. Third, the Care Study will elucidate the benefits and cost-effectiveness of a person-centered survivorship care model, whereas the Lifestyle Study will show the feasibility of eHealth to improve lifestyle. Fourth, it is important to consider that while the entire PanCareFollowUp project will reach over 800 survivors, there are currently up to 500,000 European childhood cancer survivors in need of survivorship care (1). Therefore, we will distribute the Replication Manuals of the PanCareFollowUp Care and Lifestyle Interventions after the project to everyone interested in survivorship care for inspiration, comparison with their own practice, and free use and adjustment to local circumstances

and healthcare resources. Lastly, as the survivor population continues to grow, the PanCareFollowUp project should contribute to reducing the associated economic and societal burdens by preventing or managing chronic health conditions through education, awareness, lifestyle changes and personalized surveillance.

To conclude, the PanCareFollowUp project is a highly collaborative endeavor involving 14 project partners from ten European countries. Several strategies (CPGs, targeted communication, and dissemination of Replication Manuals) will be used to ensure sustainability of the project, to advance the accessibility and quality of survivorship care, and promote the widest possible impact on QoL of European survivors.

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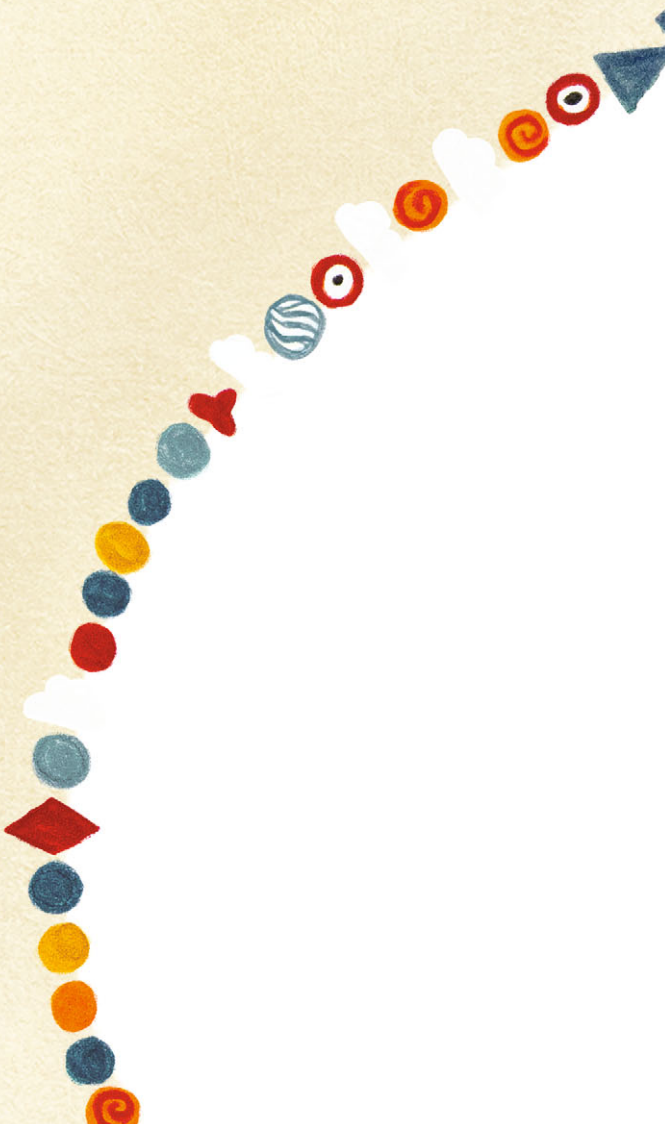

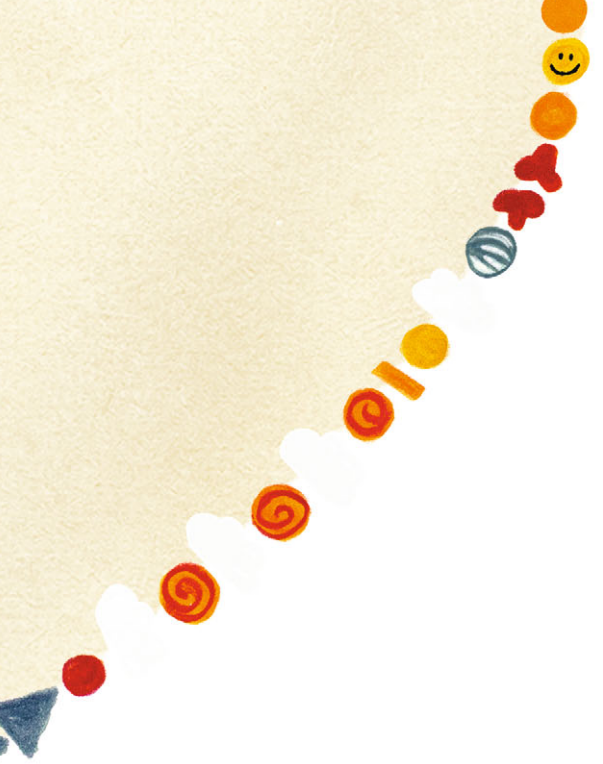

4

The PanCareFollowUp Care Intervention: a European harmonized approach to person-centered guideline-based survivorship care after childhood, adolescent and young adult cancer

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ABSTRACT

Background Long-term follow-up (LTFU) care, although endorsed, is not available for the majority of adult survivors of childhood, adolescence and young adult (CAYA) cancer. Barriers to implementation include lack of time, knowledge, personnel and funding. Sustainable solutions are urgently needed to address the needs of CAYA cancer survivors to improve the quality of life and reduce the burden of late effects on survivors, healthcare systems and society. The European Union-funded PanCareFollowUp project, initiated by the Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer, was established to facilitate the implementation of person-centered survivorship care across Europe.

Patients and methods The PanCareFollowUp Care Intervention was co-developed with survivors as part of the PanCareFollowUp project. It is a person-centered approach to survivorship care, supported by guidelines and with flexibility to adapt to local healthcare settings. The Care Intervention consists of three steps: 1) pre-visit completion of a Survivor Questionnaire (by the survivor) and Treatment Summary (by the healthcare provider (HCP)), 2) a clinic visit including shared decision-making, and 3) a follow-up call to finalize the individualized Survivorship Care Plan.

Results We developed the key components of the PanCareFollowUp Care Intervention: a PanCareFollowUp Survivor Questionnaire, Treatment Summary template, Survivorship Care Plan template, and educational materials for HCPs and survivors. Wide implementation of the PanCareFollowUp Care Intervention will be supported with a freely distributed Replication Manual on completion of the PanCareFollowUp project.

Conclusions The PanCareFollowUp Care Intervention will support the implementation of person-centered, guideline-based LTFU care in different healthcare settings across Europe to improve survivors' health and well-being.

INTRODUCTION

The importance of long-term follow-up (LTFU) care to reduce survivor, family and societal burden is widely acknowledged (1-3). At current, the European childhood, adolescent and young adult (CAYA) cancer survivor population is estimated at 500,000 individuals and is expected to increase by 12,000 each year (4). After overcoming their initial disease, these survivors are challenged with an increased risk of developing medical and psychosocial late effects (5-9). In a recent study from the United States, the average CAYA cancer survivor is suffering from 17 chronic health conditions by the age of 50 years, which is almost twice as many as in the general population (10). The type and severity of late effects is largely influenced by initial diagnosis and treatment. Survivors are consequently at higher risk of premature mortality compared to peers or siblings without a CAYA cancer diagnosis (11-13), and regular follow-up is recommended.

Although the model of care might vary, it is agreed that high-quality survivorship care should consist of prevention, early detection and management of late effects (14). Evidence-based clinical practice guidelines, developed by the International Late Effects of Childhood Cancer Guideline Harmonization Group and within European Union-funded PanCare projects (PanCareSurFup, PanCareLIFE) are available to inform effective surveillance strategies for late adverse effects (15-24). Additionally, a survivorship care plan including a summary of cancer treatment and personalized recommendations for LTFU care is endorsed as an important tool to increase knowledge and empowerment of survivors, oncologists and primary care providers (1, 14, 25). A survivorship care plan contains information about the survivor's individual risks and care requirements, based on harmonized recommendations, and can evolve with changing health and personal needs. Survivorship care plans delivered by a late effects clinic increase primary care physicians' and survivors' knowledge of late effects and contribute to earlier detection of health problems in primary care, thus potentially resulting in a lower healthcare burden (26). Furthermore, LTFU care offers an opportunity to provide age-appropriate education about the late effects of a survivor's diagnosis and treatment as well as guidance in matters of health behavior, health or life insurance, education and work (27, 28).

Despite the fact that most survivors need lifelong survivorship care, as underlined more than 40 years ago, implementing follow-up care has proven challenging across Europe (29, 30). A survey in 2012 indicated that only 32% of European pediatric oncology institutions had established services for adult CAYA cancer survivors, with considerable differences between countries (31). Nearly all institutions without such programs expressed a wish to implement survivorship care but were limited by various barriers such as lack of time, personnel, knowledge and funding.

The PanCareFollowUp project (www.pancarefollowup.eu) was initiated by the Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer (PanCare; www.pancare.eu) to improve the quality and availability of person-centered LTFU care for CAYA cancer survivors across Europe (32, 33). It includes the development and prospective cohort study of the PanCareFollowUp Care Intervention, a person-centered, guideline-based approach to survivorship care, to support future implementation of LTFU care across Europe (34).

The aim of this paper is to describe the development of four essential elements of the PanCareFollowUp Care Intervention: the Survivor Questionnaire, the Treatment Summary, the Survivorship Care Plan, and online information for survivors and healthcare providers (HCPs).The development of European PanCareFollowUp Recommendations to guide LTFU care, as well as the protocol and results of the Care Study, a prospective cohort study to evaluate the outcomes and feasibility of the Care Intervention implementation in Belgium, the Czech Republic, Italy and Sweden, will be reported in separate publications (35, 36).

METHODS

The PanCareFollowUp Care Intervention was developed by late effects specialists, pediatric oncologists, implementation and guideline experts, and survivor representatives from Childhood Cancer International - Europe (CCI Europe), representing a total of 14 stakeholders and ten European countries as part of the European Horizon 2020-funded PanCareFollowUp project. The PanCareFollowUp Consortium is described in detail previously (33). PanCareFollowUp Care Intervention is intended for five-year CAYA cancer survivors of 16 years or older. The model is based on previous experiences with person-centered survivorship care in Dutch LTFU care clinics (37). Central elements of the person-centered approach include initiating, working, and safeguarding the relationship between survivor and HCP and are incorporated in the structure of the PanCareFollowUp Care Intervention (38, 39).

The Care Intervention consists of three steps, including a pre-visit preparation, clinic visit, and follow-up call (Figure 1).

1. *Before the clinic visit:* The PanCareFollowUp Survivor Questionnaire will be sent to the survivor two to eight weeks before the clinic visit. The primary web-based questionnaire is the first step of person-centered care: initiating the partner relationship. It provides an opportunity for the survivor to share information about their health, well-being, medication use, medical and family history, lifestyle, social situation, healthcare needs, and preferences for care with their HCP. Simultaneously, the HCP prepares a PanCareFollowUp Treatment Summary, comprising details on the survivor's cancer diagnosis and treatment history. In addition, the HCP prepares the standard PanCareFollowUp Survivorship Care Plan based on the risk factors identified in the Treatment Summary, information reported in the Survivor Questionnaire, and relevant recommendations for LTFU care as described in the PanCareFollowUp Recommendations. Availability of this information before the late effects clinic visit can help establish an individual and tailored care pathway. Based on the local logistic and referral structure, this potentially enables advanced planning of surveillance tests for the day of the clinic visit, thus reducing the number of appointments required. The Survivorship Care Plan is co-developed with the survivor over the course of the Care Intervention (Figure 2).

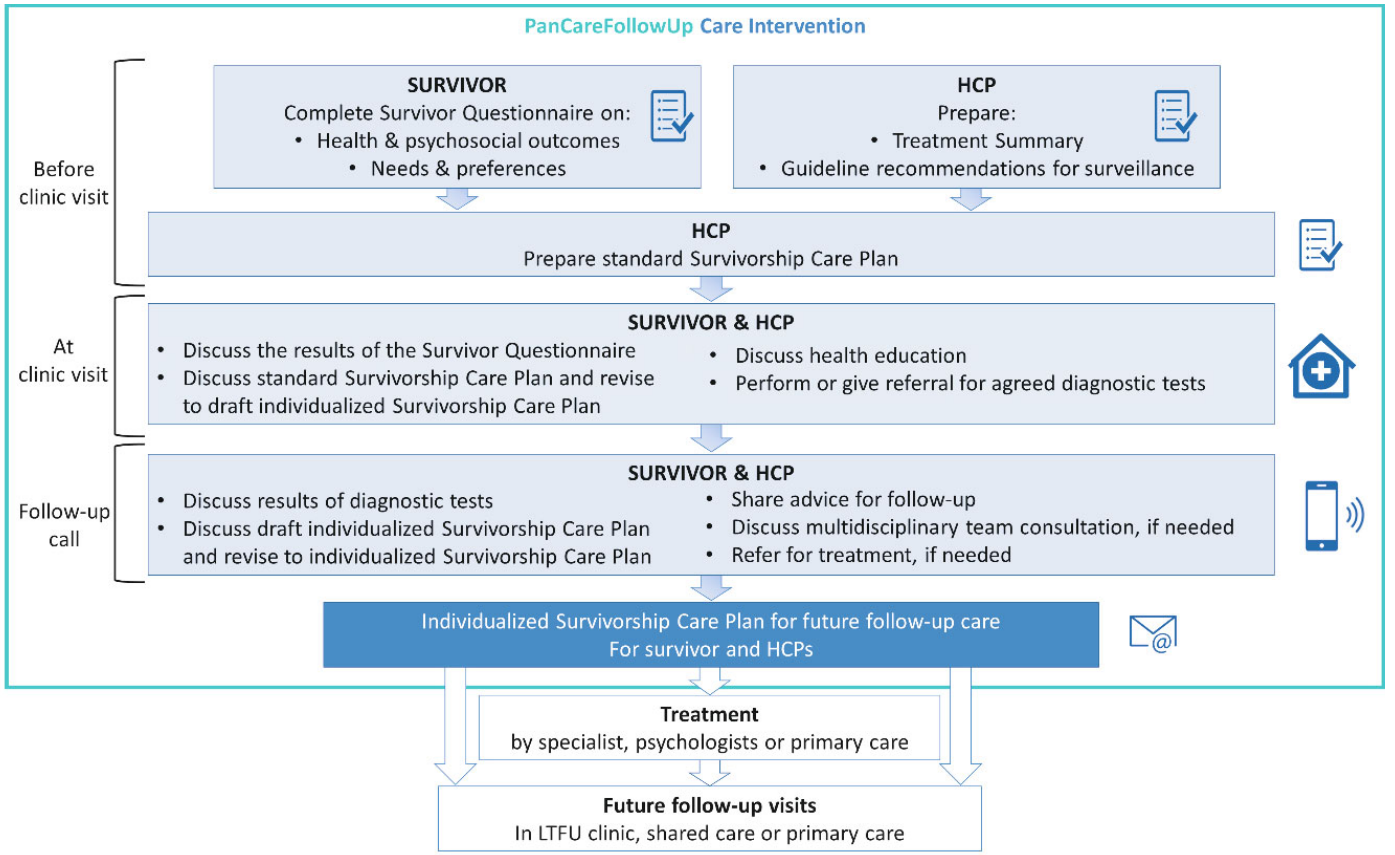


Figure 1. The PanCareFollowUp Care Intervention steps: pre-visit preparation, clinic visit, and follow-up call
HCP, healthcare provider; LTFU, long-term follow-up.

Figure 2. Development timeline of the individualized Survivorship Care Plan

2. *At the clinic visit:* The HCP and the survivor engage in a two-way sharing of information that is important for working the partnership as the second step to person-centered care. Together, they discuss the potential health concerns of the survivor, the content of the Survivor Questionnaire and Treatment Summary, and the standard Survivorship Care Plan. In addition, the HCP delivers health information relevant to the survivor, raises awareness about certain health issues the survivor is possibly faced with, and discusses the importance of a healthy lifestyle. Subsequently, the physical examinations and diagnostic tests are performed as per plan. If necessary, further appointments for more advanced tests or referrals can be scheduled for a later time. Based on this clinic visit, the HCP and the survivor develop a draft individualized Survivorship Care Plan. The structure and background of this person-centered visit will be described in more detail in a separate publication.

3. *Follow-up call:* After consultation with the multidisciplinary team, the HCP contacts the survivor to discuss the results of the diagnostic tests performed at, or in relation to, the clinic visit. Where needed, referrals for management of identified health problems are arranged, taking into account the PanCareFollowUp Recommendations and the preferences of the survivor. Furthermore, the survivor and the HCP will decide on a preferred model for future follow-up with regard to potential health conditions, the healthcare system and survivor's preferences. Shared decision-making about these issues contributes to the modified individualized Survivorship Care Plan. The survivor will receive the individualized Survivorship Care Plan by post and/or secured e-mail and can use it to communicate about their care preferences with other HCPs.

For this PanCareFollowUp Care Intervention, the Consortium developed a Survivor Questionnaire, a Treatment Summary and a Survivorship Care Plan, as well as online education materials, based on clinical examples and previous experience in setting up survivor questionnaires, treatment summaries, and care plans within Europe and the United States. In addition, PanCareFollowUp Recommendations to guide LTFU care were developed in a wider European collaboration using a pragmatic methodology and are described in a separate paper.

Development of the PanCareFollowUp Survivor Questionnaire

Development of the Survivor Questionnaire started with establishment of a core group (including HP, LK, RM, and RK) and identification of questionnaires that are currently used in LTFU care or research through the PanCareFollowUp network. A total of nine questionnaires were provided by PanCareFollowUp project partners or their network, including a holistic tool for survivorship care from Lund University, a care transition questionnaire from the Charité University Hospital Berlin, a Dutch care plan for pediatric palliative care, and study questionnaires of the British Childhood Cancer Survivor Study (BCCSS), Dutch Childhood Cancer Survivor Study (DCCSS), Swiss Childhood Cancer Survivor Study (SCCSS), Childhood Cancer Survivor Study (CCSS) from the United States, St. Jude LIFE study, and a Dutch breast cancer study. Additional questions were identified by reviewing the available Patient Reported Outcomes Measurement Information System (PROMIS) tools, the Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) (40, 41), and by including the Emotion Thermometer (ET) (42).

The core group established the following eight domains upfront to be relevant for the Survivor Questionnaire based on previous research (43) and clinical expertise: 1) self-reported physical symptoms; 2) self-reported psychosocial symptoms; 3) medication use; 4) medical history including hospital admissions; 5) family history; 6) social situation, education and employment; 7) health behavior including lifestyle; and 8) needs and preferences. Questionnaires were included for further review if they contained questions related to any of these domains.

All extracted questions were grouped by domain and discussed at regular face-to-face core group meetings. A preselection was made in collaboration with survivor representatives and distributed to the entire PanCareFollowUp Consortium for review. The questionnaire was subsequently reviewed by survivor representatives of CCI Europe external to the project. Suggestions were provided to refine the psychosocial and lifestyle sections. This included the development of a novel psychosocial tool specifically for CAYA cancer survivors addressing challenges they may face in daily life. Finally, the Survivor Questionnaire was translated to Czech, Dutch, Italian, and Swedish by native speakers from the Consortium for the purposes of the PanCareFollowUp Care Study. During the translation process, a few additional minor alterations were made to improve ease of use and understandability of the Survivor Questionnaire. The final version of this questionnaire was approved by the Consortium through a digital check.

Development of the PanCareFollowUp Treatment Summary template

A core group (HP, LK, MM, RH, RM, and RK) was assembled in the preparation phase. Treatment summaries currently used in survivorship care were requested from all

PanCareFollowUp project partners and reviewed. A total of six treatment summary templates were collected, which are currently used in Linz (Austria), Utrecht (the Netherlands), Leuven (Belgium), Lund (Sweden), Newcastle upon Tyne (the United Kingdom), and in six centers of the Italian Association of Pediatric Hematology and Oncology (AEIOP; Italy). Two of the examples consisted of databases with pre-defined variables and answer options, including the web-based Survivorship Passport used in Italy (SurPass – www.survivorshippassport.org) (44), and the Dutch treatment summary, whereas the other documents required manual completion with open text fields.

The SurPass was developed as part of previous European Union projects (e.g., European Network for Cancer Research in Children and Adolescents (ENCCA) and PanCareSurFup). Its comprehensive variable list was used as a starting point and compared to the other treatment summaries to develop a draft Treatment Summary template. In addition, the Consortium agreed on a three-tiered radiotherapy classification to systematically document radiation exposure. The Treatment Summary template was disseminated to a broader group within the PanCareFollowUp project, including researchers, clinicians, and survivor representatives. Following clarification of variables and final modifications, it was accepted by the entire PanCareFollowUp Consortium.

Development of the PanCareFollowUp Survivorship Care Plan

A core group (HP, LK, RK, and RM) was established and requested care plans among PanCareFollowUp project partners. A total of six care plan templates were collected, that are currently used in Linz, six AIEOP centers, Utrecht, Lund, Newcastle upon Tyne and Memphis (the United States). Using the SurPass as a starting point, the core group developed a draft including elements from all provided care plans. Plain language recommendations for use in the Survivorship Care Plan were developed for each of the diagnostic tests included in the PanCareFollowUp Recommendations. The statements were reviewed by CCI Europe survivor representatives for language and content. After review and endorsement by the entire PanCareFollowUp Consortium, these English recommendations were translated to Czech, Dutch, Italian and Swedish by native speakers from the Consortium and included in a User Manual for use in the PanCareFollowUp Care Study.

Development of online information for survivors and HCPs

The core group (HP, LK, RK, and RM) collaborated with survivor representatives to develop online information specifically for survivors and HCPs, using current best practices such as the COG Health Links (www.survivorshipguidelines.org) and Dutch Childhood Oncology Group (DCOG) website (www.skion.nl/voor-patienten-en-ouders/late-effecten) as an example. The information describes the challenges of childhood cancer survivorship and the importance of LTFU care, and provides an overview of the PanCareFollowUp Care Intervention.

RESULTS

PanCareFollowUp Survivor Questionnaire

The Survivor Questionnaire contains 74 (male version) or 77 (female version) standard questions, with additional follow-up questions depending on specific answers (Appendix A and B). Thereby, it is comprehensive, where needed, yet adjusted to the survivor's individual situation where possible. The average time of completion was 45 minutes, as assessed in the feedback round among seven CAYA cancer survivor representatives and one parent representative. Participants in the feedback round indicated that, although time intensive, the questionnaire was well-balanced between physical and mental well-being, lifestyle, and survivor-specific issues, encouraging them to complete it before a potential clinic visit. During the Care Study, an online version of the Survivor Questionnaire is provided through Castor EDC (www.castoredc.com), a cloud-based Electronic Data Capture platform, with paper versions available upon request.

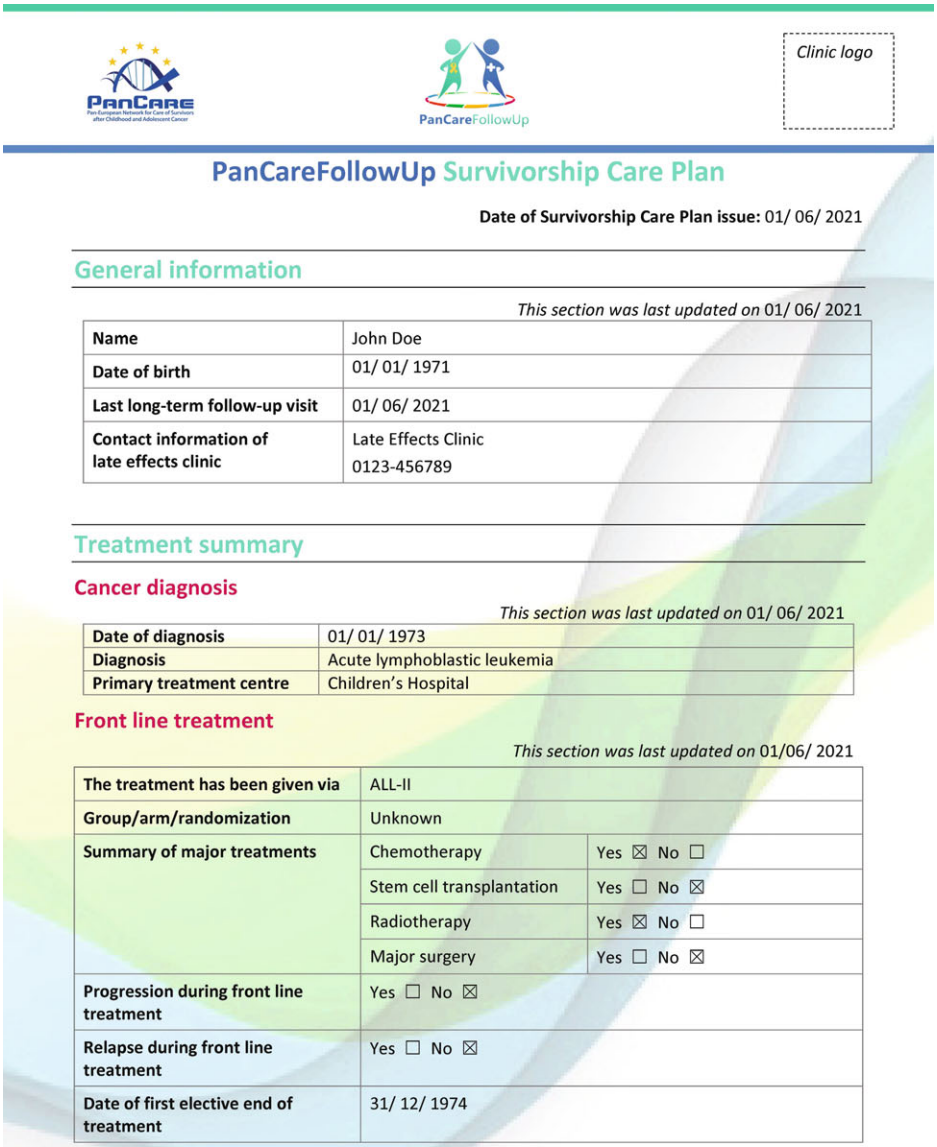
PanCareFollowUp Treatment Summary

The Treatment Summary contains sections on general information, cancer diagnosis, front line treatment, progression or relapse during front line treatment or after first elective end of treatment, health problems during cancer treatment, family history, relevant medical history, and current medication use. It specifically includes standardized cumulative treatment data with start and end dates, chemotherapy drug names and doses, other drug names and doses, radiotherapy fields and doses, details on stem cell transplantation, and surgeries (Appendix C). The treatment data covers treatments for the initial cancer, all relapses and subsequent neoplasms (either malignant or benign), and complications, if any. As such, it is a living document that can be updated by HCPs over the course of survivorship care, for example in case of a relapse or subsequent neoplasm after the elective end of therapies. During the Care Study, the Treatment Summary is completed digitally within Castor EDC (www.castoredc.com) or the SurPass platform.

PanCareFollowUp Survivorship Care Plan

The Survivorship Care Plan (Figure 3) includes the following sections: 1) general information (including name, birth date and LTFU care clinic details); 2) PanCareFollowUp Treatment Summary; 3) history and health problems (including relevant medical and family history, current health problems, and current medication based on the Survivor Questionnaire); 4) standard recommendations for LTFU care (tailored to diagnosis and treatment according to the PanCareFollowUp Recommendations) and 5) individualized decisions for LTFU care (based on the clinic visit, diagnostic test results and follow-up call) (Appendix C).

The corresponding User Manual contains clear instructions to complete all sections of the Survivorship Care Plan, as well as an overview of the plain language statements. These have been sorted and color-coded by treatment exposure, such as chemotherapy, radiation therapy, or surgery to facilitate a user-friendly layout and smooth development process of each Survivorship Care Plan. The Survivorship Care Plan can be shared with the survivor on paper or digitally through the SurPass platform.



PanCare

PanCareFollowUp

Clinic logo

PanCareFollowUp Survivorship Care Plan

Date of Survivorship Care Plan issue: 01/ 06/ 2021

General information

This section was last updated on 01/ 06/ 2021

Name	John Doe
Date of birth	01/ 01/ 1971
Last long-term follow-up visit	01/ 06/ 2021
Contact information of late effects clinic	Late Effects Clinic 0123-456789

Treatment summary

Cancer diagnosis

This section was last updated on 01/ 06/ 2021

Date of diagnosis	01/ 01/ 1973
Diagnosis	Acute lymphoblastic leukemia
Primary treatment centre	Children's Hospital

Front line treatment

This section was last updated on 01/06/ 2021

The treatment has been given via	ALL-II	
Group/arm/randomization	Unknown	
Summary of major treatments	Chemotherapy	Yes ☒ No ☐
	Stem cell transplantation	Yes ☐ No ☒
	Radiotherapy	Yes ☒ No ☐
	Major surgery	Yes ☐ No ☒
Progression during front line treatment	Yes ☐ No ☒	
Relapse during front line treatment	Yes ☐ No ☒	
Date of first elective end of treatment	31/ 12/ 1974	

Figure 3. Example of a PanCareFollowUp Survivorship Care Plan

Standard recommendations for long-term follow-up care

Because of the treatment you have had, we have listed the tests recommended for you. This advice is based on international experience with people who have received the same treatment as you.

Because you had or have been treated with ...	**... you may have a risk of ...**	**... therefore, it is recommended that you have ...**
Immunosuppressives as part of your cancer treatment	High blood pressure	A blood pressure measurement at least every 2 years and at every long-term follow-up visit
Mercaptopurine and methotrexate	Liver problems	Blood tests of the liver once
Methotrexate, corticosteroids as part of your cancer treatment, and radiotherapy to your brain	Low bone mineral density	A DXA scan once
Radiotherapy to your brain	Brain cancer	Discussed the advantages and disadvantages of regular MRIs with your doctor
Radiotherapy to your brain	Overweight	A height and weight measurement at least every 2 years
Radiotherapy to your brain	Hormonal problems	Blood tests every year

Individualised decisions for long-term follow-up care

This is an overview of the decisions regarding your long-term follow-up care that you have made together with your health care provider.

Individualised decision for long-term follow-up care:	**Comments:**	**Planned for:**
Based on the standard recommendations for long-term follow-up care		
- DXA scan 1x at entry LTFU		Already performed
- Blood pressure at least 1x/2 years and at every LTFU visit		2022
- ALT, AST, gGT, ALP 1x at entry LTFU		Already performed
- Discuss potential harms and benefits of MRI surveillance	Discussed with survivor, decided against MRI surveillance	Already discussed
- Height, weight, BMI at least 1x/2 years		2022
- fT4, TSH, morning cortisol, IGF-1 1x/year - Morning testosterone (or free testosterone if overweight) and LH 1x/year		2022
Based on clinical indication		
- Dermatological examination	History of basal cell carcinoma	2022

Figure 3 (continued). Example of a PanCareFollowUp Survivorship Care Plan

Online information for survivors and HCPs

The online information is openly available through the project website (www.pancarefollowup.eu) and will be sustained by PanCare (www.pancare.eu) after the project ends. Furthermore, plain language brochures in question-and-answer style will be developed throughout the project, explaining each of the late effects addressed in the PanCareFollowUp Recommendations. This information can be consulted and printed through the websites.

DISCUSSION

The PanCareFollowUp Care Intervention is the first European harmonized and person-centered approach to survivorship care. Furthermore, it focuses on sustainable implementation across the diverse landscape of European healthcare systems. Co-developed with survivors and representing a collaborative effort between ten European countries, it intends to address the needs of both survivors and HCPs.

Adequate knowledge of their cancer history, subsequent treatment exposure and potential risks of late effects are needed to enhance survivors' health and self-management skills. Accessible and reliable information is important to increase awareness about late effects and LTFU care among survivors and HCPs and is essential for shared decision-making. Moreover, it empowers survivors to seek medical or psychosocial help, if needed, or to take responsibility for preventive lifestyle measures and attending LTFU care. An individualized survivorship care plan including a summary of treatment history and personal recommendations for surveillance and prevention is provided to support this process (1, 14). Given the heterogeneity of existing healthcare systems across Europe, it is important that interventions for survivorship care are flexible in how the care is delivered, while respecting common core requirements such as a summary of treatment and personal recommendations for surveillance (45, 46). Endorsed models to provide LTFU care are surveillance in a survivorship clinic or shared care between the survivorship clinic and local hospital or primary care. An alternative is self-management supported by HCPs within a shared care or primary care model, with swift referral to survivorship expert centers if needed (14). The choice of a preferred model and frequency of care will depend on the survivor's risk for late effects and pre-existing health conditions, the healthcare system, and the survivor's preferences.

The PanCareFollowUp Care Intervention provides a state-of-the art structure for survivorship care, which facilitates education about survivor-important issues as well as shared decision-making about surveillance strategies. Furthermore, it empowers the survivor by providing comprehensive yet understandable information about their health and potential risks, and encouraging survivors to (co-)manage their LTFU care. HCPs are supported by the comprehensive pre-visit Survivor Questionnaire, Treatment Summary and Survivorship Care Plan so the LTFU care visit can be tailored to the survivor's needs with optimum advance planning and preparation.

By using the wide variety of available materials as a starting point, components of the PanCareFollowUp Care Intervention build upon clinical experience and preference. Efficient organisation of tasks and review cycles was achieved by establishing core groups and including the entire PanCareFollowUp Consortium in regular consultation rounds.

To strengthen the evidence base for comprehensive survivorship care, a prospective cohort study (Care Study) evaluating the feasibility, effectiveness (in terms of physical, psychological, and social outcomes) and cost-effectiveness of the PanCareFollowUp Care Intervention will be conducted across four study sites: University Hospitals of Leuven (Belgium), St. Anne's University Hospital, Brno (Czech Republic), Giannina Gaslini Children's Hospital, Genoa (Italy) and Skåne University Hospital, Lund (Sweden). The main outcome is empowerment of the survivor, as self-management and taking responsibility for their own health is fundamental to the appropriate recognition and management of late effects, and thereby the survivor's quality of life. A detailed description of survivor recruitment, study coordination and conduct, selected outcomes, data collection and data analysis will be published elsewhere. Testing the PanCareFollowUp Care Intervention under realistic circumstances in four clinics representing different healthcare systems is important to identify strategies for tailoring to specific challenges and to assure optimum replication potential across Europe. Therefore, a preimplementation study was conducted at each of the study sites, identifying barriers and facilitators to implementation of long-term follow-up care among survivors, HCPs and health policy makers. This has resulted in site-specific implementation strategies. Lessons learned during the prospective cohort study will contribute to an update of these implementation strategies at the end of the project.

After the Care Study is finalized, open access to all relevant information and tools to implement the PanCareFollowUp Care Intervention will be provided through a freely available Replication Manual on the PanCare website. Expectations are that the results of the Care Study will help to motivate survivors and HCPs to organize the LTFU care in an efficient way with sustainable financial support.

In conclusion, the PanCareFollowUp Care Intervention supports implementation of person-centered LTFU care in different healthcare models across Europe. The impact of this intervention will be explored by a prospective cohort study in four European countries and will yield a Replication Manual for sustainable replication at other institutions after the project. Ultimately, the implementation of such novel survivorship care is expected to have a robust impact on the wellbeing of CAYA cancer survivors, reduce the societal burden, and demonstrate the (cost-) effectiveness of survivorship care.

SUPPLEMENTARY MATERIAL

Appendix A, B and C are available online (https://doi.org/10.1016/j.ejca.2021.10.035).

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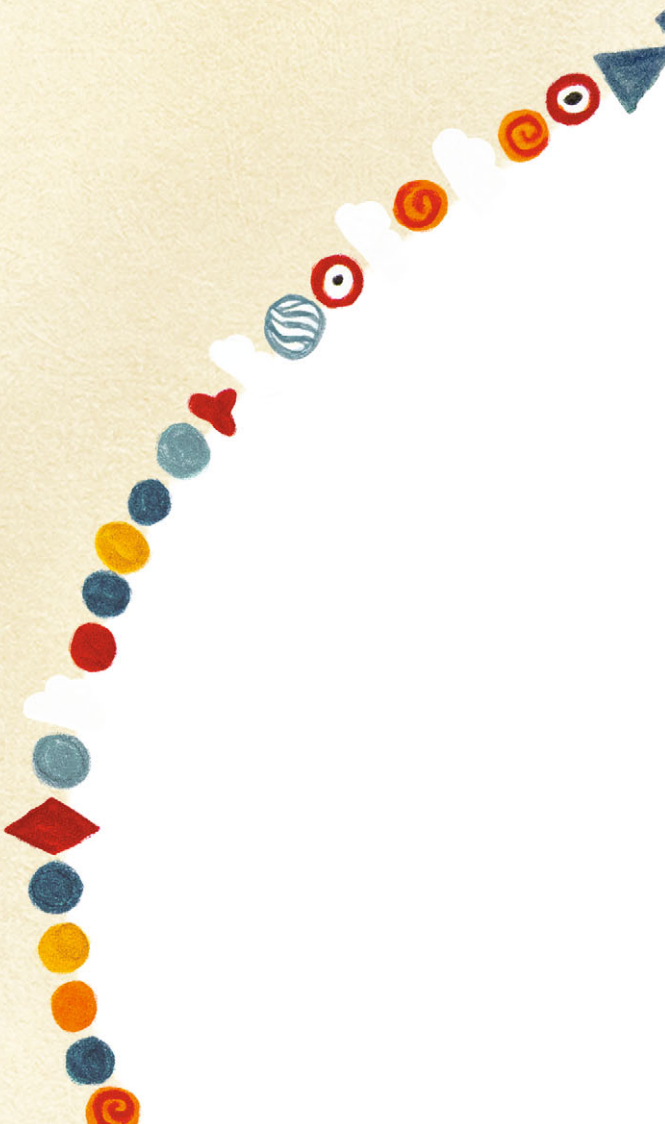

5

European PanCareFollowUp Recommendations for surveillance of late effects of childhood, adolescent and young adult cancer

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ABSTRACT

Background Long-term follow-up (LTFU) care for childhood, adolescent and young adult (CAYA) cancer survivors is essential to preserve health and quality of life. Evidence-based guidelines are needed to inform optimal surveillance strategies, but many topics are yet to be addressed by the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG). Therefore, the PanCareFollowUp Recommendations Working Group collaborated with stakeholders to develop European harmonized recommendations in anticipation of evidence-based IGHG guidelines.

Methods The PanCareFollowUp Recommendations Working Group, consisting of 23 late effects specialists, researchers, and survivor representatives from nine countries, collaborated in the first Europe-wide effort to provide unified recommendations in anticipation of evidence-based guidelines. A pragmatic methodology was used to define recommendations for topics where no evidence-based IGHG recommendations exist. The objective was to describe the surveillance requirements for high-quality care while balancing the different infrastructures and resources across European healthcare systems. The process included two face-to-face meetings and an external consultation round involving 18 experts from 14 countries.

Results Twenty-five harmonized recommendations for LTFU care were developed collaboratively and address topics requiring awareness only (n = 6), awareness, history and/or physical examination (n = 9), or additional surveillance tests (n = 10).

Conclusions The PanCareFollowUp Recommendations, representing a unique agreement across European stakeholders, emphasize awareness among survivors and healthcare providers in addition to tailored clinical evaluation and/or surveillance tests. They include existing IGHG guidelines and additional recommendations developed by a pragmatic methodology and will be used in the Horizon 2020-funded PanCareFollowUp project to improve health and quality of life of CAYA cancer survivors.

INTRODUCTION

Five-year survival rates of childhood, adolescent and young adult (CAYA) cancer have increased considerably and currently exceed 80% in the majority of European countries (1, 2). The population of CAYA cancer survivors in Europe is estimated at nearly half a million and continues to increase by approximately 12,000 per year (3). Due to their essential, but potentially toxic cancer therapies, survivors are at substantial risk for developing severe chronic health conditions, even at a young age (4-7). The burden of these physical and psychosocial late effects on the quality of life (QoL) of survivors and their families, as well as on healthcare and societal resources, is significant (8-10). Long-term follow-up (LTFU) care including prevention, surveillance for early detection of treatable disease, and timely initiation of interventions is fundamental to preserve health, improve QoL, and mitigate the impact of late effects on survivors and their families.

Clinical practice guidelines (CPGs) are powerful instruments that facilitate consistent, efficient, and high-quality clinical care for defined patient groups including CAYA cancer survivors (11). However, large variations are observed in the recommendations for survivorship care across different national and local CPG working groups (12-15). Over the last decade, members of the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) have collaborated in the development of harmonized evidence-based surveillance strategies. So far, nine IGHG guidelines for early detection and management of asymptomatic cardiomyopathy, ototoxicity, subsequent thyroid cancer, subsequent female breast cancer, subsequent central nervous system neoplasms, premature ovarian insufficiency, male gonadotoxicity, fatigue, and obstetric care have been published in peer-reviewed journals (16-24). Furthermore, structural components of LTFU care, such as transition from pediatric to adult healthcare settings or models of care, have been addressed with evidence-based methods on a European level by the PanCareSurFup project (25, 26) (Table 1).

Table 1. Overview of relevant concepts, projects and organizations

International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG)	International and multidisciplinary collaboration with the aim to develop harmonized evidence-based surveillance guidelines for survivors of childhood, adolescent and young adult cancer.
Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer (PanCare)	European multidisciplinary network with the aim of reducing the frequency, severity and impact of late adverse effects by establishing high quality and sustainable survivorship care for all survivors in Europe, among others by establishing various European Union-funded research projects.

Table 1. Overview of relevant concepts, projects and organizations (continued)

PanCareFollowUp project	PanCare project funded by the European Union under the Horizon 2020 framework (ongoing), with the overall aim to improve the health and quality of life of adult survivors of childhood cancer by facilitating person-centered survivorship care.
PanCareFollowUp Care Intervention	Person-centered model of survivorship care including surveillance recommendations, developed within the PanCareFollowUp project.
PanCareFollowUp Care Study	Prospective cohort study in four European countries, evaluating the PanCareFollowUp Care Intervention.
PanCareFollowUp Recommendations Working Group	Collaboration to develop surveillance recommendations for topics not yet addressed by the IGHG.
PanCareSurFup project	PanCare project funded by the European Commission under the 7th Framework Program (2011-2017), among others including the development of surveillance guidelines.

At present, harmonized evidence-based recommendations are not yet available for many of the late effects, even including several of those prioritized in a Delphi consensus process among survivorship experts (11). The lack of CPGs for many clinically relevant late effects is a potential barrier to optimal survivorship care (26). The Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer (PanCare) established the PanCareFollowUp project (**www.pancarefollowup.eu**) in 2019 (27). This is a European Horizon 2020-funded project, including the development and implementation of a person-centered model for survivorship care for adult survivors of CAYA cancer: the PanCareFollowUp Care Intervention. This intervention will be evaluated in a prospective cohort study across four European countries: the PanCareFollowUp Care Study (Table 1). Surveillance recommendations are, together with person-centered care, the cornerstones of this PanCareFollowUp Care Intervention. Therefore, one of the aims within the European PanCareFollowUp project was to complete harmonized recommendations for surveillance of late effects and survivorship care for topics that are not yet covered within the IGHG, using a pragmatic methodology.

METHODS

PanCareFollowUp Recommendations Working Group

To achieve the goal of completing harmonized LTFU care recommendations for the PanCareFollowUp Care Intervention, a PanCareFollowUp Recommendations Working Group was assembled. It included 23 stakeholders (late effects specialists, researchers, and survivor representatives) representing nine European countries. It was supported by a core group (HP, LK, RK, RM, and RS) whose main tasks included drafting a methodology to identify clinically relevant topics not yet addressed by the IGHG and guiding the development of harmonized CPGs for these topics using a pragmatic approach.

Selection of topics

The process of topic selection is described in detail in Figure 1.

At the outset, a total of 55 late effects were identified that require long-term follow-up strategies. Of these topics, 16 were already addressed in IGHG guidelines that are published or awaiting publication. The remaining 39 topics were included in ongoing IGHG (bone abnormalities, diabetes mellitus, dyslipidemia, hypertension, pulmonary dysfunction, mental health disorders, overweight, renal toxicity, neurocognitive deficits, psychosocial disorders, thyroid dysfunction) or PanCareSurFup (health promotion) projects that were not expected to be finished at the start of the PanCareFollowUp Care Intervention cohort study (Care Study), or were not yet assigned to guideline development groups. During the recommendation development process, it was decided to remove eight topics from the list because of inclusion in another guideline (n = 1), absence of recommendations regarding the topics in existing guidelines (n = 3), or recommendations that were similar to general population guidelines (n = 4). A further reduction of six topics was achieved by reorganization of topics.

Pragmatic methodology for developing recommendations

For topics where no evidence-based recommendations exist yet, an appropriate pragmatic methodology was drafted to define recommendations in anticipation of the future development of evidence-based CPGs.

First, for each of the designated topics, the recommendations of the four existing LTFU guidelines (from the North American Children's Oncology Group (COG), the Dutch Childhood Oncology Group (DCOG), the Scottish Intercollegiate Guidelines Network (SIGN), and the UK Children's Cancer and Leukaemia Group (UKCCLG)) were reviewed and compared for the following issues: 1) Who needs surveillance?, 2) What surveillance modality should be used?, 3) At what age or time should surveillance be initiated?, 4) At what frequency should surveillance be performed?, 5) When should surveillance be discontinued?, and 6) What should be done when abnormalities are identified? For late effects which might benefit from prevention, an additional question was reviewed: 7) What standard recommendations should be given to survivors at risk? The core group drafted a PanCareFollowUp Recommendation based on the extracted information.

For each recommendation, the objective was to describe the surveillance requirements for high-quality care, while balancing the distinct infrastructures and resources across different European healthcare systems. If at least three of the existing guidelines agreed

on a certain approach, it was adopted in the PanCareFollowUp Recommendations. If not all guidelines covered the late effect, or if fewer than three guidelines had concordant recommendations, inclusion of the recommendation was scheduled for discussion within the Recommendations Working Group in order to reach consensus. To avoid bias and acknowledging the pragmatic concept, the Working Group refrained as much as possible from adding new recommendations, considering recent experiences, or using single studies.

Internal and external consultation rounds

From June to October 2019, the Recommendations Working Group collaborated to formulate the recommendations. A two-day face-to-face Guideline Workshop in Amsterdam, the Netherlands, was attended by 16 Working Group Members near the end of the process, to review the recommendations and other overarching themes and discuss more complex topics. This was followed by an internal e-mail consultation round, a two-day face-to-face core group meeting, and an external e-mail consultation round. Eighteen European late effects experts working in research and/or clinical care representing 14 European countries reviewed the recommendations. After revision and complementing the harmonized recommendations with existing IGHG guidelines (16-23), the PanCareFollowUp Recommendations were endorsed by all PanCareFollowUp project partners in February 2020 for use in the PanCareFollowUp project. The process of developing these recommendations is depicted in Figure 2.

Considerations of the PanCareFollowUp Recommendations Working Group

Certain late effects require surveillance strategies including diagnostic tests, but in other cases, it might be more appropriate to provide guidance by awareness only or to perform a medical history or physical examination. All these types of recommendations are included in the PanCareFollowUp Recommendations.

Several consensus decisions were made during the recommendation development process. First, the occurrence of several late effects is known or suspected to be influenced by lifestyle factors or familial risk in addition to treatment-related risk factors. Furthermore, certain late effects occur more often if the survivor was exposed at a younger age, but the four existing guidelines were often inconclusive or did not mention a specific age threshold. Both for lifestyle and hereditary risk factors as well as age thresholds, more systematic evidence-based approaches were deemed necessary before informing the surveillance recommendations. Therefore, these risk factors and specific age limits were not included in the recommendations, but may nevertheless be taken into account when determining whether a survivor is at risk for a certain late effect. Second, dose effects are often assumed, but if no threshold was defined in the four existing guidelines, no new threshold was defined on consensus or single studies. Larger studies or systematic reviews are needed to appropriately address the question of the dose threshold above which surveillance is needed to improve health and QoL of survivors at risk. Third, corticosteroid exposure is usually not documented in cumulative doses in clinics. A pragmatic consensus definition of relevant corticosteroid use was agreed to be “corticosteroids as anti-cancer treatment, at least four weeks continuously”. Professional expertise may inform whether the exposure in the individual survivor is relevant in order to use the corresponding recommendation. Finally, for some of the

recommendations, especially the surveillance tests, the frequency of surveillance is well defined. For others, a more general description of frequency (for example "at least every five years", which allows for a range of yearly to five-yearly LTFU clinic appointments) was used to accommodate the wide range of survivorship care models and customs across Europe.

When merging the existing evidence-based IGHG guidelines with the newly developed recommendations resulting in the PanCareFollowUp Recommendations, a consensus decision was made to adopt the surveillance scheme for the strong (green) and moderate (yellow) IGHG recommendations, but not the weak (orange) recommendations. The strong recommendations not to do surveillance investigations (red) were also adopted. All recommendations were colored light blue to clarify their adapted methodological background.

RESULTS

Overview of the PanCareFollowUp Recommendations

A total number of 25 recommendations were developed to complement the 16 existing IGHG evidence-based guidelines. The PanCareFollowUp Recommendations were structured according to the type of guidance or surveillance needed: awareness only (*n* = 5); awareness, history, and/or physical examination (*n* = 13), and; awareness, history, and/or physical examination with surveillance tests (*n* = 23). An overview of those PanCareFollowUp Recommendations that include surveillance tests is presented in Table 2. The complete list of PanCareFollowUp Recommendations is provided in Appendix A.

In addition to regular surveillance, ongoing awareness and prompt reporting of new symptoms or signs were considered of the utmost importance for the early detection and timely treatment of late effects. To support the knowledge about relevant alarm symptoms, a symptom list specifying important alarm symptoms was provided in an appendix to the recommendations. Many of the recommendations therefore relied primarily on awareness, detailed history-taking and careful physical examination. In addition, a health promotion recommendation for all survivors was developed, since a healthy lifestyle is an effective measure in preventing chronic health conditions and lessening the burden of both mental and physical late morbidity.

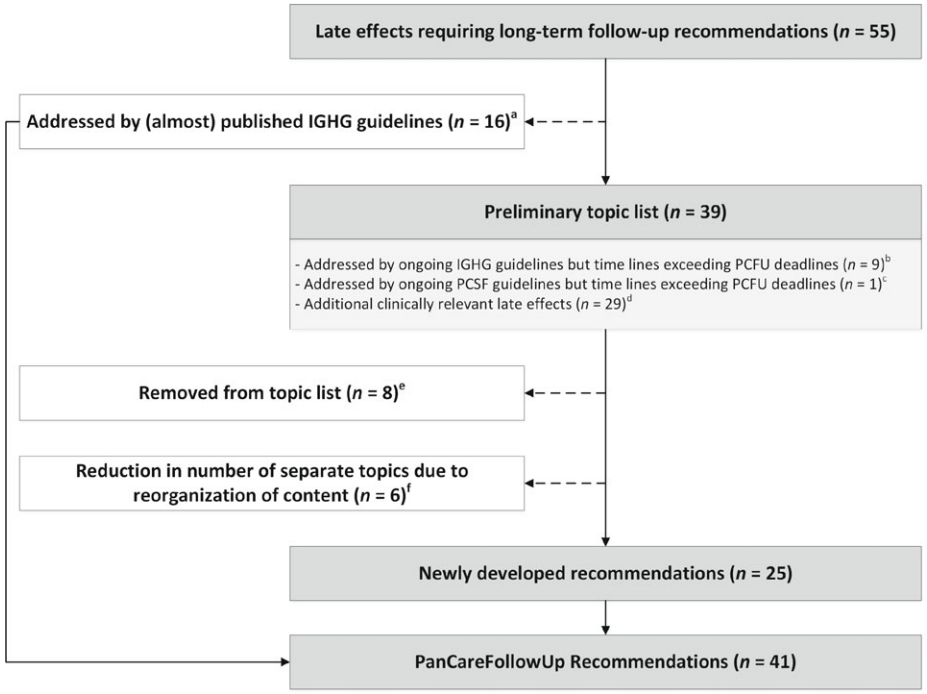

Figure 1. Flowchart of topic selection for the PanCareFollowUp Recommendations
IGHG, International Late Effects of Childhood Cancer Guideline Harmonization Group; PCFU, PanCareFollowUp; PCSF, PanCareSurFup.

[a] Includes the topics Cardiomyopathy, Breast cancer, Cancer-related fatigue, Central precocious puberty, Coronary artery disease, CNS neoplasms, Late liver injury, Iron overload, Hypothalamic-pituitary dysfunction, Male gonadotoxicity, Mental health problems, Obstetric risks, Ototoxicity, Premature ovarian failure, Psychosocial problems, Thyroid cancer.

[b] Includes the topics Bone abnormalities, Pulmonary dysfunction, Metabolic syndrome (including Overweight, Hypertension, Diabetes and Dyslipidemia), Renal toxicity, Neurocognitive deficits, Thyroid dysfunction.

[c] Includes the topic Health promotion.

[d] Includes the topics Acute myeloid leukemia or myelodysplasia, Alopecia, Primary adrenal insufficiency, Arrhythmia, Bladder cancer, Bone cancer, Cerebrovascular problems, Cervical cancer, Chronic pain, Colorectal cancer, Craniofacial growth disturbance, Dental and oral problems, Endometrial cancer, Epilepsy, Gastrointestinal abnormalities, Lower urinary tract abnormalities, Lung cancer, Melanoma and non-melanoma skin cancer, Esophageal cancer, Oral cancer, Pericardial disease, Peripheral neuropathy, Prostate cancer, Scoliosis, Spleen problems, Stomach cancer, Testicular cancer, Visual abnormalities, Valvular disease.

[e] Included in other guideline (CNS neoplasms): Epilepsy. Not (sufficiently) addressed in existing guidelines: Primary adrenal insufficiency, Esophageal cancer and Stomach cancer. Existing guidelines similar to general population recommendations: Endometrial Cancer, Cervical cancer, Testicular cancer and Prostate cancer.

[f] The topic Cardiac problems now includes Arrhythmia, Valvular disease and Pericardial disease; the topic Subsequent neoplasms now includes Acute myeloid leukemia or myeloid dysplasia, Bladder cancer, Bone cancer, Lung cancer and Oral cancer.

Figure 2. Process of developing PanCareFollowUp Recommendations for topics not yet addressed by the IGHG
PCFU, PanCareFollowUp.

Table 2. Overview of harmonized recommendations developed by a pragmatic methodology and IGHG evidence-based recommendations including surveillance tests included in the PanCareFollowUp Recommendations

PanCareFollowUp Recommendation for surveillance of:	**Who is at risk?** CAYA cancer survivors treated with or with a history of …	**What surveillance test should be used and at what frequency?**[a] (Positive recommendations only[b])
Bone problems (reduced bone mineral density) *Pragmatic methodology*	- Prolonged corticosteroids as anti-cancer treatment, at least 4 weeks continuously - Methotrexate - HSCT, especially with any history of cGvHD - TBI - Cranial and/or spinal radiotherapy - Gonadal failure - GHD	- DXA scan once, if possible, and thereafter as clinically indicated Note: It might be considered to postpone the DXA-scan in pre-pubertal and pubertal survivors.
Breast cancer (female) *Updated evidence-based IGHG guideline*	- Radiotherapy ≥ 10 Gy to a volume exposing the breasts - Upper abdominal field radiation that can extend above the diaphragm likely exposing breast tissue at a young age[c]	- Mammography and breast MRI every year if ≥ 25 years of age or ≥ 8 years from radiation, whichever occurs last
Cardiac problems (arrhythmia) *Pragmatic methodology*	- Radiotherapy ≥ 15 Gy to a volume exposing the heart - Anthracyclines, including doxorubicin, daunorubicin, epirubicin, idarubicin and mitoxantrone[d]	- ECG once at entry into LTFU - Repeat ECG once after the age of 18 years if entry into LTFU was at a younger age

Cardiac problems (cardiomyopathy) *Evidence-based IGHG guideline*	- Radiotherapy to a volume exposing the heart - Anthracyclines, including doxorubicin, daunorubicin, epirubicin, idarubicin and mitoxantrone[d]	- Echocardiogram with specific attention to left ventricular systolic function, starting 2 years after treatment *If treated with a total cumulative anthracycline dose[d] ≥ 250 mg/m², or radiotherapy ≥ 35 Gy to a volume exposing the heart, or a combination of a total cumulative anthracycline dose[d] ≥100 - 250 mg/m² and radiotherapy ≥ 15 Gy:* at least every 2 - 3 years *If treated with a total cumulative anthracycline dose[d] ≥100 - 250 mg/m² or radiotherapy ≥ 15 Gy to a volume exposing the heart:* at least every 5 years - Echocardiogram with specific attention to left ventricular function, prior to pregnancy or in the first trimester, if female and treated with anthracyclines and/or radiotherapy to a volume exposing the heart - Screening for modifiable cardiovascular risk factors (hypertension, diabetes, dyslipidemia, obesity, smoking and low levels of physical activity)
Cardiac problems (pericardial disease) *Pragmatic methodology*	- Radiotherapy ≥ 15 Gy to a volume exposing the heart	- Echocardiogram with specific attention to the pericardium, at least every 5 years, starting 2 years after radiotherapy
Cardiac problems (valvular heart disease) *Pragmatic methodology*	- Radiotherapy ≥ 15 Gy to a volume exposing the heart	- Echocardiogram with specific attention to valvular structure and function, at least every 5 years, starting 2 years after radiotherapy

Table 2. Overview of harmonized recommendations developed by a pragmatic methodology and IGHG evidence-based recommendations including surveillance tests included in the PanCareFollowUp Recommendations (continued)

PanCareFollowUp Recommendation for surveillance of:	**Who is at risk?** CAYA cancer survivors treated with or with a history of …	**What surveillance test should be used and at what frequency?**[a] (Positive recommendations only[b])
CNS neoplasms *Evidence-based IGHG guideline; to be published* (including meningiomas, (high-grade) gliomas and other CNS neoplasms)	- Radiotherapy to a volume exposing the head or brain, including TBI	- No recommendation can be formulated for routine MRI surveillance for **a**symptomatic survivors; the decision to undertake MRI surveillance should be made by the CAYA cancer survivor and HCP after careful consideration of the potential harms and benefits of MRI surveillance
Colorectal cancer *Pragmatic methodology*	- Radiotherapy to a volume exposing the colon and rectum, including TBI	- FOBT every 3 years - As an alternative surveillance method, colonoscopy might be considered every 5 years starting 5 years after radiation or at the age of 30 years, whichever occurs last
Coronary artery disease (asymptomatic) *Evidence-based IGHG guideline; to be published*	- Radiotherapy to a volume exposing the heart	- Surveillance for modifiable cardiovascular disease risk factors (hypertension, dyslipidemia, diabetes, overweight or obesity, smoking and low levels of physical activity) according to local or national guidelines, starting no later than the age of 40 years, and at least every 5 years subsequently[e]
Dyslipidemia *Pragmatic methodology*	- TBI - HSCT	- Fasting lipid profile starting no later than at the age of 40 years, and at least every 5 years subsequently[e]

Ear problems *Evidence-based IGHG guideline* (including hearing loss and tinnitus)	- Cisplatin (with or without carboplatin > 1500 mg/m^2) - Radiotherapy ≥ 30 Gy to a volume exposing the head or brain	*Survivors < 6 years of age at risk:* - Extensive testing by audiologist every year, to begin no later than the end of treatment *Survivors ≥ 6 years of age at risk:* - Pure tone conventional audiometry testing at 1000-8000 Hz - Additional testing with high frequency audiometry > 8000 Hz (whenever equipment is available), to begin no later than the end of treatment - every other year if 6-12 years of age - every 5 years for adolescents and young adults ≥ 12 years of age
Fertility problems and sexual dysfunction (male) *Evidence-based IGHG guideline* (including impaired fertility, impaired spermatogenesis, testosterone deficiency and physical sexual dysfunction)	- Alkylating agents - Radiotherapy to a volume exposing the testes, including TBI - Surgery to the spinal cord, sympathetic nerves or pelvis - Hypogonadism	*Post-pubertal survivors treated with radiotherapy ≥ 12 Gy to a volume exposing the testes, including TBI:* - Early morning testosterone at clinically appropriate time intervals - LH in addition to (early morning) testosterone if clinical signs of hypogonadism, previous low or borderline testosterone concentrations, or if an early morning testosterone sample cannot be obtained at least every 2-3 years *Post-pubertal survivors at risk that desire assessment of potential for future fertility:* - Semen analysis

Table 2. Overview of harmonized recommendations developed by a pragmatic methodology and IGHG evidence-based recommendations including surveillance tests included in the PanCareFollowUp Recommendations (continued)

PanCareFollowUp Recommendation for surveillance of:	**Who is at risk?** CAYA cancer survivors treated with or with a history of …	**What surveillance test should be used and at what frequency?**[a] (Positive recommendations only[b])
HP axis problems *Evidence-based IGHG guideline; to be published* (including GHD, TSHD, LH/FSHD and ACTHD)	- Radiotherapy to a volume exposing the HP region, including TBI (if ≥ 30 Gy, refer directly to (pediatric) endocrinologist or see in multidisciplinary team) - Surgery near or within the HP region (refer directly to (pediatric) endocrinologist or see in multidisciplinary team) - A CNS tumor near or within the HP region (refer directly to (pediatric) endocrinologist or see in multidisciplinary team) - Hydrocephalus or CSF shunt (at risk for GHD)	*Pre-pubertal and peri-pubertal survivors at risk:* - fT4, TSH, morning cortisol every year, starting 6-12 months after completion of radiotherapy or directly after hydrocephalus or CSF shunt occurrence *Post-pubertal survivors at risk:* - fT4, TSH, morning cortisol, IGF-1 - Morning testosterone, or free testosterone in survivors with overweight, and LH (males) - Estradiol, FSH and LH (females) every year, starting 6-12 months after completion of radiotherapy or directly after hydrocephalus or CSF shunt occurrence Note: an IGF-1 level even as high as 0 SDS does not rule out GHD. Note: continue surveillance at least 15 years from exposure. Continuation of surveillance should be a shared decision between survivor and HCP considering available healthcare resources. If surveillance is terminated, the survivor should be educated about possible signs and symptoms of HP axis problems.

Hypertension *Pragmatic methodology*	- Radiotherapy to a volume exposing the kidneys, or to a volume exposing the heart and associated large vessels, including TBI - Nephrectomy - Ifosfamide - Platinum based chemotherapy - Nitrosoureas - Immunosuppressives,e.g., ciclosporin, tacrolimus, and prolonged corticosteroids as anti-cancer treatment (at least 4 weeks continuously)	- Blood pressure measurement at least every 2 years and at every LTFU visit
Impaired glucose metabolism and diabetes mellitus *Pragmatic methodology*	- Radiotherapy to a volume exposing the pancreas, including TBI	- Fasting blood glucose with or without HbA1c at least every 5 years
Iron overload *Evidence-based IGHG guideline; to be published*	- HSCT - Multiple red blood cell transfusions	- Serum ferritin once at entry into LTFU

Table 2. Overview of harmonized recommendations developed by a pragmatic methodology and IGHG evidence-based recommendations including surveillance tests included in the PanCareFollowUp Recommendations (continued)

PanCareFollowUp Recommendation for surveillance of:	**Who is at risk?** CAYA cancer survivors treated with or with a history of …	**What surveillance test should be used and at what frequency?**[a] (Positive recommendations only[b])
Late liver injury *Evidence-based IGHG guideline; to be published* (including liver fibrosis or cirrhosis, hepatocellular liver injury, hepatobiliary dysfunction, biliary tract injury or liver synthetic dysfunction)	- Radiotherapy to a volume exposing the liver, including TBI - HSCT - Methotrexate - Mercaptopurine - Thioguanine - Dactinomycin - Busulfan - Sinusoidal obstruction syndrome - cGvHD - Liver surgery - Chronic viral hepatitis (it is assumed that these survivors are followed by an appropriate specialist, e.g. hepatologist or infectious disease specialist, according to local or national hepatitis CPGs)	- Serum liver enzyme concentrations (ALT, AST, gGT, ALP) once at entry into LTFU
Overweight and obesity *Pragmatic methodology*	- A CNS tumor near or within the HP region - Radiotherapy to a volume exposing the HP region, including TBI - Surgery near or within the HP region	- Height, weight and BMI at least every 2 years and at every LTFU visit

Precocious puberty (central) *Evidence-based IGHG guideline; to be published*	- Radiotherapy to a volume exposing the HP region, including TBI (if ≥ 30 Gy, refer directly to (pediatric) endocrinologist or see in multidisciplinary team) - Surgery near or within the HP region (refer directly to (pediatric) endocrinologist or see in multidisciplinary team) - A CNS tumor near or within the HP region (refer directly to (pediatric) endocrinologist or see in multidisciplinary team) - Hydrocephalus or CSF shunt	*Pre- and peri-pubertal survivors at risk:* - Height velocity in relation to parental height - Tanner stage every 6 months, starting 6-12 months after completion of radiotherapy or directly after hydrocephalus or CSF shunt occurrence Note: Continue surveillance until the age of 8 years (girls) and 9 years (boys). Boys exposed to radiotherapy to the testes may have testes small for pubertal stage while in puberty. Instead, morning testosterone (before 10:00 AM) should be used as screening modality as testicular volume may be unreliable.
Premature ovarian insufficiency (female) *Evidence-based IGHG guideline* (including impaired fertility, amenorrhea and premature menopause)	- Alkylating agents - Radiotherapy to a volume exposing the ovaries, including TBI	*Pre- and peri-pubertal survivors at risk:* - FSH and estradiol[f] in case of failure to initiate or progress through puberty at least for girls ≥ 11 years of age, and for girls with primary amenorrhea (16 years of age) *Post-pubertal survivors at risk:* - FSH and estradiol[f, g] in case of menstrual cycle dysfunction suggesting premature ovarian insufficiency, or if assessment of potential for future fertility is desired

Table 2. Overview of harmonized recommendations developed by a pragmatic methodology and IGHG evidence-based recommendations including surveillance tests included in the PanCareFollowUp Recommendations (continued)

PanCareFollowUp Recommendation for surveillance of:	**Who is at risk?** CAYA cancer survivors treated with or with a history of …	**What surveillance test should be used and at what frequency?**[a] (Positive recommendations only[b])
Pulmonary problems *Pragmatic methodology* (including pulmonary dysfunction and worsening pulmonary fibrosis after high oxygen exposure in survivors treated with bleomycin who already have evidence of pulmonary fibrosis)	- Carmustine (BCNU) - Lomustine (CCNU) - Busulfan - Bleomycin - Radiotherapy to a volume exposing the lungs, including TBI - Allogeneic HSCT - Thoracic surgery	- Pulmonary function tests, including spirometry and diffusing capacity for carbon monoxide (DLCO), once at entry into LTFU
Renal problems *Pragmatic methodology* (including glomerular and tubular dysfunction)	- Ifosfamide - Cisplatin - Carboplatin - Radiotherapy to a volume exposing the kidney or urinary tract, including TBI - Nephrectomy - HSCT	*All survivors at risk:* - Glomerular function testing including blood testing (creatinine), urine testing (creatinine, proteinuria), eGFR calculation, at least every 5 years *Survivors treated with ifosfamide, cisplatin or carboplatin:* - Additional tubular function testing including blood testing (Na, K, Mg, P, Ca, phosphate, albumin) and urine testing (glucose, phosphate) at least every 5 years *Other advice:* - Education about caution in the use of NSAIDs - Counselling about single kidney-related health risks

Thyroid cancer *Evidence-based IGHG guideline*	- Radiotherapy to a volume exposing the thyroid gland, including TBI - MIBG therapy (I-131 MIBG therapy)	- Counselling regarding options for differentiated thyroid carcinoma surveillance, at least every 5 years *If the decision to commence surveillance is made, make a shared decision for one of these two surveillance modalities[h]:* - Neck palpation, every 1-2 years, starting 5 years after radiotherapy, or - Thyroid ultrasonography[i], every 3-5 years, starting 5 years after radiotherapy
Thyroid function problems *Pragmatic methodology* (including hypothyroidism and hyperthyroidism[j])	- Radiotherapy to a volume exposing the thyroid gland, including TBI - Radioiodine therapy (I-131 ablation therapy) - MIBG therapy (I-131 MIBG therapy)[k] - Allogeneic HSCT - Total thyroidectomy (follow-up by an endocrinologist starting directly after surgery)	- TSH and fT4 measurement – every year in survivors ≤ 18 years of age and at least every 2-3 years in survivors > 18 years of age *Female survivors at risk for hypothyroidism:* - Measure TSH and fT4 prior to attempting pregnancy and periodically during pregnancy

Note that only the green (strong recommendation to do), yellow (moderate recommendation to do) and red (recommendation not to do) IGHG recommendations were included in the PanCareFollowUp Recommendations. ACTHD, adrenocorticotropic hormone deficiency; CAYA, childhood, adolescent and young adult; cGvHD, chronic graft-versus-host disease; CPG, clinical practice guideline; CSF, cerebrospinal fluid; DXA, dual-energy X-ray absorptiometry; FOBT, fecal occult blood testing; GHD, growth hormone deficiency; HBV, hepatitis B virus; HCP, healthcare provider; HCV, hepatitis C virus; HP, hypothalamic-pituitary; HSCT, hematopoietic stem cell transplantation; LTFU, long-term follow-up; LH/FSHD, luteinizing hormone/follicle stimulating hormone deficiency; MIBG, metaiodobenzylguanidine; NSAIDs, non-steroidal anti-inflammatory drugs; RBC, red blood cell; TBI, total body irradiation; TSHD, thyroid stimulating hormone deficiency; ULN, upper limit of normal.

[a] Surveillance should be initiated no later than five years after treatment or five years from diagnosis, depending on the individual healthcare systems, and surveillance should be continued life-long, unless specified otherwise.

[b] Due to a lack of benefit or insufficient evidence, certain surveillance strategies were not recommended or recommendations could not be formulated and were not included in this table. Appendix A presents the complete recommendations.

[c] For survivors treated with upper abdominal field radiation that can extend above the diaphragm likely exposing breast tissue at a young age, the surveillance decision should be an individual one, taking into account additional risk factors (patient age, family history, menopausal status, other previous cancer treatment) and personal values regarding the potential advantages and disadvantages of surveillance.

[d] Use the following formulas to convert to doxorubicin isotoxic equivalents prior to calculating total cumulative anthracycline dose. Doxorubicin: multiply total dose x 1; Daunorubicin: multiply total dose x 0.6 (Feijen, 2019); Epirubicin: multiply total dose x 0.8 (Feijen, 2019); Idarubicin: multiply total dose x 5 (COG guideline); Mitoxantrone: multiply total dose x 10 (Feijen, 2019). References: EAM Feijen, WM Leisenring, KL Stratton et al. Derivation of anthracycline and anthraquinone equivalence ratios to doxorubicin for late-onset cardiotoxicity. JAMA Oncology. 2019;5(6):864-871. EAM Feijen, A Font-Gonzalez, HJH van der Pal et al. Risk and temporal changes of heart failure among 5-year childhood cancer survivors: a DCOG-LATER study. J Am Heart Assoc. 2019;8(1):e009122.

[e] Timing of initiation and frequency should be based on the intensity of treatment exposure, family history, presence of co-morbid conditions associated with disease risk or by general risk management guidelines.

[f] If amenorrhea, measure FSH and estradiol randomly; if oligomenorrhea, measure during early follicular phase (day 2-5).

[g] This assessment should be performed after ending oral contraceptive pill/sex steroid replacement therapy use, if applicable, ideally after two months discontinuation.

[h] The decision to commence surveillance and which modality to use should be made by the HCP in consultation with the survivor after careful consideration of the advantages and disadvantages of differentiated thyroid carcinoma surveillance in the context of the survivor's individual preferences, practice setting, the HCP's experience and expertise of local diagnosticians (radiology). HCPs should be aware that both diagnostic tests have advantages and disadvantages and can identify benign as well as malignant nodules resulting in need for invasive procedures.

[i] Ultrasound, fine needle aspiration and/or biopsy should be performed in centers where there is experience in assessment of thyroid cancers so that appropriate interpretation of radiographic features and clinical risk factors can minimize the number of unnecessary invasive and additional diagnostic procedures. When ultrasound is used for surveillance, the cervical lymph node stations should always be visualized.

[j] Risk of hypothyroidism for all mentioned exposures. Risk of hyperthyroidism after radiotherapy to a volume exposing the thyroid gland, including TBI, or allogeneic HSCT.

[k] MIBG used for diagnostic purposes (e.g. MIBG scanning) does not put patients at risk for hypothyroidism if adequate preventive measures were used.

DISCUSSION

Harmonized long-term follow-up recommendations are urgently needed to guide optimal care for survivors of CAYA cancer. Despite ongoing international evidence-based efforts, many relevant issues are not yet addressed by an integrated approach. The recommendations developed within the PanCareFollowUp project address this gap through the first Europe-wide effort to provide unified recommendations in anticipation of evidence-based guidelines. They represent a unique agreement across European LTFU expert groups. Moreover, these recommendations have been co-developed with CAYA cancer survivor representatives from start to finish to ensure a survivor-centered approach in the recommended strategies.

The PanCareFollowUp Recommendations guide healthcare providers in providing education or surveillance to allow early detection of, and timely intervention for, adverse health effects. Importantly, they are central to the guideline-based PanCareFollowUp Care Intervention which aims to implement person-centered survivorship care across Europe. Aside from surveillance, these PanCareFollowUp Recommendations emphasize the importance of awareness and survivor education. Knowledge about their treatment history and related risks may empower survivors to adopt a lifestyle that reduces the risk of chronic health conditions (28). Within the PanCareFollowUp Care Intervention, the survivor-specific recommendations are translated to plain, understandable language in their individual Survivorship Care Plans. Survivors can share this information with their healthcare provider, if desired, and consult it at a time of their own convenience.

Our pragmatic methodology does not provide the power needed to draw definitive conclusions about optimum LTFU care. Ongoing and upcoming evidence-based guidelines, as well as innovative research, are awaited to provide more informed insights into the best strategies of surveillance. Another limitation of any CPG is that they can be quickly outdated with emerging evidence. Therefore, the development of a living guideline tool that enables real-time updating of recommendations based on new evidence is included in the PanCareFollowUp project, facilitated by a platform which will be constructed to continuously search for newly published studies. IGHG topic working groups will be regularly updated with the search results. As such, they can efficiently review new findings and decide whether adaptation of the existing recommendations is required.

Considering the fact that two-thirds of European CAYA cancer survivors currently do not have access to LTFU care (3), these recommendations already require a substantial investment of logistics and resources and may be expected to have an impressive impact on survivor's health and well-being. CPGs alone are not enough to change healthcare – they need to be implemented and consistently used. The PanCareFollowUp Care Study will provide deeper insight into the barriers and facilitators of guideline-based person-centered survivorship care in different European countries. This will include the evaluation of the digital Survivorship Passport tool to facilitate the process of creating a personal care plan and sharing it with a survivor's healthcare provider (29). Experience with these PanCareFollowUp Recommendations in the Care Study will elucidate both effectiveness and feasibility of screening as well as potential areas of improvement.

In conclusion, the PanCareFollowUp Recommendations for LTFU care fill an important gap of current European survivorship care. Through a highly collaborative effort involving 41 late effects specialists, researchers, and survivor representatives a total of 25 harmonized recommendations were developed, with a large emphasis on awareness among survivors and healthcare providers, in addition to surveillance tests in those at risk. Early recognition of late effects as well as effective surveillance and treatment strategies will help alleviate the burden on survivors and their families as well as their healthcare and societal resources. By providing suitable, comprehensive and easily accessible information, survivors are supported and empowered in the self-management of their health and care. Whilst awaiting the development of internationally harmonized evidence-based CPGs, these recommendations can bridge the gap and improve survivorship care for issues relevant to survivor's health and well-being.

SUPPLEMENTARY MATERIAL

Appendix A is available online (https://doi.org/10.1016/j.ejca.2021.06.004).

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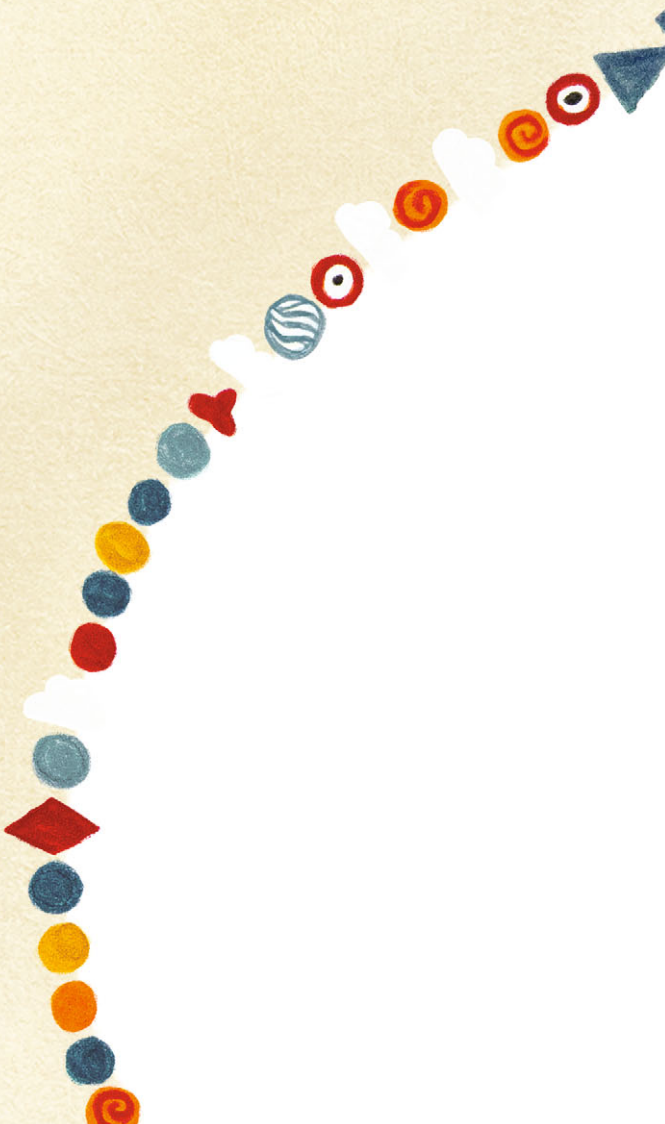

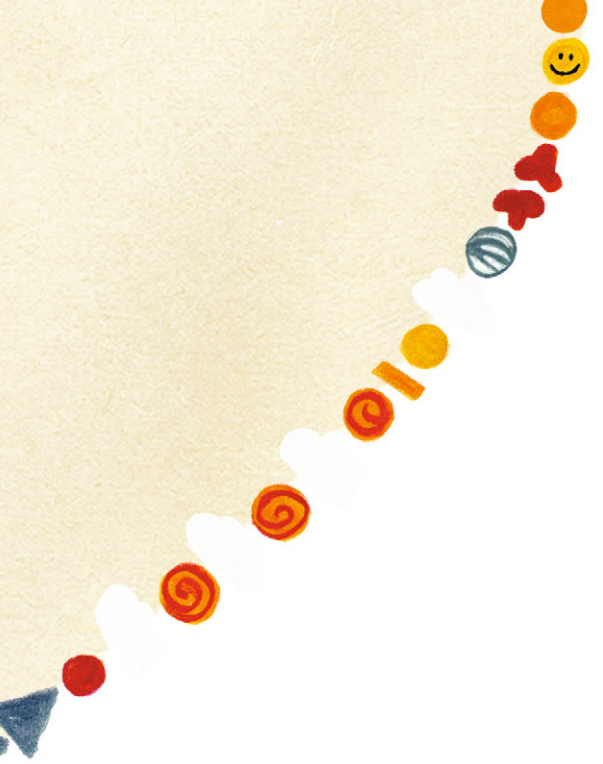

6

Evaluating the feasibility, effectiveness and costs of implementing person-centered follow-up care for childhood cancer survivors in four European countries: the PanCareFollowUp Care Intervention prospective cohort study protocol

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ABSTRACT

Introduction Long-term survival after childhood cancer often comes at the expense of late, adverse health conditions. However, survivorship care is often not available for adult survivors in Europe. The PanCareFollowUp Consortium therefore developed the PanCareFollowUp Care Intervention, an innovative person-centered survivorship care model based on experiences in the Netherlands. This paper describes the protocol of the prospective cohort study (Care Study) to evaluate the feasibility and the health economic, clinical and patient-reported outcomes of implementing PanCareFollowUp Care as usual care in four European countries.

Methods and analysis In this prospective, longitudinal cohort study with at least six months of follow-up, 800 childhood cancer survivors will receive the PanCareFollowUp Care Intervention across four study sites in Belgium, the Czech Republic, Italy and Sweden, representing different healthcare systems. The PanCareFollowUp Care Intervention will be evaluated according to the Reach, Effectiveness, Adoption, Implementation and Maintenance framework. Clinical and research data are collected through questionnaires, a clinic visit for multiple medical assessments, and a follow-up call. The primary outcome is empowerment, assessed with the Health Education Impact Questionnaire. A central data center will perform quality checks, data cleaning, and data validation, and provide support in data analysis. Multilevel models will be used for repeated outcome measures, with subgroup analysis, for example by center, attained age, sex or diagnosis.

Ethics and dissemination This study will be conducted in accordance with the guidelines of Good Clinical Practice and the Declaration of Helsinki. The study protocol has been reviewed and approved by all relevant ethics committees. The evidence and insights gained by this study will be summarized in a Replication Manual, also including the tools required to implement the PanCareFollowUp Care Intervention in other countries. This Replication Manual will become freely available through PanCare and will be disseminated through policy and press releases.

Trial registration NL8918, registered at the Netherlands Trial Register at 24 September 2020, https://www.trialregister.nl/trial/8918.

INTRODUCTION

Over the last decades, five-year survival rates of childhood cancer in Europe have increased substantially, from 30% in the 1970s to 80% in the early 2000s (1). Today, the European population of childhood cancer survivors, estimated at minimally 300,000, is rising by about 12,000 per year (2). Yet, many survivors not only experience the burden of previous cancer diagnosis, but also face treatment-related late effects (3, 4). These may become apparent years or even decades after finishing therapy (5) and might have a significant adverse impact on quality of life (6, 7). Moreover, the transition from pediatric to adult healthcare settings often lacks continuity. As a result, many adults who survived childhood cancer have increased healthcare use and experience problems in participation, which generate a substantial burden for survivors and societies in general (8-10). Early detection of new health conditions is essential as it could prevent further harm (11). This requires lifelong survivorship care with frequent adaptations of the follow-up plan.

Currently, only one-third of European pediatric oncology clinics provide survivorship care to adult survivors of childhood cancer (12). In 2006, an international group of pediatric oncologists, psychologists, nurses, epidemiologists, survivors and their parents agreed in the Erice statement that has recently been updated and reconfirmed (13, 14) that follow-up care should be available and accessible for all survivors throughout their lifespan.

In the past decade, international evidence-based clinical practice guidelines have been developed to support early detection and treatment of (a)symptomatic late effects, including those developed by the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG), sometimes in collaboration with the PanCareSurFup project (15-23). A European models of care guideline is published and guidelines for the transition from childhood to adult healthcare settings and health promotion are currently being developed (24, 25). Yet, implementation lags behind. Recently, a person-centered approach for survivorship care for adult survivors has been implemented in Nijmegen, the Netherlands (26). All Dutch survivors of childhood cancer are invited for follow-up care in which multidisciplinary teams deliver person-centered care based on contemporary surveillance guidelines (27). The first positive effects of this person-centered approach have been reported (24, 26). The next step is to validate this person-centered approach for survivorship care in other countries.

The PanCareFollowUp Consortium, established in 2018, is a unique multidisciplinary European collaboration between 14 project partners from ten European countries, including survivors (www.pancarefollowup.eu) (28). The aim of the consortium is to improve the quality of life for survivors of childhood, adolescent and young adult cancer by bringing evidence-based, person-centered care to clinical practice. The PanCareFollowUp Consortium has developed two interventions: 1) a person-centered and guideline-based model of survivorship care (PanCareFollowUp Care Intervention) (see Box 1) (29) and 2) an eHealth lifestyle coaching model (PanCareFollowUp Lifestyle Intervention). The protocol of the first intervention is described in this paper (version 3, January 21st, 2021), the protocol of the second one will be described separately. Both will be evaluated within the PanCareFollowUp project. The consortium published a Care Intervention Manual that contains instructions and tools required for implementing

the PanCareFollowUp Care Intervention. At the project end, Replication Manuals that contain the instructions and tools required for implementation of the PanCareFollowUp Interventions will be freely distributed.

The overall aim of the PanCareFollowUp Care Study is to evaluate the feasibility, effectiveness and costs of implementing PanCareFollowUp Care as usual care for adult survivors of childhood cancer in four study sites in four European countries. Four objectives have been formulated: 1) To what extent is implementing PanCareFollowUp Care in the participating study sites feasible?; 2) What are the patient-reported experiences and outcomes, including survivor empowerment, of PanCareFollowUp Care and how do they change?; 3) What is the number and nature of pre-existing and new clinical events detected by PanCareFollowUp Care among participating survivors?; and 4) What are the short-term (six months) and projected long-term costs per unit change of empowerment and other outcomes after implementing PanCareFollowUp Care from the perspective of survivors and healthcare providers (HCPs)?

METHODS AND ANALYSIS

Study population, setting and recruitment

Survivors fulfil the inclusion criteria if they are or have been: diagnosed with cancer before the age of 19 years; treated or registered at one of the four study sites; treated with chemotherapy and/or radiation therapy for childhood cancer with or without surgery; at least five years from primary cancer diagnosis; at least one year off treatment (also applying to treatment of subsequent benign or malignant neoplasms or relapse of the primary cancer); and currently at least 16 years of age.

Exclusion criteria consist of: being unable to complete the study questionnaires because of severe neurocognitive sequelae or insufficient understanding of the language used (even with help from another person); or having previously received complete follow-up care that is similar to the care as described in the PanCareFollowUp Care Intervention Manual (Box 1).

This international prospective cohort study will be conducted at four study sites located in four European countries: Belgium, Czech Republic, Italy, and Sweden. All sites currently provide long-term follow-up care, either within a pediatric (Belgium, Italy) or adult (Czech Republic, Sweden) oncology center, using a set of (inter)national guidelines and protocols. Each study site aims to include 200 survivors who complete the study. With an estimated non-response and early drop-out (informed consent signed, but no actual participation in the study) of 40-50% based on previous experience and an estimated late drop-out (at any point after completing the T1 questionnaire) of 5-10% during the study, approximately 350 to 400 survivors will therefore be invited at each site. To assess the feasibility of this recruitment strategy, each center screened their respective registries and estimated a total of 5,944 eligible survivors.

Box 1. The PanCareFollowUp Care Intervention

The PanCareFollowUp Care Intervention is based on a person-centred care model (reference 26) that aims to meet the physical, psychological and social needs of (adult) survivors of childhood cancer through shared decision-making about prevention, surveillance and treatment options. The Care Intervention consists of three steps:

A. *Preparation of the clinic visit by both the survivor and the health care provider (HCP).* The survivor provides information about their health, wellbeing, needs and preferences by completing the PanCareFollowUp Survivor Questionnaire. The HCP prepares a Treatment Summary describing the childhood cancer treatment that the survivor has received, reviews the relevant surveillance recommendations and the PanCareFollowUp Survivor Questionnaire provided by the survivor, and thereupon prepares the Standard Survivorship Care Plan.
B. *Clinic visit including tailored follow-up care.* After obtaining a medical history and performing a physical examination, the survivor and HCP jointly discuss the results of the Survivor Questionnaire, and the Standard Survivorship Care Plan. Together, they agree on a plan for diagnostic tests and potential referral if needed, based on surveillance guidelines or clinical indication. Based on these shared decisions, as well as potential test results, the HCP creates a Draft Individualized Survivorship Care Plan and provides tailored health education.
C. *Follow-up call.* The survivor and HCP discuss the test results and the preferred model of care for future follow-up care. The results of these shared decisions are incorporated in the final Individualized Survivorship Care Plan, that the survivor may share with other HCPs.

The PanCareFollowUp Care Intervention ends after co-creation and delivery of the Individualized Survivorship Care Plan. Survivors will thereafter remain under surveillance either at or under the guidance of their clinic, frequently adjusting their Individualized Survivorship Care Plan when needed.

Each study site developed a recruitment strategy within the prerequisites of this study that fits best within their own logistics (Appendix A). Selected survivors will be invited by an invitation letter, an invitation e-mail or by phone (depending on the usual procedure at each study site), and receive an information sheet, including contact details for additional information and an informed consent form. Reasons for non-participation can be provided. One option of the pre-set reasons is 'not participating because the questionnaires are being provided via internet'. In this case, the study site may decide to offer the option for paper questionnaires. Survivors who give informed consent but do not respond to the first questionnaire, even after reminders, are considered early drop-outs and will be excluded from the study, as essential data about these survivors will not be available. The first participant was enrolled in February 2021, and at 1 March 2022 456 participants were enrolled and completed the clinic visit. The estimated last inclusion is on 30 September 2022, with last data collection on 31 May 2023.

PROMs or PREMs: survivors	Premature ovarian insufficiency (females) (d)	Neurocognitive problems: language	Telangiectasias of the eye
Empowerment (heiQ)[a] (primary outcome)	Testosterone deficiency (males) (d)	Neurocognitive problems: memory	Xerophthalmia
Patient satisfaction (Satisfaction Qx)[b]	TSH deficiency (d)	Neurocognitive problems: motor integration	**Feasibility outcomes: survivor**
Shared decision-making (SDM-Q-9)[c]	*Gastro-intestinal*	Neurocognitive problems: processing speed	Received care according to SCP
Resilience (CD-RISC 25)[d]	Bowel obstruction	Psychological distress (q)	Success of communication
HRQoL (EQ-5D-5L, SF-36, ICECAP-A)[e]	Chronic enterocolitis	Stress-related mental disorder	Missing information
Psychological distress (BSI-18)[f]	Gastro-intestinal strictures or fistula	Suicidal ideation (q)	*Italian study site only:* Use of and satisfaction with SurPass
Post-traumatic stress symptoms (PCL-5)[g]	*Hepato-biliary*	Unemployment (q)	
Distress (ET)[h]	Cholelithiasis	*Renal and urinary tract*	**Feasibility outcomes: HCP (per clinic)**
Fatigue (SQx + PROMIS Fatigue – Short Form 8a +)[i,j]	Hepatobiliary dysfunction (d)	Bladder fibrosis	No. of eligible survivors invited
Pain (BPI)[k]	Hepatocellular liver injury (stage 1) (d)	Dysfunctional voiding (q)	No. of participating survivors per time point
Lifestyle (SQx)	Iron overload (d)	Glomerular kidney dysfunction (d)	No. of non-responders
Social functioning (SQx)	Liver cirrhosis	Hemorrhagic cystitis	Reasons for non-response
Clinical outcomes	Liver fibrosis	Hydronephrosis	No. of drop-outs per time point
Auditory	Liver synthetic dysfunction (d)	Tubular kidney dysfunction (d)	Reasons for drop-outs per time point
Hearing loss (d + q)	*Immunological*	Vesicoureteral reflux	Composition of multidisciplinary team
Tinnitus (q)	Spleen problems (overwhelming infections)	*Reproductive*	Use of the SCP
Cardiac	*Musculoskeletal*	Impaired fertility (q)	Reasons for non-use of SCP, if applicable
Arrhythmia (d + q)	Craniofacial growth problems	Impaired spermatogenesis (males) (d + q)	Shared decision making (HCP perspective; SDM-Q-Doc)[c]
Cardiomyopathy (d)	Osteonecrosis	Low birth weight of offspring (females) (q)	Extent to which SCP of participating survivors has been implemented and reasons for deviating
Pericardial disease (d)	Reduced bone mineral density (d)	Miscarriage (females) (q)	

Valvular heart disease (d)	Spine kyphosis	Physical sexual dysfunction (males) (q)	*Italian study site only:* no. of SurPasses delivered, recommendation brochures given and SurPasses shared with physicians, SurPass user statistics
Dental	Spine scoliosis	Premature birth of offspring (females) (q)	
Dental caries	*Neurological*	*Respiratory*	
Dental developmental problems	Cavernomas	Pulmonary dysfunction (d + q)	**Health economic outcomes: survivor**
Xerostomia (q)	Cerebrovascular accidents	*Subsequent neoplasm*	Time investment of survivor (preparation for clinic visit, travel, total time in clinic, follow-up appointments)
Dermatologic	Neurogenic bladder	Subsequent neoplasm (benign or malignant) (d + q)	
Alopecia	Neurogenic bowel	*Vascular*	Time investment of relatives (travel, total time in clinic, follow-up appointments)
Endocrine	Optic chiasm neuropathy	Aneurysms	
ACTH deficiency (d)	Pain (q)	Asymptomatic coronary artery disease	Travel costs of survivor and relatives
Amenorrhea (females) (q)	Peripheral motor neuropathy (q)	Carotid artery disease	Other extra costs for survivor and relatives
Central precocious puberty (d)	Peripheral sensory neuropathy (q)	Dyslipidemia (d)	Loss of time for survivor and relatives at paid work or in education
Diabetes mellitus (d)	*Psychosocial and neurocognitive*	Hypertension	
Failure in pubertal progression	Adjustment difficulties	*Visual*	**Health economic outcomes: HCP**
Growth hormone deficiency (d)	Anxiety (q)	Cataract	Time investment of HCP and other staff tasks related to clinic visit (preparation, clinic visit, tasks following clinic visit, follow-up call)
Hyperthyroidism (d)	Behavioral problems	Chronic painful eye	
Hypothyroidism (peripheral) (d)	Fatigue (q)	Glaucoma	
Impaired glucose metabolism (d)	Low educational status (q)	Keratitis	Costs for diagnostic and screening tests
LH/FSH deficiency (d)	Neurocognitive problems: academics	Lacrimal duct atrophy	Costs for other consumables for clinic visit
Obesity	Neurocognitive problems: attention	Maculopathy	
Overweight	Neurocognitive problems: executive function	Papillopathy	
Premature menopause (females) (d)	Neurocognitive problems: intelligence	Retinopathy	

Figure 1. Overview of all patient-reported outcome measures (PROMs) and experience measures (PREMs), clinical outcomes, feasibility outcomes and health economic outcomes used in the Care Study

Outcomes that are specific for males or females are indicated as such between brackets. For the clinical outcomes, it is indicated whether they are assessed through a diagnostic test according to the guidelines (d), Survivor Questionnaire (q), or both (d+q). Other clinical outcomes are assessed through medical history and/or physical examination. BPI, Brief Pain Inventory; BSI-18, Brief Symptom Inventory-18; CD-RISC 25. Connor-Davidson Resilience Scale (25 items); ET, Emotion Thermometer; HCP, healthcare provider; heiQ, health education impact questionnaire; HRQoL, health-related quality of life; ICECAP-A, ICEpop CAPability measure for Adults; LH/FSH, luteinizing hormone/follicle-stimulating hormone; PROMIS, Patient-Reported Outcomes Measurement Information System; PCL-5, PTSD Checklist for DSM-5; QoL, quality of life; Satisfaction Qx, Satisfaction questionnaire by Blaauwbroek et al.; SCP, Survivorship Care Plan; SDM-Q-9, 9-item shared decision-making questionnaire (patient perspective); SF-36, Short Form-36 (36 items, version 1); SQx, Survivor Questionnaire (part of the PanCareFollowUp Care Intervention); TSH, thyroid-stimulating hormone; SDM-Q-Doc, 9-item Shared Decision-Making Questionnaire (HCP perspective).

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Participating survivors can withdraw from the study at any time if they wish. They are not obliged to provide a reason for withdrawal, although it will be asked and recorded if available. To assess representativeness of the final study sample, the four centers will provide aggregated data about their total eligible population of survivors including population distributions of gender, current age, age at diagnosis, type of cancer and distance to the late effects clinic. This will be compared to the distributions among the included survivors per clinic.

During recruitment and data collection, careful monitoring of enrolment, (non-) response, reasons for non-response and early and late drop-out will be performed by the four study sites in close collaboration with the central data center at the Danish Cancer Society Research Center.

Intervention

Survivors of childhood cancer who receive PanCareFollowUp Care (i.e., care in accordance with the PanCareFollowUp Care Intervention Manual and as outlined in Box 1) will be followed up until six months after the clinic visit. The implementation of person-centered care in this project is facilitated by a narrated Powerpoint and an on-site workshop for all HCPs involved in the study. An add-on study investigating the feasibility of delivering PanCareFollowUp Care using the digital Survivorship Passport (SurPass) tool (30) will be conducted at the Italian clinic, where SurPass is already implemented.

Primary and secondary outcomes

This study uses a variety of outcomes to answer the four research objectives (Figure 1).

These are measured from time point 1 (T1) before the clinic visit until T5 at six months after the clinic visit (Figure 2). Outcomes are provided by survivors and HCPs through questionnaires, a clinic visit and diagnostic tests.

1) To what extent is implementing PanCareFollowUp Care in the participating study sites feasible?

Feasibility of implementation is of major importance to ensure sustainability of the PanCareFollowUp Care Intervention. Therefore, feasibility indicators measured by questionnaires among survivors and HCPs as well as an evaluation of barriers and facilitators are included to inform about the experiences of implementing PanCareFollowUp Care (Figure 2). Items include, among others, drop-outs at different time-points, use of and experiences with the Survivorship Care Plan, and shared decision-making (Figure 1).

2) What are the experiences and outcomes as reported by participating survivors receiving PanCareFollowUp Care?

The primary outcome for this study is empowerment measured by the Health Education Impact Questionnaire (heiQ) (31). Empowerment has been defined by the EU Joint Action on Patient Safety and Quality of Care as a “multidimensional process that helps people gain control over their own lives and increase their capacity to act on issues that they themselves define as important”, a definition adapted from Lutrell et al. (32, 33). Empowerment has been selected as the primary outcome because childhood cancer survivors encounter several transition moments starting from diagnosis, after which a

greater responsibility for their own health and care is required. It is essential that survivors receive the support they need to manage and advocate for their needs. Moreover, empowerment is important to manage future health problems. We have included six of the eight scales of the heiQ relevant to cancer survivors in our study (social integration and support, health services navigation, constructive attitudes and approaches, skill and technique acquisition, emotional distress, an self-Monitoring and insight). The heiQ has previously been used in cancer patient and survivor populations (34-36). It allows to calculate a mean for each scale indicating higher or lower empowerment in the respective domain within a participant compared to the baseline assessment.

Secondary outcomes consist of a variety of patient-reported experiences and outcomes (PREMs and PROMs), such as satisfaction and quality of life (Figure 1).

3) What is the number and nature of pre-existing and new clinical events detected by PanCareFollowUp Care among participating survivors?

Clinical outcomes are outcomes of symptoms and diseases and have been defined based on published or almost published guidelines of the IGHG and the PanCareFollowUp Recommendations. A total of 116 clinical outcomes were defined, which reflects the wide range of late effects that survivors may encounter affecting both physical health and psychosocial well-being (Figure 1). Clinical outcomes including medical history, are collected through survivor self-report in the Survivor Questionnaire (with verification at the clinic visit), physician-report in the Treatment Summary, after the clinic visit and after potential diagnostic tests (Figure 2). The number and range of pre-existing and newly detected health problems (symptomatic and asymptomatic) per survivor will be described, including the results of clinical examinations (e.g., echocardiogram or blood tests).

4) What are the short-term (six months) and projected long-term costs per unit change of empowerment and other outcomes after implementing PanCareFollowUp Care from the perspective of survivors and HCPs?

The costs associated with implementing the care model will be determined by using health economic outcomes (Figure 1). These reflect the time, time off work and monetary investments made by the survivor, accompanying relatives or friends, the HCP and other staff in relation to the clinic visit while receiving or providing PanCareFollowUp Care, and are collected using questionnaires (Figure 2). We do not take costs outside the clinic visit into account, that is, costs related to possible primary care physician visits, mental health services or referrals to other specialists outside the clinical setting. Costs related to the clinic visit, as associated with PanCareFollowUp Care, are compared to potential benefits measured in terms of PREMs and PROMs.

An overall evaluation of implementing the PanCareFollowUp Care Intervention will be performed throughout the project according to the Reach, Effectiveness, Adoption, Implementation and Maintenance framework to assess the impact (www.re-aim.org) (37) (Table 1).

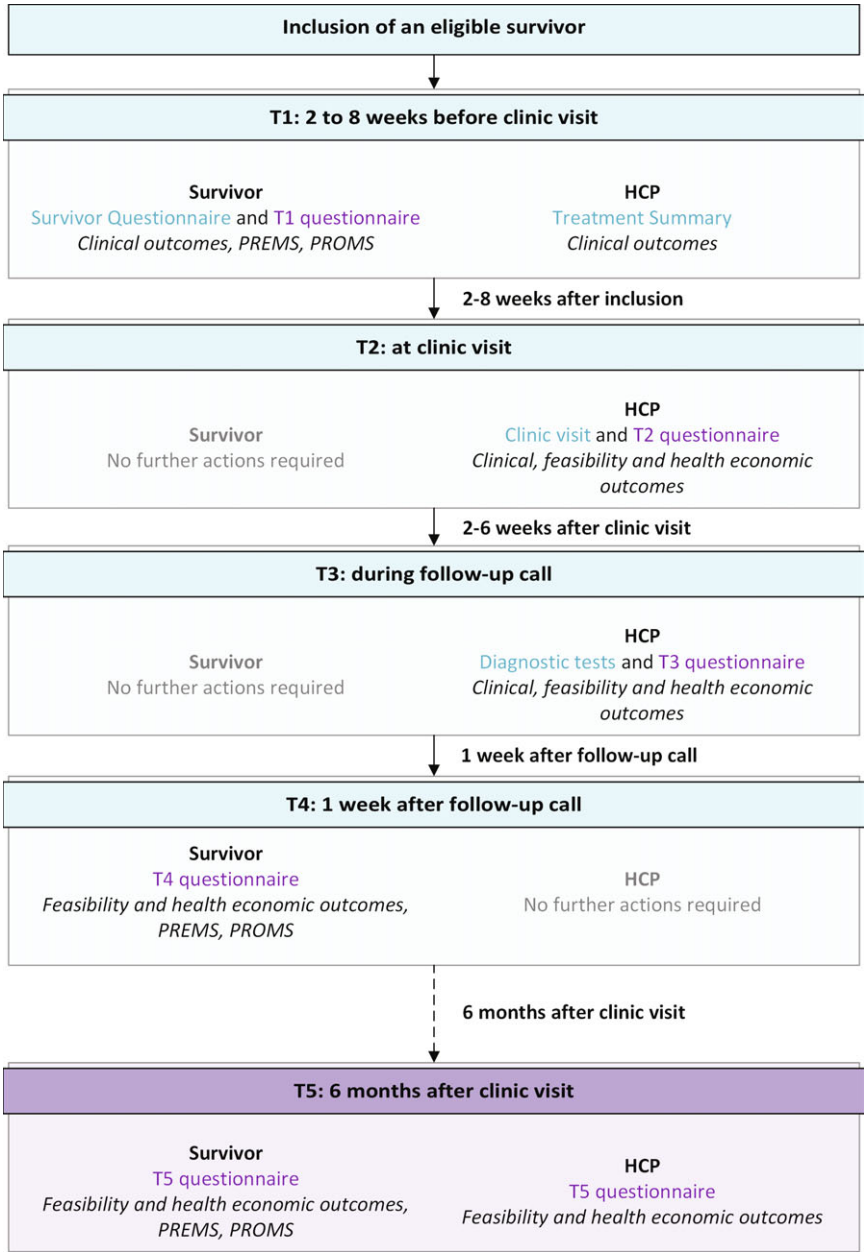

Figure 2. Flowchart of data collection after inclusion of an eligible survivor
The boxes describe for each time point the timing of data collection, the person providing data (survivor, HCP or both), the data collection instruments (Survivor Questionnaire, Treatment Summary or T1-T5 study questionnaire), and the types of outcomes collected. Depicted in blue are data collected for care, and in purple for research purposes. HCP, healthcare provider; PREMs, patient-reported experience measures; PROMs, patient-reported outcome measures; T1, time point 1; T2, time point 2; T3, time point 3; T4, time point 4; T5, time point 5.

Table 1. RE-AIM framework applied to the PanCareFollowUp Care Intervention

Components	Related outcomes/actions in the Care Study
Reach	No. and proportion of participants vs. non-responders Representativeness of participating survivors[a] (comparison of distribution: gender, current age, age at diagnosis and type of cancer) Reasons for (non-)participation
Effectiveness/ efficacy	Main outcome empowerment[a] Patient-reported outcome and experience measures, and clinical, feasibility and health economic outcomes[a]
Adoption[b]	Multidisciplinarity of HCPs involved Recruitment rate Barriers and facilitators for recruitment
Implementation[b]	Use of SCP and reasons for non-use Adaptations made to the PanCareFollowUp Care Intervention or implementation strategy Time and costs of PanCareFollowUp Care for survivors and HCPs Barriers and facilitators for implementation
Maintenance	Replication Manual including updated implementation and recruitment strategy, publicly available for current and new centers Overview of requirements for study sites to make the PanCareFollowUp Care Intervention routine care

HCPs, healthcare providers; SCP, Survivorship Care Plan. [a] Comparisons will be made according to subgroups of gender, current age, age at diagnosis and type of cancer. [b] This information will be collected at each study site separately.

Patient and public involvement

Survivor representatives from Childhood Cancer International-Europe are included in the project as members of the PanCareFollowUp Consortium (28). They are involved throughout the project and reach out to their respective national and international networks when needed. Survivors were involved in setting the research agenda by writing the grant application and the study protocol, developing and reviewing the PanCareFollowUp Care Intervention materials, evaluating the study questionnaires, monitoring the progress of the PanCareFollowUp Care Study, and creating awareness on social media (29). They helped consider ways to mitigate the burden of completing the study questionnaires or remembering the childhood cancer history for participants. After the end of data collection, survivor representatives will be involved in the interpretation of the study results and dissemination to participants, survivor networks and the general public.

Power calculation

We aim to include 200 participants at each of the four study sites (total $n = 800$). The primary outcome measure is change in empowerment between T1 and T5 as measured by the heiQ (34). We use six constructs (cancer version including five constructs plus one additional construct, namely self-monitoring and insight) with mean scores ranging

from 2.9 (standard deviation (SD): 0.64) to 3.2 (SD: 0.48). Taking the construct with the largest SD (thus needing the highest number of participants to demonstrate a statistically significant change), limiting it to a single study site, with a 2-sided α of 0.05 and a power of 80%, we will need 200 participants per center to identify an effect size of 0.2 given a mean score of 2.9 (SD: 0.64). That is enough power to demonstrate a small to medium effect. The actual power is larger since we ignored measuring empowerment repeatedly and using constructs with smaller SDs.

Data collection

Data will be collected from participating survivors as well as from their HCPs at five time points (T1-T5) during a follow-up period of six to eight months (Figure 2). We will use data collected in the context of care delivery, and combine them with additional data collected specifically for research purposes. For the latter, there are three data collection moments for survivors and four for HCPs. These time points are linked to the structure of the PanCareFollowUp Care Intervention, which consists of three steps: 1) Preparation of the clinic visit by survivor and HCP (corresponding with T1), 2) Clinic visit (corresponding with T2), and 3) Follow-up call (two to four weeks after T2, corresponding with T3). Thereafter, there is data collection at 1 week after the follow-up call (T4) and 6 months after the clinic visit (T5).

The main data collection instruments consist of the PanCareFollowUp Survivor Questionnaire (care), the Treatment Summary (care), medical history, physical examinations and diagnostic tests during and after the clinic visit (care), and additional online study questionnaires for survivors and HCPs (research). The Survivor Questionnaire and Treatment Summary are available through open access (29). The English versions of the study questionnaires for survivors have been pretested by three survivors, whereas the English questionnaires for HCPs have been pretested with at least two HCPs in each center before the start of the data collection. The questionnaires for survivors have subsequently been translated to the local languages of the study sites, that is, Czech, Dutch, Italian and Swedish.

Statistical analysis

For analyzing outcomes measured multiple times, like the primary outcome, we will use multilevel models for repeated measures applying a fixed effect to control for study site. Next, we will perform subgroup analyses for relevant groups by including interaction terms. These subgroups will be identified based on the literature combined with knowledge from professionals. The final selection will be determined during the study. However, possible subgroups may be distinguished according to study site, sex, time since cancer diagnosis, treatment type, or distance to late effects clinic. The models will be adjusted for confounders, which will be identified during the study based on the literature and expert opinion. Clinical findings will be described at each time point, like the number of prevalent conditions as well as new diseases detected, diagnoses of subclinical diseases, relapse of the original tumor, late effects and diagnostic measurements. The results will be adjusted for multiple testing.

For the health economic evaluation, we will calculate the costs associated with the implementation of the PanCareFollowUp Care Intervention in order to achieve change in different outcomes. The analysis of costs and benefits will be based on within-subject

changes until six months of follow-up, and on model-based evaluations for longer-term predictions. The estimated benefits of the intervention are measured in terms of empowerment (heiQ) and quality of life (Short-Form 36, EQ-5D-5L, ICEpop CAPability measure for Adults). Costs include resources incurred at the level of the hospital and the survivor. At the hospital level, we measure the time of physicians and other hospital staff for tasks related to the clinic visit and the follow-up call, costs for diagnostic and screening tests and other consumables for the clinic visit. At the survivor level, we measure the time investment and travel costs of survivors and relatives or friends, and loss of productive time at the workplace or in education. These costs are investigated separately on each level, hospital and survivor, as well as on an aggregated level.

The calculation of cost per unit change of outcomes needs to be interpreted in light of the relatively short follow-up period of six months within the study. This implies that the cost evaluation mainly focuses on short-run effects, while longer-run effects of PanCareFollowUp Care on outcomes such as survival cannot be measured within the study. Moreover, effects on other outcomes such as quality of life may be small. In order to provide information about the potential medium- to long-run effects, we will complement our analysis with a model-based economic evaluation approach using data from this study and information from the literature on longer-term effects of follow-up interventions and patient pathways, as well as related cost estimations. This will allow us to gain a more comprehensive picture on the costs associated with the implementation of PanCareFollowUp Care.

Handling missing data

Automated reminders and phone calls by the clinics are used to ensure that all patients and HCPs complete all questionnaires to minimize the number of missing data. In case of missing data for certain PROMs and PREMs, we will replace missing values with the mean of the remaining items of the scale as recommended by the manuals. In case of other missing data, we will perform sensitivity analyses, that is, perform the analyses with the complete cases and repeat the analyses with imputed values.

Data management

A cloud-based Electronic Data Capture (EDC) platform has been developed by the Danish Cancer Society using Castor EDC (**www.castoredc.com**). This platform can be accessed by each of the four study sites for data entry. Castor EDC is compliant with all the important regulations regarding research: GDPR, ISO 27001 and ISO 9001 with servers located in the Netherlands including several measures to ensure security, adequacy and veracity of the collected data: regular back-ups (four times per day); personal accounts with individual user rights; audit, data and edit trail of all entered and changed data; and real-time edit checks to identify discrepancies in entered data.

Participating survivors complete their questionnaires directly in Castor EDC through a personalized link they receive by email. Clinical data will be provided by HCPs or retrieved from survivors' medical records and entered into Castor EDC by local data managers according to a data entry instruction manual. All personal and sensitive data collected in the PanCareFollowUp project will be pseudonymized.

After the end of the data collection period, data will be exported from Castor to servers at the Danish Cancer Society. Experienced data managers will perform quality

checks, data cleaning, and validation of data collected at the four sites and will set up data for the respective statistical analyses as subsets of the main database, governed by Data Transfer Agreements. The investigators will properly address all the ethical, legal, and safety aspects of the study and comply fully with EU Regulation 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation or GDPR).

ETHICS AND DISSEMINATION

This study will be conducted in accordance with the guidelines of Good Clinical Practice by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and the Declaration of Helsinki, written to protect those involved in clinical studies. The study protocol has been reviewed and approved by all relevant ethics committees: Brno, Ethics Committee of St. Anne's University Hospital (13 August 2019); Leuven, Ethics Committee Research University Hospitals Leuven (16 December 2020); Stockholm, Ethics Review Authority Stockholm (26 October 2020); and Genoa, N. Liguria Regional Ethics Committee (13 July 2020).

Written informed consent will be obtained from all study participants before enrolment and data collection. An independent ethics advisor from Denmark is available to provide feedback and advice on ethics issues that may arise. An external study steering committee has been appointed to act as an advisory capacity with study oversight and external advice. The committee includes a survivor representative, a clinical oncologist, a late effects specialist, an ethicist and a statistician.

Incidental findings based on participants' completion of the questionnaires are unlikely given the nature of the questions, except for one question of the Brief Symptom Inventory-18 on suicidal thoughts. The central data center and the four study sites will regularly check for any positive answers on this specific question, and inform the HCP as soon as possible, but within a maximum of two weeks. Worrisome answers at the pre-visit questionnaire will be discussed at the clinic visit. In the post-visit questionnaires, the survivor is informed that he or she can contact their general physician or late effects clinic in case of worrisome symptoms or complaints.

After the project, a Replication Manual will be developed for anyone interested in implementing the PanCareFollowUp Care for adult survivors of childhood cancer. It will include an updated Intervention Manual based on the Care Study results and additional focus groups with project stakeholders after the study closes. The Replication Manual will include all materials required for implementation in different languages and will become freely available through PanCare. PanCareFollowUp is aligned with EC Open Science Initiative, providing open access to all publications, and participates in the H2020 Open Research Data Pilot. The PanCareFollowUp Consortium will ensure that the collected data is findable, accessible, interoperable and reusable. A dissemination plan including policy and press releases has been created warranting publications and lay language summaries on the different outcomes collected, to be distributed through the networks of PanCare and several (inter)national childhood cancer organizations. In addition, results will be published in peer-reviewed journals and presented on the project website.

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APPENDIX A. RECRUITMENT STRATEGY OF EACH STUDY SITE

Sweden starts with inviting a random sample, prioritizing survivors who are lost to follow-up or have not visited the study site in the past five years, and might invite survivors who received care more recently depending on the recruitment rate among the initial population.

Italy starts with inviting survivors who already have a scheduled appointment at their clinic, but who did not already receive the Survivorship Passport, and are resident in the Liguria region. They will invite 350 to 400 survivors to be able to include 200 survivors. They will subsequently recruit scheduled survivors resident in other regions, and if the number is still insufficient, they will actively invite other survivors to the clinic.

The Czech Republic starts with selecting a random sample of 250 survivors from the clinic's database whom they will gradually invite over the recruitment period. If more survivors need to be invited to reach the inclusion aim within the recruitment period, they will invite survivors who have a scheduled appointment at their clinic and who meet the study inclusion criteria.

Belgium starts to invite, in alphabetical order, the survivors of 18 years and older with a primary cancer diagnosis with a date of diagnosis in or before 1990, regardless of whether or not they already received some long-term follow-up. Simultaneously, 20 survivors who were scheduled for a clinic visit in March and April 2021 have also been invited to participate in this study. In the second wave, they will invite the survivors with a diagnosis in 1990-2000 in alphabetic order. And, if needed, the survivors diagnosed in 2001-2020, again in alphabetic order.

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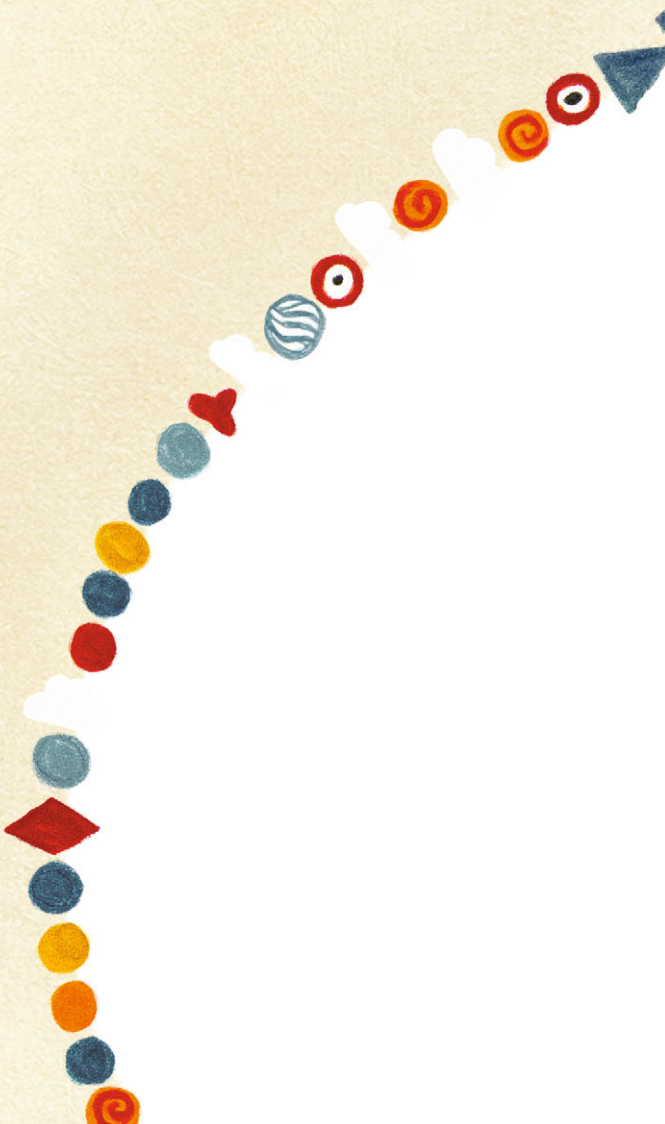

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Cyclophosphamide is not associated with clinically relevant late pulmonary dysfunction in Dutch survivors of childhood cancer – the DCCSS-LATER 2 PULM sub-study

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Submitted

ABSTRACT

Background Treatment for childhood cancer may increase the risk of long-term pulmonary complications, including lung fibrosis, radiation-induced lung injury, respiratory infections, and pulmonary dysfunction. Pulmonary surveillance is recommended after established pulmonary toxic exposures, including bleomycin, busulfan, carmustine (BCNU), lomustine (CCNU), radiotherapy to a field exposing the lungs, and pulmonary surgery. However, the role of cyclophosphamide as a pulmonary toxic agent is debated.

Aim To establish whether cyclophosphamide is associated with late pulmonary dysfunction among survivors of childhood cancer.

Methods In this Dutch Childhood Cancer Survivor Study (DCCSS)-LATER 2 PULM sub-study, we included 828 survivors with a median follow-up of 26.6 years, treated with cyclophosphamide and/or established pulmonary toxic treatment, or neither. Pulmonary function tests were used to measure the primary outcomes of diffusion impairment (diffusing capacity for carbon monoxide (DLCO) z-score), restriction (total lung capacity (TLC) z-score), and obstruction (forced expiratory volume in the first second/forced vital capacity (FEV1/FVC) z-score. Secondary outcomes comprised chronic cough, recurrent respiratory tract infections, shortness of breath, and supplemental oxygen need.

Results Diffusion and restrictive abnormalities were highly prevalent among those treated with pulmonary toxic treatment, with cyclophosphamide (41.0 and 50.4%, respectively) and without (34.3 and 41.9%, respectively). In multivariable logistic and linear regression analyses, cyclophosphamide did not have a clinically relevant effect on any of the primary or secondary outcomes. There was also no significant interaction between cyclophosphamide and established pulmonary toxic treatment.

Conclusions This study suggests that cyclophosphamide is not associated with clinically relevant pulmonary dysfunction in long-term childhood cancer survivors.

INTRODUCTION

Nowadays, five-year overall survival in children and adolescents diagnosed with cancer is more than 80% (1). However, as cancer treatment also affects healthy and developing tissues, cure often comes at the cost of late effects (2-4). Survivors of childhood cancer experience twice as many serious health conditions as their healthy peers, with pulmonary diseases contributing substantially to the excess cumulative burden of morbidity (5). Several chemotherapeutic agents (bleomycin, busulfan, carmustine (BCNU) and lomustine (CCNU)) (6-8) and radiotherapy exposure (8-14) are known to contribute to varying degrees of lung damage, ranging from microscopic injury to lung fibrosis. These toxicities may initially manifest as diffusion impairment and restriction on a pulmonary function test and clinically present with dyspnea, exercise intolerance, and a chronic cough (15). Furthermore, thoracic surgery is associated with chest wall deformities and a reduced lung volume (8, 10, 13, 16), and stem cell transplantation may be complicated by bronchiolitis obliterans syndrome as a rare but serious form of chronic graft-versus-host disease (17).

There is conflicting evidence about the role of cyclophosphamide, a widely used alkylating agent, as a cause of late adverse pulmonary outcomes. The few studies reporting on cyclophosphamide are hampered by small cohort sizes, difficulty in separating the effects of cyclophosphamide from those of established pulmonary toxic treatments, limited follow-up duration, and lack of adequate controlling for potentially confounding comorbidities or lifestyle factors, such as heart failure or smoking (9, 10, 12, 13, 18-20). In addition, previous studies varied widely in outcome assessment, ranging from self-report to clinical assessment, and differ in definitions used to characterize abnormalities.

Long-term follow-up care using evidence-based guidelines is an important tool to preserve and improve childhood cancer survivors' health through early detection and timely treatment of late effects (21). Pulmonary surveillance is advised after exposure to bleomycin, busulfan, carmustine, lomustine, radiotherapy to a field exposing the lungs, and thoracic surgery, and often includes one or multiple pulmonary function tests (22, 23). However, the uncertainty regarding cyclophosphamide poses a challenge to the development of evidence-based recommendations for childhood cancer survivors treated with cyclophosphamide but no other established pulmonary toxic therapies.

In this pulmonary sub-study of the nationwide Dutch Childhood Cancer Survivor Study (DCCSS)-LATER cohort (1963-2001) part 2: clinic visit & questionnaire study (24), we sought to i) determine the prevalence of late pulmonary dysfunction (diffusion impairment, restriction, or obstruction) among survivors treated with cyclophosphamide with or without other pulmonary toxic therapy and controls using pulmonary function tests with contemporary and clinically relevant cut-offs, ii) establish whether cyclophosphamide is associated with late pulmonary dysfunction as an independent risk factor, iii) examine potential effect modification by established pulmonary toxic treatment, as well as iv) explore the association between cyclophosphamide and respiratory symptoms.

METHODS

Study design and population

The DCCSS-LATER 2 PULM sub-study is part of the cross-sectional DCCSS-LATER 2 study in a well-established population-based cohort in the Netherlands (24, 25). The PULM sub-study was approved by the Medical Ethical Committee of the Amsterdam University Medical Center, the Netherlands on 23 January 2015 (number 2011/011). Informed consent was obtained from all participants. Inclusion and exclusion criteria for the LATER 2 PULM study are shown in Figure 1.

Among the DCCSS-LATER 2 participants, four exposure-based groups were defined: group A (cyclophosphamide without established pulmonary toxic treatment), B (established pulmonary toxic treatment without cyclophosphamide), C (both cyclophosphamide and pulmonary toxic treatment), and D (neither cyclophosphamide nor pulmonary toxic treatment). For groups A and D, eligible survivors were randomly selected with the aim to recruit at least 260 participants in each group. Groups B and C, who are recommended to receive pulmonary surveillance, were included if a pulmonary function was available in their medical record at the Amsterdam University Medical Center, Erasmus Medical Center, Radboud University Medical Center or University Utrecht Medical Center.

Data collection

Study procedures

Participants were invited to complete a study questionnaire and a clinic visit with physical examination. Groups A and D completed a study-related pulmonary function test, whereas medical records were reviewed for groups B and C to collect the most recent complete pulmonary function test. Pulmonary function measurements were performed according to American Thoracic Society/European Respiratory Society (ATS/ERS) criteria (26), and interpreted by clinical experts including a quality check. Reports mentioning poor quality were excluded. The investigation was rescheduled in case of an acute pulmonary infection.

We extracted forced expiratory volume in the first second (FEV1) in liters (L) and forced vital capacity (FVC) in L from spirometry; total lung capacity (TLC) in L from whole body plethysmography; and diffusing capacity for carbon monoxide corrected for hemoglobin level (DLCO) in mmol/min/kPa, carbon monoxide transfer coefficient (KCO) in mmol/min/kPa, and alveolar volume (VA) in L from carbon monoxide diffusion testing. Absolute values were transformed into age-, sex- and height-corrected z-scores using the Global Lung Function Initiative (GLI) reference equations (http://gli-calculator.ersnet.org) (27, 28).

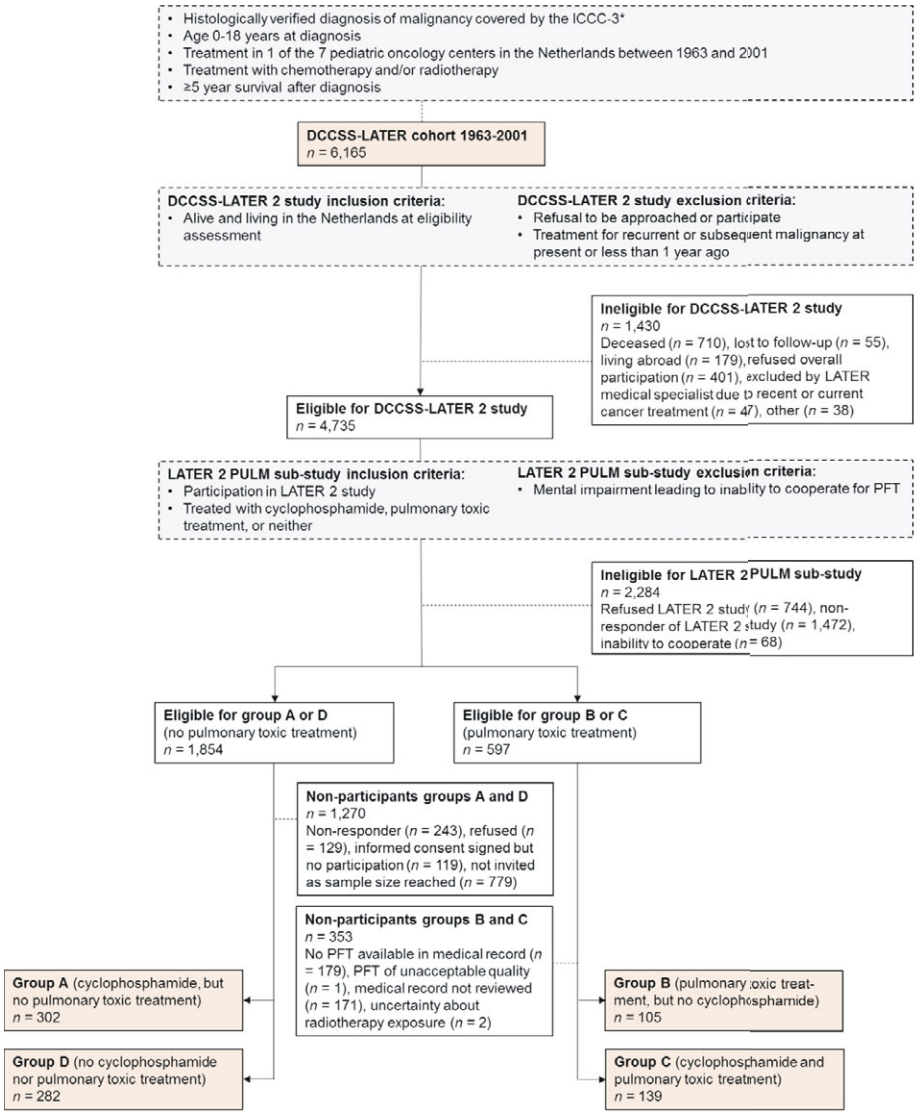

Figure 1. Flowchart of the DCCSS-LATER 2 PULM sub-study
Pulmonary toxic treatment was defined according to the Dutch long-term follow-up guidelines as exposure to bleomycin, busulfan, carmustine, lomustine, radiotherapy involving (partial) lung or mediastinal tissue including total body irradiation or spinal irradiation, or thoracic surgery. *Including selected low-grade brain tumors, and Langerhans Cell Histiocytosis treated with chemotherapy and/or radiotherapy. DCCSS, Dutch Childhood Cancer Survivor Study; ICCC-3, International Classification of Childhood Cancer (third edition); PFT, pulmonary function test.

Primary and secondary pulmonary outcomes

Our primary outcomes included pulmonary diffusion impairment (defined as DLCO below the lower limit of normal (LLN)), restrictive pulmonary dysfunction (TLC < LLN), and obstructive pulmonary dysfunction (FEV1/FVC < LLN). Diffusion impairment was further classified as pulmonary vascular abnormality (VA > LLN), gas exchange problem due to alveolar damage (VA < LLN and KCO < upper limit of normal (ULN)) or loss of lung volume (VA < LLN and KCO > ULN) (26). Lower and upper limits of normal were defined as z-scores <-1.65 and >1.65, respectively. In addition, we evaluated FEV1/FVC, TLC and DLCO z-scores as continuous outcomes.

Secondary pulmonary outcomes were collected through the questionnaire (i.e., persistent coughing ≥6 weeks in the past year, and respiratory tract infections ≥3 times a year) and clinic visit (i.e., shortness of breath and supplemental oxygen use). Clinically relevant shortness of breath was defined as symptoms at mild exertion or at rest, representing the most severe levels.

Childhood cancer diagnosis and treatment

Details on demographic variables, primary childhood cancer diagnosis and treatment have previously been collected from medical charts for all DCCSS-LATER 2 study participants (25). Treatment data was available for the primary cancer and all recurrences, but not for subsequent malignancies. Radiotherapy information was reviewed in detail to better capture the impact of lower neck irradiation and high abdominal fields on lung tissue (Appendix A).

Comorbidities and lifestyle

Comorbidities and lifestyle were examined as potential confounders. Clinically relevant cardiac dysfunction was defined as questionnaire-based self-reported heart failure or cardiomyopathy with self-reported use of cardiovascular medication (Appendix B). Self-reported smoking was also collected.

Statistical analyses

Continuous variables were described by median, mean, and (interquartile) range as appropriate, and categorical variables by frequency or percentage. Causal diagrams to identify potential confounders and colliders led to the decision to control for attained age, age at diagnosis, clinically relevant cardiac dysfunction and pack years smoked in all multivariable models. The prevalence of the primary and secondary pulmonary outcomes was stratified by cyclophosphamide exposure group. To evaluate the association between cyclophosphamide and pulmonary dysfunction (primary outcome) or respiratory symptoms (secondary outcomes), we constructed multivariable logistic and linear regression models adjusting for pulmonary toxic treatment on a binary (yes/no) and detailed (type of therapy) level. Effect modification regarding the primary outcomes was explored by including an interaction term between pulmonary toxic treatment (yes/no) and cyclophosphamide (categorical). Assumptions were met for the logistic and linear models. All analyses were performed in R version 4.3.0 using two-sided tests at an alpha of 0.05, with Bonferroni correction for multiple testing where appropriate.

Multiple imputation
We reviewed the proportion of missing data and performed multiple imputation to improve the accuracy and statistical power of our analyses (Appendix C). All analyses were also performed on the subset of complete cases for comparison.

RESULTS

Patient and cohort characteristics
The DCCSS-LATER 2 PULM sub-study included 828 participants who completed a questionnaire, clinic visit, and pulmonary function test (Figure 1). Participants were diagnosed at a median age of 5.8 years (range: 0.0-17.9), most often with leukemia/lymphoma (60.1%) or non-central nervous system solid tumor (31.5%), and had a median follow-up of 26.6 years (range 14.9-54.9) after diagnosis (Table 1) (Appendix D).

Prevalence of pulmonary dysfunction
Survivors treated with cyclophosphamide but without established pulmonary toxic treatment (group A) did not demonstrate an increased prevalence of pulmonary dysfunction or respiratory symptoms compared to controls (group D) (Figure 2). Restrictive dysfunction and diffusion abnormalities, especially gas exchange disorders (64.2% of all diffusion impairments), were observed much more frequently after established pulmonary toxic treatments (groups B and C). In our cohort, 87 out of the 159 participants with diffusion impairment also had restrictive dysfunction, indicating the presence of subclinical therapy-induced interstitial inflammation and alveolar damage.

Prevalence of respiratory symptoms
The prevalence of respiratory symptoms in group A (cyclophosphamide only) was similar to that in group D (controls) (Figure 2). Survivors treated with cyclophosphamide and established pulmonary toxic treatment reported more chronic cough (8.6% in groups B and C vs. 5.7% in group D) and shortness of breath (7.6% in group B, 17.3% in group C and 9.9% in group D). None of the participants required supplemental oxygen.

Association of cyclophosphamide dose with late pulmonary dysfunction
In the multivariable logistic models, the odds of diffusion impairment (DLCO z-score < LLN) was 2.2 times increased (95% confidence interval (CI) 1.2-3.8) after a cumulative cyclophosphamide dose of 5-10 g/m^2 compared to no cyclophosphamide exposure, but this effect was not carried forward in the highest dose category, providing no evidence for a dose-response relationship (Table 2, model 2). In the multivariable linear models, a cumulative cyclophosphamide dose of ≥10 g/m^2 was associated with a 0.3 point reduction (95% CI -0.6 to 0.0) in TLC z-score (Table 2, model 4).

All multivariable models included adjustment for age at diagnosis, attained age, clinically relevant cardiac dysfunction, pack years smoked, as well as pulmonary toxic therapy, the latter of which was strongly related to diffusion impairment (OR 5.3, 95% CI 3.6-7.9) and restrictive dysfunction (OR 8.2, 95% CI 5.5-12.2) (full models in Appendix E). Interaction terms between cyclophosphamide and pulmonary toxic therapy tested in models 1 and 3 were not significant (data not shown).

Table 1. Baseline characteristics of the DCCSS-LATER 2 PULM sub-study cohort (*n* = 828) by exposure group

	Group A: cyclophosphamide (*n* = 302)	**Group B: pulmonary toxic treatment** (*n* = 105)	**Group C: cyclophosphamide and pulmonary toxic treatment** (*n* = 139)	**Group D: no cyclophosphamide and no pulmonary toxic treatment** (*n* = 282)
Patient characteristics				
Sex				
Female, n (%)	155 (51.3)	51 (48.6)	59 (42.4)	153 (54.3)
Male, n (%)	147 (48.7)	54 (51.4)	80 (57.6)	129 (45.7)
Cancer characteristics				
Primary childhood cancer (ICCC)				
Leukemia/lymphoma, n (%)	227 (75.2)	46 (43.8)	109 (78.4)	116 (41.1)
CNS tumor, n (%)	2 (0.7)	8 (7.6)	5 (3.6)	54 (19.1)
Other solid tumor[a], n (%)	73 (24.2)	51 (48.6)	25 (18.0)	112 (39.7)
Age at diagnosis (y), median (range)	5.4 (0.0-17.8)	9.6 (0.1-17.9)	8.4 (0.3-17.9)	4.7 (0.0-17.4)
0 to 4.99, n (%)	141 (46.7)	31 (29.5)	48 (34.5)	147 (52.1)
Cancer characteristics				
Primary childhood cancer (ICCC)				
5 to 9.99, n (%)	87 (28.8)	27 (25.7)	38 (27.30	78 (27.7)
10 to 14.99, n (%)	56 (18.5)	33 (31.4)	42 (30.2)	44 (15.6)
15 to 17.99, n (%)	18 (6.0)	14 (13.3)	11 (7.9)	13 (4.6)

Table 1. Baseline characteristics of the DCCSS-LATER 2 PULM sub-study cohort (*n* = 828) by exposure group (continued)

	Group A: cyclophosphamide (*n* = 302)	**Group B: pulmonary toxic treatment** (*n* = 105)	**Group C: cyclophosphamide and pulmonary toxic treatment** (*n* = 139)	**Group D: no cyclophosphamide and no pulmonary toxic treatment** (*n* = 282)
Treatment characteristics				
Treatment period				
1963 to 1979, n (%)	46 (15.2)	22 (21.0)	14 (10.1)	41 (14.5)
1980 to 1989, n (%)	58 (19.2)	29 (27.6)	51 (36.7)	94 (33.3)
1990 to 2001, n (%)	198 (65.6)	54 (51.4)	74 (53.2)	147 (52.1)
Overall treatment modality				
No therapy, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	7 (2.5)
Surgery only, n (%)	0 (0.0)	1 (1.0)	0 (0.0)	33 (11.7)
Chemotherapy only (± surgery), n (%)	243 (80.5)	36 (34.3)	41 (29.5)	123 (43.6)
Radiotherapy only (± surgery), n (%)	0 (0.0)	10 (9.5)	0 (0.0)	34 (12.1)
Chemotherapy and radiotherapy (± surgery), n (%)	59 (19.5)	58 (55.2)	98 (70.5)	85 (30.1)
Missing, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Allogeneic stem cell transplantation				
Allogeneic stem cell transplantation, n (%)	0 (0.0)	0 (0.0)	37 (26.6)	0 (0.0)
No allogeneic stem cell transplantation, n (%)	302 (100.0)	105 (100.0)	102 (73.4)	282 (100.0)
Missing, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cyclophosphamide median dose if given, g/m^2 (IQR)	3,000 (1,920-5,800)	N/A	5,623 (3,600-7,912)	N/A

Table 1. Baseline characteristics of the DCCSS-LATER 2 PULM sub-study cohort (*n* = 828) by exposure group (continued)

	Group A: cyclophosphamide (*n* = 302)	**Group B: pulmonary toxic treatment** (*n* = 105)	**Group C: cyclophosphamide and pulmonary toxic treatment** (*n* = 139)	**Group D: no cyclophosphamide and no pulmonary toxic treatment** (*n* = 282)
Allogeneic stem cell transplantation				
No cyclophosphamide, n (%)	0 (0.0)	105 (0.0)	0 (0.0)	282 (100.0)
< 5 g/m^2, n (%)	191 (63.2)	0 (0.0)	56 (40.3)	0 (0.0)
5-10 g/m^2, n (%)	59 (19.5)	0 (0.0)	43 (30.9)	0 (0.0)
≥10 g/m^2, n (%)	23 (11.3)	0 (0.0)	23 (16.5)	0 (0.0)
Given, but dose missing, n (%)	18 (6.0)	0 (0.0)	17 (12.2)	0 (0.0)
Pulmonary toxic chemotherapy				
No pulmonary toxic chemotherapy, n (%)	302 (100.0)	58 (55.2)	71 (51.1)	282 (100.0)
Bleomycin, n (%)	0 (0.0)	44 (41.9)	45 (32.4)[b]	0 (0.0)
Busulfan, n (%)	0 (0.0)	0 (0.0)	16 (11.5)	0 (0.0)
Carmustine, n (%)	0 (0.0)	0 (0.0)	3 (2.2)[b]	0 (0.0)
Lomustine, n (%)	0 (0.0)	3 (2.9)	5 (3.6)	0 (0.0)
Pulmonary toxic radiotherapy				
No pulmonary toxic radiotherapy, n (%)	302 (100.0)	47 (44.8)	56 (40.3)	282 (100.0)
Pulmonary toxic radiotherapy <30 Gy, n (%)	0 (0.0)	27 (25.7)	24 (17.3)	0 (0.0)
Pulmonary toxic radiotherapy ≥30 Gy, n (%)	0 (0.0)	31 (29.5)	22 (15.8)[c]	0 (0.0)
TBI only, n (%)	0 (0.0)	0 (0.0)	38 (27.3)[c]	0 (0.0)

Table 1. Baseline characteristics of the DCCSS-LATER 2 PULM sub-study cohort (*n* = 828) by exposure group (continued)

	Group A: cyclophosphamide (*n* = 302)	**Group B: pulmonary toxic treatment** (*n* = 105)	**Group C: cyclophosphamide and pulmonary toxic treatment** (*n* = 139)	**Group D: no cyclophosphamide and no pulmonary toxic treatment** (*n* = 282)
Pulmonary toxic surgery				
Yes, n (%)	0 (0.0)	19 (18.1)[d]	2 (1.4)[e]	0 (0.0)
No, n (%)	302 (100.0)	86 (81.9)	137 (98.6)	282 (100.0)
Follow-up				
Age at invitation (y), median (range)	31.8 (15.5-63.6)	36.5 (20.8-61.6)	35.7 (16.4-54.3)	33.5 (15.7-67.7)
<18, n (%)	9 (3.0)	0 (0.0)	1 (0.7)	16 (5.7)
18-30, n (%)	121 (40.1)	23 (21.9)	35 (25.2)	92 (32.6)
30-40, n (%)	100 (33.1)	42 (40.0)	59 (42.4)	98 (34.8)
≥40, n (%)	72 (23.8)	40 (38.1)	44 (31.7)	76 (27.0)

Table 1. Baseline characteristics of the DCCSS-LATER 2 PULM sub-study cohort (*n* = 828) by exposure group (continued)

	Group A: cyclophosphamide (*n* = 302)	**Group B: pulmonary toxic treatment** (*n* = 105)	**Group C: cyclophosphamide and pulmonary toxic treatment** (*n* = 139)	**Group D: no cyclophosphamide and no pulmonary toxic treatment** (*n* = 282)
Follow-up after primary cancer diagnosis (y), median (range)	25.4 (15.0-53.1)	28.0 (15.0-54.9)	28.3 (14.9-47.4)	27.3 (14.9-54.7)
10 to 19.99, n (%)	59 (19.5)	19 (18.1)	20 (14.4)	80 (28.4)
20 to 29.99, n (%)	156 (51.7)	40 (38.1)	63 (45.3)	83 (29.4)
30 to 39.99, n (%)	52 (17.2)	29 (27.6)	44 (31.7)	92 (32.6)
≥40, n (%)	35 (11.6)	17 (16.2)	12 (8.6)	27 (9.6)
Lifestyle and comorbidities				
Pack years smoked if ever smoker, median (IQR)[f]	4.6 (2.0-11.2)	5.3 (1.0-7.9)	2.7 (0.9-4.9)	2.9 (0.8-8.4)
Ever smoker, n (%)	96 (31.8)	25 (23.8)	33 (23.7)	80 (28.4)
Never smoker, n (%)	192 (63.6)	77 (73.3)	93 (66.9)	182 (64.5)
Missing, n (%)	14 (4.6)	3 (2.9)	13 (9.4)	20 (7.1)

Table 1. Baseline characteristics of the DCCSS-LATER 2 PULM sub-study cohort (*n* = 828) by exposure group (continued)

	Group A: cyclophosphamide (*n* = 302)	**Group B: pulmonary toxic treatment** (*n* = 105)	**Group C: cyclophosphamide and pulmonary toxic treatment** (*n* = 139)	**Group D: no cyclophosphamide and no pulmonary toxic treatment** (*n* = 282)
Clinically relevant cardiac dysfunction[g]				
Yes, n (%)	7 (2.3)	6 (5.7)	12 (8.6)	3 (1.1)
No, n (%)	285 (94.4)	89 (84.8)	111 (79.9)	263 (93.3)
Missing, n (%)	10 (3.3)	10 (9.5)	16 (11.5)	16 (5.7)

CNS, central nervous system; CT, chemotherapy; DCCSS, Dutch Childhood Cancer Survivor Study; Gy, Gray; ICCC, International Classification of Childhood Cancer; IQR, interquartile range; *n*, number; TBI, total body irradiation; y, years.

[a] Other solid tumors including neuroblastomas and other peripheral nervous cell tumors, retinoblastomas, renal tumors, hepatic tumors, bone tumors, soft tissue and other extraosseous sarcomas, germ cell tumors, trophoblastic tumors, and neoplasms of the gonads, other malignant epithelial tumors, malignant melanomas, and other and unspecified malignant neoplasms.

[b] One participant received both bleomycin and carmustine.

[c] One participant received both conventionally fractionated radiotherapy (30 Gy) and TBI.

[d] Local excision of the lung (*n* = 9), segmental resection of the lung (*n* = 6), local excision and segmental resection of the lung (*n* = 1), segmental resection and lobectomy of the lung (*n* = 1), thoracic wall surgery (*n* = 2).

[e] Segmental resection of the lung (*n* = 1), segmental resection and lobectomy of the lung (*n* = 1).

[f] Pack years smoked missing for participants in group A (*n* = 29), B (*n* = 5), C (*n* = 18) and D (*n* = 29).

[g] Self-reported heart failure or cardiomyopathy with cardiovascular medication as defined in Appendix B.

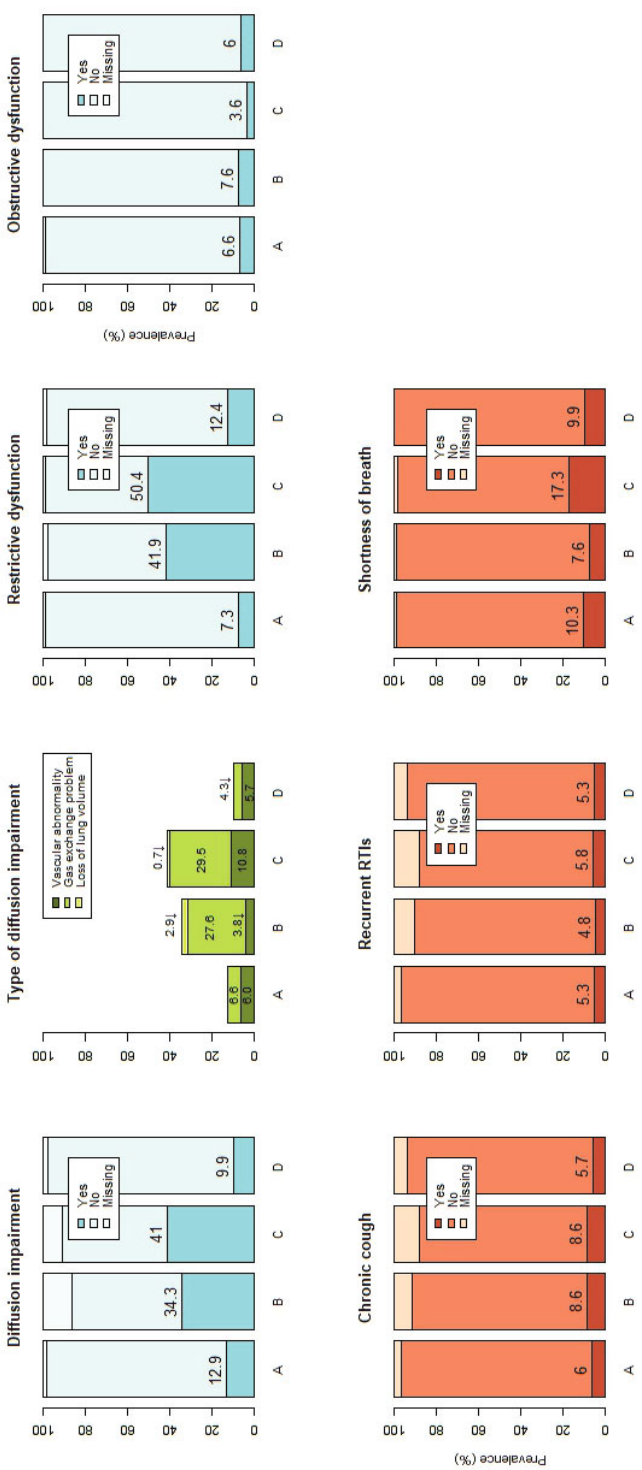

Figure 2. Prevalence of primary and secondary outcomes in the DCCSS-LATER 2 PULM sub-study
The bars represent exposure group A (cyclophosphamide but no pulmonary toxic treatment), group B (pulmonary toxic treatment but no cyclophosphamide), group C (cyclophosphamide and pulmonary toxic treatment) and group D (neither cyclophosphamide nor pulmonary toxic treatment). The first row contains the primary outcomes measured by a pulmonary function test (in blue) and a specification of the types of diffusion impairment (in green). The second row contains the secondary outcomes. The numbers within the bars describe the percentage of survivors with the outcome within each exposure group.

Table 2. Multivariable logistic and linear regression models for the association between cyclophosphamide and the primary outcomes

	Restrictive dysfunction	Diffusion impairment	Obstructive dysfunction
Model 1: multivariable **logistic** model adjusted for **any** established pulmonary toxic treatment (and other confounders)			
Cumulative cyclophosphamide dose	OR 0.79 (0.49 to 1.27)	OR 1.21 (0.77 to 1.92)	OR 0.73 (0.36 to 1.48)
>0-5 g/m^2	OR 1.04 (0.58 to 1.86)	OR 1.69 (0.98 to 2.94)	OR 1.23 (0.51 to 2.94)
5-10 g/m^2	OR 0.91 (0.45 to 1.85)	OR 1.21 (0.61 to 2.37)	OR 0.51 (0.14 to 1.96)
≥10 g/m^2			
Model 2: multivariable **logistic** model adjusted for **type** of established pulmonary toxic treatment (and other confounders)			
Cumulative cyclophosphamide dose	OR 0.79 (0.48 to 1.30)	OR 1.25 (0.78 to 2.00)	OR 0.68 (0.33 to 1.38)
>0-5 g/m^2	OR 1.43 (0.79 to 2.58)	**OR 2.17 (1.23 to 3.82)**	OR 1.21 (0.50 to 2.90)
5-10 g/m^2	OR 0.99 (0.47 to 2.06)	OR 1.29 (0.64 to 2.59)	OR 0.48 (0.12 to 1.83)
≥10 g/m^2			
Model 3: multivariable **linear** model adjusted for **any** established pulmonary toxic treatment (and other confounders)			
Cumulative cyclophosphamide dose	β 0.00 (-0.17 to 0.17)	β 0.01 (-0.19 to 0.20)	β -0.07 (-0.22 to 0.09)
>0-5 g/m^2	β -0.10 (-0.33 to 0.13)	β -0.15 (-0.42 to 0.11)	β 0.10 (-0.11 to 0.32)
5-10 g/m^2	β -0.25 (-0.53 to 0.04)	β -0.18 (-0.51 to 0.16)	β 0.22 (-0.05 to 0.49)
≥10 g/m^2			
Model 4: multivariable **linear** model adjusted for **type** of established pulmonary toxic treatment (and other confounders)			
Cumulative cyclophosphamide dose	β -0.01 (-0.18 to 0.15)	β 0.00 (-0.19 to 0.19)	β -0.05 (-0.21 to 0.11)
>0-5 g/m^2	β -0.21 (-0.44 to 0.02)	β -0.26 (-0.52 to 0.01)	β 0.11 (-0.11 to 0.33)
5-10 g/m^2	**β -0.29 (-0.57 to 0.00)**	β -0.21 (-0.54 to 0.12)	β 0.24 (-0.03 to 0.51)
≥10 g/m^2			

The estimates represent the odds ratio (logistic models 1 and 2) or beta coefficient (linear models 3 and 4) with 95% confidence interval between brackets. The reference category is no cyclophosphamide exposure. Values in bold represent statistical significance. All models were adjusted for pulmonary toxic treatment, age at diagnosis, attained age, clinically relevant cardiac dysfunction, and pack years smoked. All analyses were performed on the multiply imputed dataset. g, gram; m, meter; OR, odds ratio.

Association of cyclophosphamide dose with respiratory symptoms

Cyclophosphamide was not significantly associated with any of the respiratory symptoms (Table 3, Appendix E).

Diffusion impairment and restrictive dysfunction were significantly associated with shortness of breath (p-values <0.01 and 0.03, respectively), although more than 80% of survivors with these types of pulmonary dysfunction reported no dyspnea (Appendix F).

Multiple imputation

In total, 194 out of 828 records (23.4%) were incomplete, mainly because diffusion measurement was not always performed during guideline-based surveillance (groups B and C), or because questions on smoking habits and respiratory symptoms remained unanswered. When the analysis was restricted to complete cases only, the coefficients were similar, but the findings regarding cyclophosphamide were not statistically significant (data not shown).

DISCUSSION

We studied the effect of cyclophosphamide on long-term pulmonary dysfunction in Dutch childhood cancer survivors with a median follow-up of more than 25 years. Our study indicates that, after adjustment for pulmonary toxic treatment and other relevant confounders, cyclophosphamide does not seem to be associated with clinically relevant long-term lung damage.

Our main findings include a 0.3-point reduction of TLC z-score after a high cumulative dose of cyclophosphamide. Although dosages of ≥10 g/m^2 still occur in contemporary treatment protocols, the effect on TLC is modest relative to the lower limit of normal for restrictive dysfunction at a z-score of -1.65. A cumulative cyclophosphamide dose of 5-10 g/m^2 doubled the odds of diffusion impairment, but without evidence for a dose-response relationship. Consistent with previous studies, we found that the prevalence of pulmonary function test abnormalities is high among those exposed to pulmonary toxic treatment (10, 12, 29). Pulmonary toxic radiotherapy and surgery had a stronger effect on pulmonary dysfunction than pulmonary toxic chemotherapy. In addition, other variables including age at diagnosis, attained age, clinically relevant cardiac dysfunction, and smoking were also significantly associated to several of the outcomes. Heart failure, a well-recognized late effect, was for example influential in restrictive dysfunction, diffusion impairment, and shortness of breath. As these factors were previously not consistently included, our results encourage future researchers to consider causality relations during the design of their study and to carefully adjust for potential confounders.

A potential long-term adverse effect of cyclophosphamide on pulmonary health was first mentioned in the 1970s (18), but clinical suspicion remained low. Our study was designed specifically to address this knowledge gap, implementing a robust methodology and high quality standards in the conduct and evaluation of pulmonary function tests. Its strengths include sampling from a long-term and near-complete population-based cohort of childhood cancer survivors (25), recruitment of a sufficiently large number to distinguish between consequences arising from cyclophosphamide versus those of known pulmonary toxic treatment, and including a control group with no established pulmonary toxic treatment nor cyclophosphamide. Furthermore, we performed clinical evaluation of

Table 3. Multivariable logistic regression models for the association between cyclophosphamide and the secondary outcomes

	Chronic cough	Recurrent RTIs	Shortness of breath
Model 5: multivariable **logistic** model adjusted for **any** established pulmonary toxic treatment (and other confounders)			
Cumulative cyclophosphamide dose	OR 0.96 (0.60 to 1.85)	OR 1.04 (0.51 to 2.10)	OR 1.18 (0.68 to 2.02)
>0-5 g/m^2	OR 1.16 (0.52 to 2.62)	OR 0.71 (0.23 to 2.14)	OR 1.22 (0.57 to 2.59)
5-10 g/m^2	OR 0.73 (0.23 to 2.30)	OR 1.43 (0.50 to 4.10)	OR 2.05 (0.94 to 4.46)
≥10 g/m^2			
Model 6: multivariable **logistic** model adjusted for **type** of established pulmonary toxic treatment (and other confounders)			
Cumulative cyclophosphamide dose	OR 0.97 (0.50 to 1.88)	OR 1.00 (0.49 to 2.03)	OR 1.22 (0.70 to 2.12)
>0-5 g/m^2	OR 1.26 (0.55 to 2.88)	OR 0.62 (0.20 to 1.90)	OR 1.42 (0.66 to 3.04)
5-10 g/m^2	OR 0.76 (0.24 to 2.41)	OR 1.30 (0.44 to 3.80)	OR 2.18 (0.99 to 4.82)
≥10 g/m^2			

The estimates represent the odds ratio with 95% confidence interval between brackets. The reference category is no cyclophosphamide exposure. Values in bold represent statistical significance. All models were adjusted for pulmonary toxic treatment, age at diagnosis, attained age, clinically relevant cardiac dysfunction and pack years smoked. All analyses were performed on the multiply imputed dataset. g, gram; m. meter; OR, odds ratio; RTIs, respiratory tract infections.

the outcomes, and adjusted for relevant confounders including age at diagnosis, attained age, comorbidities and lifestyle (30, 31). Increased detail on radiotherapy fields allowed to accurately classify lung exposure, also for the neck and abdominally irradiated patients.

Nevertheless, long-term pulmonary health is not only affected by cancer treatment, but also by early pulmonary complications during treatment (32-34). Unfortunately, such information or baseline pulmonary function tests were unavailable for our analysis. Also, there is a risk of selection bias among those exposed to known pulmonary toxic treatment, because for this group we included only eligible survivors with a pulmonary function test in their medical record. Lastly, due to our cross-sectional design, we could not capture longitudinal changes in pulmonary function (13, 14, 35).

Following clinical practice and ERS/ATS endorsement, we defined our three main pulmonary outcomes using the updated Global Lung Function Initiative reference equations using z-scores instead of percentage of predicted (36). Important improvements include coverage of all ages, a more representative reference population, and correction for lung maturation (28). As the introduction of the GLI criteria primarily affects conclusions regarding obstruction (37, 38), we expect a lesser impact on the data related to restriction and diffusion, which are most common among childhood cancer survivors (12).

Clinically, our findings imply that there is no need for pulmonary surveillance among those treated with cyclophosphamide, but without other established pulmonary toxic treatment. As cyclophosphamide is included in numerous pediatric oncology treatment protocols, this is a relevant finding. Future research should concentrate on a better understanding of the impact of the distinct pulmonary toxic therapies, elucidating their underlying pathophysiology, and refining the timing and methods of surveillance. Cohorts with longitudinal assessment of pulmonary outcomes, including prospective follow-up of newly diagnosed children, will be highly informative in this regard (39). Another focus should be the significance of identifying diffusion and restriction abnormalities in at-risk groups. It is crucial to differentiate between patients with (subclinical) confirmed interstitial lung disease and asymptomatic individuals who only exhibit microscopic damage to the lung tissue.

In conclusion, our study shows that cyclophosphamide is not associated with clinically relevant long-term pulmonary dysfunction or respiratory symptoms. This knowledge strengthens surveillance recommendations not to perform pulmonary function tests in childhood cancer survivors treated with cyclophosphamide without other established pulmonary toxic treatment.

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APPENDIX A. DETAILED METHODOLOGY OF RADIOTHERAPY CLASSIFICATION

Classification of pulmonary toxic exposure to radiotherapy was performed in more detail for the DCCSS-LATER 2 PULM sub-study compared to the overall DCCSS-LATER 2 study. Radiotherapy records and simulation images were reviewed for all LATER 2 PULM participants that had received radiotherapy to the neck, chest and/or abdominal area, or had received total body irradiation. The thorax was divided into eight segments (see Figure A.1). For each participant, we collected information on the radiation field, type of beam, radiation technique, cranial and caudal y-value of the radiation field, left and right x-value of the radiation field, prescribed dose in Gy, boost with location and dose in Gy, and total body irradiation with dose in Gy. We included radiotherapy of the primary childhood cancer and all recurrences, but not of subsequent malignant neoplasms. This information was then translated to the eight segment classification, resulting in the coding of each of the eight segments as either exposed or non-exposed, with a cumulative prescribed dose if applicable. Because radiation fields are variable and do not match exactly with the eight thorax segments, we coded a thorax segment as exposed if ≥50% of the segment was included in the field. For the current study, we defined pulmonary toxic radiation exposure as ≥1 of the eight thorax segments exposed to any dose of radiotherapy.

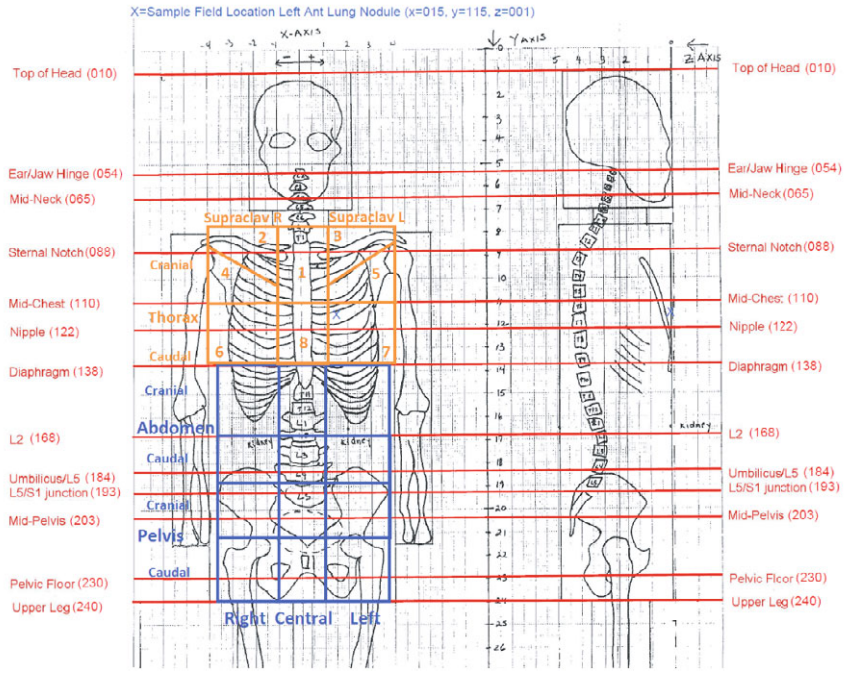


Figure A.1 Thorax classification into eight segments (orange lining) with corresponding x- and y-values

APPENDIX B

Table B.1 Self-reported cardiovascular medication used to define clinically relevant cardiac dysfunction

Category	ATC code (category name)
Cardiovascular medication	C01 (cardiac therapy) C02 (antihypertensives) C03 (diuretics) C04 (peripheral vasodilators) C05 (vasoprotectives) C07 (beta blocking agents) C08 (calcium channel blockers) C09 (agents acting on the renin-angiotensin system)

ATC, Anatomical Therapeutical Chemical.

APPENDIX C

Table C.1 Variables included in the multiple imputation process

Variable	Type of variable	Role	Missing in original data (n, %)
Primary outcomes			
FEV1/FVC z-score	Continuous	Dependent variable	2 (0.2%)
FEV1/FVC < LLN	Binary	Dependent variable	2 (0.2%)
TLC z-score	Continuous	Dependent variable	10 (1.2%)
TLC < LLN	Binary	Dependent variable	10 (1.2%)
DLCO z-score	Continuous	Dependent variable	35 (4.2%)
DLCO < LLN	Binary	Dependent variable	35 (4.2%)
Pulmonary vascular abnormality	Binary	Dependent variable	36 (4.3%)
Gas exchange problem	Binary	Dependent variable	36 (4.3%)
Volume problem	Binary	Dependent variable	36 (4.3%)
RV/TLC z-score	Continuous	Dependent variable	10 (1.2%)
RV/TLC > ULN	Binary	Dependent variable	10 (1.2%)
Secondary outcomes			
Chronic cough	Binary	Dependent variable	52 (6.3%)
Recurrent respiratory tract infections	Binary	Dependent variable	52 (6.3%)
Shortness of breath	Binary	Dependent variable	6 (0.7%)
Independent variables (of interest)			

Table C.1 Variables included in the multiple imputation process (continued)

Variable	Type of variable	Role	Missing in original data (n, %)
Cyclophosphamide cumulative dose	Continuous	Independent variable (of interest)	35 (4.2%)
Any cyclophosphamide	Binary	Independent variable (of interest)	0 (0.0%)
Cyclophosphamide cumulative dose categories	Categorical	Independent variable (of interest)	35 (4.2%)
High cumulative dose cyclophosphamide	Binary	Independent variable (of interest)	35 (4.2%)
Exposure group (A-D)	Categorical	Independent variable (of interest)	0 (0.0%)
Independent variables (for adjustment)			
Age at diagnosis	Continuous	Independent variable (adjustment)	0 (0.0%)
Attained age	Continuous	Independent variable (adjustment)	0 (0.0%)
Any pulmonary toxic treatment	Binary	Independent variable (adjustment)	0 (0.0%)
Pulmonary toxic radiotherapy	Binary	Independent variable (adjustment)	0 (0.0%)
Pulmonary toxic chemotherapy	Binary	Independent variable (adjustment)	0 (0.0%)
Pulmonary toxic surgery	Binary	Independent variable (adjustment)	0 (0.0%)
Clinically relevant heart failure	Binary	Independent variable (adjustment)	52 (6.3%)
Smoking (ever or never)	Binary	Independent variable (adjustment)	50 (6.0%)
Smoking (pack years)	Continuous	Independent variable (adjustment)	81 (9.8%)
Auxiliary variables (to further inform the multiple imputation)			
Main diagnosis group	Categorical	Auxiliary variable	0 (0.0%)

Table C.1 Variables included in the multiple imputation process (continued)

Variable	Type of variable	Role	Missing in original data (n, %)
Allogeneic stem cell transplantation	Binary	Auxiliary variable	37 (4.5%)
Sex	Binary	Auxiliary variable	0 (0.0%)
Body mass index	Continuous	Auxiliary variable	5 (0.6%)
Clinically relevant fatigue	Binary	Auxiliary variable	7 (0.8%)

Using the mice package version 3.16.0 in R, we created and analyzed 24 multiply imputed datasets (determined by percentage of cases with at least one missing variable). We assumed missingness at random after consideration of different reasons for missingness, and imputed both dependent and independent variables. Continuous variables were imputed using predictive mean matching, binary variables using logistic regression, and categorical variables using polytomous logistic regression, which are considered the most robust methods for these types of variables. Predictor matrix relations between associated variables (e.g., FEV1/FVC z-score and FEV1/FVC < LLN) were removed to avoid linear dependencies. Model diagnostics were performed to evaluate the convergence of the model and plausibility of the imputed data. Final models were constructed by performing the model in each of the imputed datasets and then pooling the results. RV/TLC z-score and RV/TLC > ULN were included in the multiple imputation as they were considered potentially relevant for further exploration, but were not included in the manuscript. Auxiliary variables are variables that are considered important to inform the multiple imputation, but will not be used in the final models. DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; LLN, lower limit of normal; *n*, number; RV, residual volume; TLC, total lung capacity; ULN, upper limit of normal.

APPENDIX D

Table D.1 Baseline characteristics of the DCCSS-LATER 2 PULM sub-study cohort (*n* = 828) and the underlying DCCSS-LATER cohort (1963-2001)

	DCCSS-LATER 2 PULM sub-study participants (*n* = 828)	**Underlying DCCSS-LATER cohort (1963-2001)** (*n* = 6,165)
Patient characteristics		
Sex		
Female, n (%)	418 (50.5)	2,731 (44.3)
Male, n (%)	410 (49.5)	3,433 (55.7)
Transgender, n (%)	0 (0.0)	1 (0.02)
Cancer characteristics		
Primary childhood cancer (ICCC)		
Leukemia/lymphoma, n (%)	498 (60.1)	3,165 (51.2)
CNS tumor, n (%)	69 (8.3)	844 (13.7)
Other solid tumor, n (%)	261 (31.5)	2,165 (35.1)
Age at diagnosis (y), median (range)	5.8 (0.0-17.9)	5.6 (0.0-17.9)
0 to 4.99, n (%)	367 (44.3)	2,727 (44.2)
5 to 9.99, n (%)	230 (27.8)	1,628 (26.4)
10 to 14.99, n (%)	175 (21.1)	1,285 (20.8)
15 to 17.99, n (%)	56 (6.8)	376 (6.1)

Table D.1 Baseline characteristics of the DCCSS-LATER 2 PULM sub-study cohort (*n* = 828) and the underlying DCCSS-LATER cohort (1963-2001) (continued)

	DCCSS-LATER 2 PULM sub-study participants (*n* = 828)	**Underlying DCCSS-LATER cohort (1963-2001)** (*n* = 6,165)
Treatment characteristics		
Treatment period		
1963 to 1979, n (%)	123 (14.9)	1,097 (17.8)
1980 to 1989, n (%)	232 (28.0)	1,931 (31.3)
1990 to 2001, n (%)	473 (57.1)	3,137 (50.9)
Overall treatment modality		
No therapy, n (%)	7 (0.8)	61 (1.0)
Surgery only, n (%)	34 (4.1)	575 (9.3)
Chemotherapy only (± surgery), n (%)	443 (53.5)	2,967 (48.1)
Radiotherapy only (± surgery), n (%)	44 (5.3)	484 (7.9)
Chemotherapy and radiotherapy (± surgery), n (%)	300 (36.2)	2,030 (32.9)
Missing, n (%)	0 (0.0)	48 (0.8)
Follow-up		
Age at invitation[a] (y), median (range)	33.8 (15.5-67.7)	34.0 (16.0-71.0)
<18, n (%)	26 (3.1)	49 (0.8)
18-30, n (%)	271 (32.7)	1,313 (21.3)
30-40, n (%)	299 (36.1)	1,511 (24.5)

Table D.1 Baseline characteristics of the DCCSS-LATER 2 PULM sub-study cohort (*n* = 828) and the underlying DCCSS-LATER cohort (1963-2001) (continued)

	DCCSS-LATER 2 PULM sub-study participants (*n* = 828)	**Underlying DCCSS-LATER cohort (1963-2001)** (*n* = 6,165)
Follow-up		
≥40, n (%)	232 (28.0)	1,118 (18.1)
Follow-up after primary cancer diagnosis (y)[b,c], median (range)	26.6 (14.9-54.9)	27.0 (15.0-56.0)
10 to 19.99, n (%)	178 (21.5)	981 (15.9)
20 to 29.99, n (%)	342 (41.3)	1,931 (31.3)
30 to 39.99, n (%)	217 (26.2)	1,393 (22.6)
≥40, n (%)	91 (11.0)	506 (8.2)

[a] Missing for survivors refusing participation.

[b] Defined as time until pulmonary function test for LATER 2 PULM participants and time until invitation for overall cohort.

[c] Missing for survivors refusing registration. CNS, central nervous system; DCCSS, Dutch Childhood Cancer Survivor Study; ICCC, International Classification of Childhood Cancer; IQR, interquartile range; *n*, number; y, years.

APPENDIX E

Table E.1 Full models of the logistic regression analysis for pulmonary dysfunction in the DCCSS-LATER 2 PULM sub-study (*n* = 828)

Exposure	Restrictive dysfunction TLC z-score < LLN		Diffusion impairment DLCO z-score < LLN		Obstructive dysfunction FEV1/FVC z-score < LLN	
	OR	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
Model 1: pulmonary toxic treatment (yes/no)						
Cyclophosphamide cumulative dose						
0 g/m^2	1.0 (ref)		1.0 (ref)		1.0 (ref)	
≥0-5 g/m^2	0.79	0.49 to 1.27	1.21	0.77 to 1.92	0.73	0.36 to 1.48
5-10 g/m^2	1.04	0.58 to 1.86	1.69	0.98 to 2.94	1.23	0.51 to 2.94
≥10 g/m^2	0.91	0.45 to 1.85	1.21	0.61 to 2.37	0.51	0.14 to 1.96
Any pulmonary toxic treatment (ref: no)	**8.19**	5.49 to 12.23	**5.33**	3.58 to 7.92	0.72	0.35 to 1.45
Age at diagnosis (per year increase)	**0.93**	0.89 to 0.97	0.96	0.92 to 1.00	**1.10**	1.03 to 1.18
Attained age (per year increase)	**1.04**	1.01 to 1.06	1.02	1.00 to 1.04	0.98	0.94 to 1.01
Clinically relevant cardiac dysfunction (ref: no)	2.54	0.93 to 6.98	**2.85**	1.19 to 6.82	2.17	0.58 to 8.04
Pack years smoked (per pack year increase)	0.96	0.92 to 1.02	**1.06**	1.06 to 1.09	**1.07**	1.03 to 1.12
Model 2: specific pulmonary toxic exposures						
Cyclophosphamide cumulative dose						
0 g/m^2	1.0 (ref)		1.0 (ref)		1.0 (ref)	
≥0-5 g/m^2	0.79	0.48 to 1.30	1.25	0.78 to 2.00	0.68	0.33 to 1.38
5-10 g/m^2	1.43	0.79 to 2.58	**2.17**	1.23 to 3.82	1.21	0.50 to 2.90

Table E.1 Full models of the logistic regression analysis for pulmonary dysfunction in the DCCSS-LATER 2 PULM sub-study (*n* = 828) (continued)

Exposure	Restrictive dysfunction TLC z-score < LLN		Diffusion impairment DLCO z-score < LLN		Obstructive dysfunction FEV1/FVC z-score < LLN	
	OR	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
Model 2: specific pulmonary toxic exposures						
Cyclophosphamide cumulative dose						
≥10 g/m^2	0.99	0.47 to 2.06	1.29	0.64 to 2.59	0.48	0.12 to 1.83
Any pulmonary toxic chemotherapy (ref: no)	**2.05**	1.21 to 3.47	**1.82**	1.08 to 3.07	0.51	0.18 to 1.40
Any pulmonary toxic radiotherapy (ref: no)	**10.36**	6.62 to 16.22	**6.25**	4.03 to 9.69	1.11	0.51 to 2.42
Any pulmonary toxic surgery (ref: no)	**10.13**	3.42 to 30.07	**5.61**	1.90 to 16.52	0.00	0 to infinity
Age at diagnosis (per year increase)	**0.94**	0.89 to 0.98	0.96	0.92 to 1.01	**1.10**	1.03 to 1.18
Attained age (per year increase)	**1.03**	1.00 to 1.05	1.02	0.99 to 1.04	0.98	0.94 to 1.01
Clinically relevant cardiac dysfunction (ref: no)	**3.71**	1.32 to 10.49	**3.74**	1.52 to 9.18	2.50	0.67 to 9.23
Pack years smoked (per pack year increase)	0.96	0.91 to 1.01	**1.06**	1.02 to 1.09	**1.07**	1.03 to 1.12

The analyses were performed on the multiply imputed dataset. All models describe the effect of cyclophosphamide on pulmonary dysfunction, adjusted for age at diagnosis, attained age, clinically relevant cardiac dysfunction and pack years smoked. Values in bold represent statistical significance. CI, confidence interval; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; g, gram; m, meter; OR, odds ratio; ref, reference category; TLC, total lung capacity.

Table E.2 Full models of the linear regression analysis for pulmonary dysfunction in the DCCSS-LATER 2 PULM sub-study (*n* = 828)

Exposure	Restrictive dysfunction TLC z-score		Diffusion impairment DLCO z-score		Obstructive dysfunction FEV1/FVC z-score	
	β	*95% CI*	β	*95% CI*	β	*95% CI*
Model 3: pulmonary toxic treatment (yes/no)						
Cyclophosphamide cumulative dose						
0 g/m^2	0.0 (ref)		0.0 (ref)		0.0 (ref)	
≥0-5 g/m^2	0.00	-0.17 to 0.17	0.01	-0.19 to 0.20	-0.07	-0.22 to 0.09
5-10 g/m^2	-0.10	-0.33 to 0.13	-0.15	-0.42 to 0.11	0.10	-0.11 to 0.32
≥10 g/m^2	-0.25	-0.53 to 0.04	-0.18	-0.51 to 0.16	0.22	-0.05 to 0.49
Any pulmonary toxic treatment (ref: no)	**-1.17**	-1.34 to -1.00	**-1.02**	-1.22 to -0.83	0.08	-0.08 to 0.24
Age at diagnosis (per year increase)	**0.04**	0.02 to 0.06	0.02	-0.00 to 0.04	**-0.02**	-0.04 to -0.01
Attained age (per year increase)	**-0.02**	-0.03 to -0.01	-0.01	-0.02 to 0.00	0.01	-0.00 to 0.02
Clinically relevant cardiac dysfunction (ref: no)	-0.23	-0.65 to 0.19	**-0.77**	-1.25 to -0.29	-0.30	-0.68 to 0.08
Pack years smoked (per pack year increase)	0.00	-0.01 to 0.02	**-0.02**	-0.04 to -0.00	**-0.03**	-0.04 to -0.01
Model 4: specific pulmonary toxic exposures						
Cyclophosphamide cumulative dose						
0 g/m^2	0.0 (ref)		0.0 (ref)		0.0 (ref)	
≥0-5 g/m^2	-0.01	-0.18 to 0.15	0.00	-0.19 to 0.19	-0.05	-0.21 to 0.11
5-10 g/m^2	-0.21	-0.44 to 0.02	-0.26	-0.52 to 0.01	0.11	-0.11 to 0.33
≥10 g/m^2	**-0.29**	-0.57 to 0.00	-0.21	-0.54 to 0.12	0.24	-0.03 to 0.51

Table E.2 Full models of the linear regression analysis for pulmonary dysfunction in the DCCSS-LATER 2 PULM sub-study (*n* = 828) (continued)

Exposure	Restrictive dysfunction TLC z-score		Diffusion impairment DLCO z-score		Obstructive dysfunction FEV1/FVC z-score	
	β	*95% CI*	β	*95% CI*	β	*95% CI*
Model 4: specific pulmonary toxic exposures						
Cyclophosphamide cumulative dose						
Any pulmonary toxic chemotherapy (ref: none)	**-0.51**	-0.72 to -0.29	**-0.38**	-0.63 to -0.13	0.11	-0.10 to 0.31
Any pulmonary toxic radiotherapy (ref: none)	**-1.25**	-1.45 to -1.06	**-1.16**	-1.38 to -0.93	-0.03	-0.21 to 0.15
Any pulmonary toxic surgery (ref: none)	**-1.37**	-1.83 to -0.92	**-1.17**	-1.71 to -0.62	0.27	-0.17 to 0.70
Age at diagnosis (per year increase)	**0.04**	0.02 to 0.05	0.01	-0.01 to 0.03	**-0.02**	-0.04 to -0.01
Attained age (per year increase)	**-0.02**	-0.03 to -0.01	0.01	-0.02 to 0.00	**0.01**	0.00 to 0.02
Clinically relevant cardiac dysfunction (ref: no)	-0.36	-0.78 to 0.06	**-0.89**	-1.39 to -0.40	-0.31	-0.69 to 0.07
Pack years smoked (per pack year increase)	0.00	-0.01 to 0.02	**-0.02**	-0.04 to -0.00	**-0.03**	-0.04 to -0.01

The analyses were performed on the multiply imputed dataset. All models describe the effect of cyclophosphamide on pulmonary dysfunction, adjusted for age at diagnosis, attained age, clinically relevant cardiac dysfunction and pack years smoked. Values in bold represent statistical significance. CI, confidence interval; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; g, gram; m, meter; ref, reference category; TLC, total lung capacity.

Table E.3 Full models of the logistic regression analysis for respiratory symptoms in the DCCSS-LATER PULM 2 sub-study (*n* = 828)

Exposure	Chronic cough		Recurrent RTIs		Shortness of breath	
	OR	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
Model 5: pulmonary toxic treatment (yes/no)						
Cyclophosphamide cumulative dose						
0 g/m^2	1.0 (ref)		1.0 (ref)		1.0 (ref)	
≥0-5 g/m^2	0.96	0.50 to 1.85	1.04	0.51 to 2.10	1.18	0.68 to 2.02
5-10 g/m^2	1.16	0.52 to 2.62	0.71	0.23 to 2.14	1.22	0.57 to 2.59
≥10 g/m^2	0.73	0.23 to 2.30	1.43	0.50 to 4.10	2.05	0.94 to 4.46
Any pulmonary toxic treatment (ref: no)	1.40	0.77 to 2.56	1.19	0.59 to 2.43	0.99	0.60 to 1.66
Age at diagnosis (per year increase)	1.06	0.99 to 1.13	0.95	0.88 to 1.03	1.04	0.99 to 1.10
Attained age (per year increase)	1.00	0.96 to 1.03	1.00	0.96 to 1.03	1.00	0.97 to 1.02
Clinically relevant cardiac dysfunction (ref: no)	1.38	0.36 to 5.32	2.03	0.54 to 7.59	**6.09**	2.67 to 13.90
Pack years smoked (per pack year increase)	1.03	0.98 to 1.08	0.99	0.92 to 1.07	1.00	0.95 to 1.05
Model 6: specific pulmonary toxic exposures						
Cyclophosphamide cumulative dose						
0 g/m^2	1.0 (ref)		1.0 (ref)		1.0 (ref)	
≥0-5 g/m^2	0.97	0.50 to 1.88	1.00	0.49 to 2.03	1.22	0.70 to 2.12
5-10 g/m^2	1.26	0.55 to 2.88	0.62	0.20 to 1.90	1.42	0.66 to 3.04
≥10 g/m^2	0.76	0.24 to 2.41	1.30	0.44 to 3.80	2.18	0.99 to 4.82
Any pulmonary toxic chemotherapy (ref: no)	0.97	0.44 to 2.15	1.74	0.73 to 4.15	0.56	0.27 to 1.18

Table E.3 Full models of the logistic regression analysis for respiratory symptoms in the DCCSS-LATER PULM 2 sub-study (*n* = 828) (continued)

Exposure	Chronic cough		Recurrent RTIs		Shortness of breath	
	OR	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
Model 6: specific pulmonary toxic exposures						
Cyclophosphamide cumulative dose						
Any pulmonary toxic radiotherapy (ref: no)	1.10	0.55 to 2.20	1.03	0.45 to 2.40	1.22	0.69 to 2.17
Any pulmonary toxic surgery (ref: no)	1.60	0.32 to 7.92	0.00	0.00 to inf	2.44	0.78 to 7.59
Age at diagnosis (per year increase)	1.06	1.00 to 1.14	0.95	0.87 to 1.03	1.05	0.99 to 1.11
Attained age (per year increase)	1.00	0.96 to 1.03	1.00	0.96 to 1.04	0.99	0.96 to 1.02
Clinically relevant cardiac dysfunction (ref: no)	1.49	0.39 to 5.75	2.06	0.55 to 7.67	**6.51**	2.83 to 14.98
Pack years smoked (per pack year increase)	1.02	0.97 to 1.07	0.99	0.92 to 1.07	1.00	0.95 to 1.05

The analyses were performed on the multiply imputed dataset. All models describe the effect of cyclophosphamide on pulmonary dysfunction, adjusted for age at diagnosis, attained age, clinically relevant cardiac dysfunction and pack years smoked. Values in bold represent statistical significance. CI, confidence interval; g, gram; inf, infinity; m, meter; OR, odds ratio; ref, reference category; RTI, respiratory tract infection.

APPENDIX F

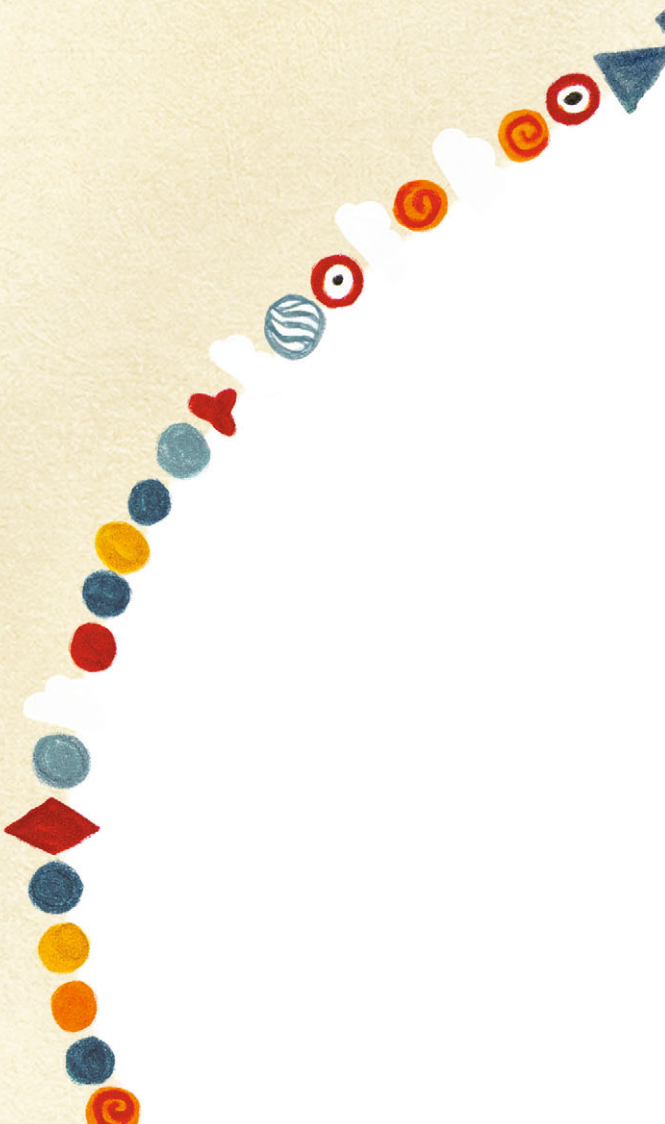
Table F.1 Relation between pulmonary function test abnormalities and respiratory symptoms

		Obstruction		**Restriction**		**Diffusion**	
	n total	*n (%)*	*p-value*	*n (%)*	*p-value*	*n (%)*	*p-value*
Recurrent RTIs	44	3 (6.0)	1.000	8 (4.7)	1.000	7 (4.4)	1.000
Chronic cough	55	4 (8.0)	1.000	14 (8.2)	0.644	14 (8.8)	0.572
Shortness of breath	91	9 (18.0)	0.543	28 (16.4)	**0.033**	30 (18.8)	**0.003**

Shown are the number with each symptom (n total), and the number and percentage of those with late pulmonary dysfunction experiencing the respiratory symptom (n, %). P-values for the association between each symptom and pulmonary function test abnormality were calculated using a Fisher's exact test on the multiply imputed data with Bonferroni correction for multiple testing. Values in bold represent statistical significance. ***n***, number; RTIs, respiratory tract infections.

Part 2

Evaluating the quality of care for childhood cancer patients and survivors



8

The critical role of clinical practice guidelines and indicators in high-quality survivorship after childhood cancer

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ABSTRACT

Childhood cancer survivors are at significant risk for late cancer treatment-related morbidity and mortality. Physicians involved in the care of childhood cancer survivors should be aware of these specific health problems and provide high-quality, long-term follow-up care to preserve and improve survivors' health. The steps required to achieve high-quality care include synthesizing evidence (systematic reviews are helpful tools in this regard), developing clinical policy from evidence into evidence-based clinical practice guidelines, disseminating and implementing clinical practice guidelines, and evaluating their impact on quality of care and survivor health outcomes with quality indicators. This article describes these cornerstones of evidence-based medicine.

INTRODUCTION

Continuing advances in the treatment of childhood cancer during the last 50 years have contributed to greatly increased survival rates (1, 2). However, improvement in prognosis has been accompanied by the occurrence of late, treatment-related complications (3, 4). Consequently, the number of childhood cancer survivors at high risk for premature morbidity and mortality is growing. Late adverse effects of cancer treatment contribute to an increased incidence of chronic diseases in adult survivors of childhood cancer and may ultimately reduce life expectancy (5).

Long-term follow-up care is important to facilitate early detection of late effects and timely initiation of interventions to preserve and improve health. Childhood cancer survivors and healthcare providers need guidance to increase awareness and proactive surveillance of cancer-related and treatment-related health risks to initiate timely intervention. Moreover, those caring for childhood cancer survivors need resources to address the emerging needs of their patients at risk for therapy-related late complications.

To provide high-quality care for childhood cancer survivors and optimize their quality of life and life expectancy, clinicians must stay informed about this field and its developments, including data generated by a rapidly expanding area of research. Keeping up, however, is challenging since the number of survivorship studies has increased substantially in recent decades, and quadrupled since 1996 (6). These data underscore the need for more reliable and relevant information to translate this information into evidence-based clinical practice guidelines (CPGs). The steps required to achieve this include synthesizing evidence into evidence summaries and systematic reviews, developing clinical policy from evidence into evidence-based CPGs, disseminating and implementing CPGs, and evaluating their impact on quality of care and survivor health outcomes. These elements form the cornerstones of evidence-based medicine, as shown in the quality of care cycle (Figure 1).

EVIDENCE-BASED MEDICINE

The term “evidence-based medicine” (EBM) was introduced by the EBM Working Group in 1992. They defined EBM as “the process of integrating clinical expertise with the best research evidence to make high-quality decisions about the care of individual patients” (7). A clinical decision based on the EBM principles combines high-quality clinical research with clinical expertise, patient values (such as preferences and expectations), and social considerations (such as cost) (8, 9). The introduction of EBM has informed clinical decision-making in healthcare by clarifying the quality of the evidence available and knowledge gaps related to specific clinical topics.

Cochrane Collaboration

In 1993 the Cochrane Collaboration was founded in response to the introduction of EBM. The mission of the Cochrane Collaboration is to improve the availability of the best evidence in healthcare by facilitating the preparation and maintenance of systematic reviews. Cochrane systematic reviews help clinicians evaluate all of the evidence concerning a particular clinical problem using standardized methodology for

searching and appraising the literature and for reporting the results (10). The Cochrane Collaboration, which represents the largest provider of systematic reviews for healthcare, has produced approximately 6,000 systematic reviews available in the Cochrane Library.

Cochrane Childhood Cancer has been registered within the Cochrane Collaboration since 2006 (**www.ccg.cochrane.org**). The aim of Cochrane Childhood Cancer is to perform and sustain systematic reviews about interventions and diagnosis in childhood and young adult patients with cancer and survivors with respect to prevention, treatment, supportive care, psychosocial care, palliative and terminal care, nursing care, and late adverse effects. Systematic reviews form the basis of evidence-based CPGs.

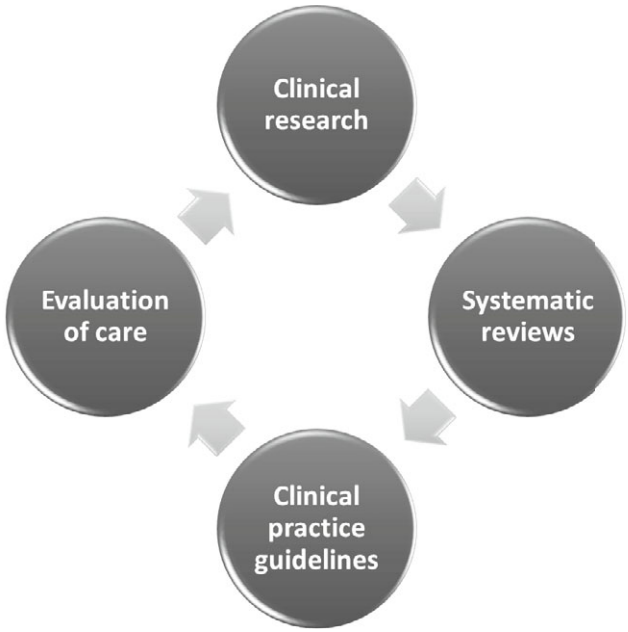

Figure 1. Quality of care cycle

EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES

Translation of evidence into clinical practice is essential to deliver high-quality clinical care. Guidelines can facilitate bridging the gap between research and clinical practice. CPGs are increasingly used to assist both clinical and healthcare policy decision-making (11). As defined by the US Institute of Medicine, CPGs are "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" (12). CPGs help the practitioner provide clinical care based on the best available evidence.

CPGs are seen as powerful tools to improve quality of care. Their main aim is to improve healthcare processes and health outcomes. Guidelines recommending proven

effective interventions and discouraging ineffective ones may reduce morbidity and mortality. In many fields of medicine, care that is consistent with evidence-based recommendations has led to improved patient outcomes and more efficient care delivery (11, 13-18). Guidelines facilitate uniform care, thereby reducing variability in daily healthcare practice. They can also contribute to the reduction of inconsistencies in healthcare decisions between physicians, and promote effective care, communication, and collaboration among healthcare professionals, and among healthcare professionals and patients (11). Finally, CPGs can contribute to reduced healthcare costs by standardizing care, increasing the efficiency of care provision, and reducing unnecessary or inefficient components of healthcare. CPGs can decrease expenses for hospitalization, drug prescriptions, surgery, and other procedures (11).

Before the wider implementation of CPGs, clinical practice was usually guided by nonsystematic observations based on clinical experience. Systematic development of CPGs within a well-defined program started in the late 1970s, with these first efforts featuring consensus-based recommendations. The US National Institutes of Health initiated the development of "consensus statements" by convening consensus conferences (19). During the 1980s, several organizations outside the United States adopted this program to develop their national and regional consensus statements and standards for good medical care. Since the introduction of the principles of EBM introduced in the 1990s, the method of evidence-based guideline development has become the international standard in which the best available evidence, clinical judgment, and patients' perspectives are integrated (12, 14).

CHILDHOOD CANCER SURVIVORSHIP CARE GUIDELINES

Over recent decades several North American and European groups have developed evidence-based CPGs for long-term follow-up of childhood cancer survivors (20-23). The main goal of these CPGs is to facilitate opportunities for early detection and timely intervention to treat or prevent late effects. In addition, these survivorship guidelines highlight surveillance tests that may be unnecessary or inadvisable due to the potential for overdiagnosis, psychological distress, or lack of availability of appropriate interventions (24).

Despite all efforts, the recommendations between existing survivorship guidelines differ, sometimes greatly, in terms of risk groups, surveillance modalities and intervals. This may have resulted from differences in methodologies used for guideline development, and diversity in clinical expertise and cultural variation. To combine international expertise, reduce duplication of work, and further improve survivorship care, a worldwide collaboration was initiated in 2010 to harmonize the existing CPGs for long-term follow-up of survivors of childhood and young adult cancer: the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG; www.ighg.org**)** (25). Its main goal is to establish a common vision and integrated strategy for the surveillance of late effects in childhood and young adult cancer survivors worldwide. The IGHG focuses on harmonizing surveillance of the more highly prevalent persistent and late-onset adverse effects experienced by childhood cancer survivors and provides recommendations regarding which patients need surveillance, what surveillance modalities should be used, when surveillance should be initiated, at what frequency

surveillance should be performed, and what should be done when abnormalities are identified. The IGHG is a multidisciplinary collaboration that includes late effects experts in pediatric and radiation oncology, pediatric and medical subspecialties, primary care, nursing, and patient advocates. In addition, the effort involves individuals with formal training in evidence-based guideline development. The recommendations are developed to permit implementation in a variety of different healthcare and resource settings.

So far, the IGHG has developed guidelines related to surveillance for subsequent breast cancer (26), cardiomyopathy (27), premature ovarian insufficiency (28), male gonadotoxicity (29), subsequent thyroid cancer (30), and ototoxicity (31). In addition, many guidelines are currently under development (Table 1).

Table 1. Overview of clinical practice guidelines of the International Guideline Harmonization Group that are currently available and in progress

Available IGHG guidelines
Breast cancer surveillance (reference 26)
Cardiomyopathy surveillance (reference 27)
Premature ovarian insufficiency surveillance (reference 28)
Male gonadotoxicity surveillance (reference 29)
Thyroid cancer surveillance (reference 30)
Ototoxicity surveillance (reference 31)
IGHG guidelines currently being developed
Obstetric care surveillance
Central nervous system neoplasms surveillance
Coronary artery disease surveillance
Hypothalamic-pituitary dysfunction surveillance
Fatigue surveillance
Mental health surveillance
Psychosocial problems surveillance
Metabolic syndrome surveillance
Pulmonary dysfunction surveillance
Bone toxicity surveillance
Nephrotoxicity surveillance
Thyroid dysfunction surveillance
Neurocognitive problems surveillance
Colorectal cancer surveillance
Hepatic toxicity surveillance

Evidence-based methods IGHG guidelines

The IGHG guidelines are developed following consideration of the available evidence, benefits and harms of the particular surveillance intervention, and knowledge and expertise of healthcare professionals and patients. Guideline development involves three phases: 1) the preparation phase, 2) the development phase, and 3) the finalization phase.

For the preparation phase a guideline panel is convened and the scope of the guideline defined. Diversity is an essential feature of a guideline panel. Its exact composition should be tailored to the guideline topic and reflect the range of stakeholders involved.

The development phase consists of five steps:

1. Evaluation of concordant and discordant guideline areas among recommendations in existing survivorship guidelines.
2. Formulation of clinical questions in the PICO format (participants, interventions, control group, and outcome). The questions should be clear, focused, and closely define the boundaries of the topic. They serve as a starting point for the systematic literature search that aims to identify all the available evidence.
3. Identification of available evidence by systematic literature searches based on predefined inclusion and exclusion criteria.
4. Summarization of the evidence using standardized data extraction forms including the methodological quality of the included evidence. For each clinical question a conclusion of evidence is formulated. The quality of the total body of evidence is graded using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group methodology.
5. Formulation and grading of the recommendations using the GRADE Evidence to Decision (EtD) framework. The EtD framework ensures that all important criteria for making a decision are considered and informs the guideline panel about the relative pros and cons of the interventions or options being considered. This approach makes the decision-making process structured and transparent. The panel discusses the benefits, harms, patient values, and other important factors, and formulates recommendations. Recommendations are classified into three categories: strong recommendation to do (green), moderate recommendation to do (yellow), and recommendation not to do (red).

In the finalization phase the guideline is written, including a specific description of the process and the considerations made in formulating recommendations. The manuscript is sent out for external review by experts in the field and patient advocates, and subsequently published in peer-reviewed journals.

The development of CPGs does not guarantee improvement in the quality of care. The success of a guideline not only depends on the clinical context and rigor of methodology, but also on dissemination and implementation strategies (32).

DISSEMINATION AND IMPLEMENTATION OF CHILDHOOD CANCER SURVIVORSHIP CARE GUIDELINES

Once the IGHG recommendations are developed and published, they are integrated into the existing region/country-specific survivorship guidelines.

Within the United States, the Children's Oncology Group (COG) Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers (COG-LTFU Guidelines) provide risk-based, exposure-related recommendations for screening and management of late effects resulting from therapeutic exposures used during treatment for pediatric malignancies (33). The COG-LTFU Guidelines include 165 sections that detail potential late effects observed following specific chemotherapeutic agents, radiation treatment fields exposing targeted organs and tissues, blood product transfusions, hematopoietic cell transplantation, and surgical procedures. In addition, the COG-LTFU Guidelines offer surveillance recommendations for survivors who are

at excess risk of subsequent neoplasms related to pediatric cancer treatment. They are updated on a five-year cycle by system-based task forces that assess the quality of the evidence emerging in the literature and present recommendations for guideline revisions for approval by a multidisciplinary late effects expert panel. The COG-LTFU Guidelines are disseminated through a website (www.survivorshipguidelines.org) that includes surveillance recommendations, patient educational materials (Health Links), and other resources to facilitate risk-based survivorship care, such as the web-based Passport of Care that provides tailored late effects screening recommendations to individual survivors based on their therapeutic exposures (34). In addition, COG members have disseminated guideline recommendations through local, regional, and national academic and community forums and in numerous scholarly publications. COG investigators are highly committed and engaged in the global harmonization of surveillance recommendations for childhood cancer survivors advocated by the IGHG.

Development and dissemination of long-term follow-up guidelines across Europe has been led by the PanCare society (Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer, www.pancare.eu) (35). Two EU-funded projects have played particularly important roles. PanCareSurFup (PanCare Survivor Follow-Up Studies, **www.pancaresurfup.eu**) contributed strongly to the development of evidence-based surveillance CPGs in the IGHG consortium, and also worked independently to develop evidence-based CPGs for the delivery of LTFU care. A CPG for models of long-term follow-up care has been published, and CPGs for requirements for transition of care from the pediatric to adult healthcare setting and health promotion are under development. The PanCareFollowUp project (www.**pancarefollowup.eu**) is developing consensus-based surveillance guidelines for those late effects topics not addressed by published or imminent IGHG guidelines. Dissemination of the evidence- and consensus-based CPGs has been achieved by presentations at the biannual PanCare meetings, the international PanCareSurFup closing conference (held in Brussels in May 2016), and several European and international late effects and other specialist conferences. The guidelines will also be accessible on the PanCare and PanCareFollowUp websites. Finally, many PanCare members have publicized and disseminated the CPGs within their own countries. It is important that dissemination includes provision of appropriate and readily understandable information for survivors and their families. PanCare has established a PLAIN Information Group to develop lay language summaries of the guideline recommendations. In addition, PanCare helped to develop the Survivorship Passport (SurPass), a web-based tool that provides a treatment summary and individual recommendations for surveillance of late effects, to empower survivors to seek the care they need (35).

EVALUATION OF THE QUALITY OF CARE

The last essential feature of the on-going process of quality improvement is the evaluation of the quality of care delivered. Although developing and distributing CPGs is important in optimizing clinical care, insight into actual care given and received is necessary to achieve successful implementation.

Quality of care can be defined as “whether individuals can access the healthcare structures and processes of care which they need and whether the care received is

effective" (36). The Institute of Medicine elaborates on this by stating that high-quality care should also be safe, patient-centered, timely, efficient and equitable (37). The quality of the actual care delivered can be measured with so called quality indicators. Quality indicators are "measurable elements of practice performance for which there is evidence of consensus that they can be used to assess quality and hence change in quality, of care provided" (38). They are statements that can be used to precisely quantify structural, procedural and outcome-related aspects of care quality (39, 40).

Indicator measurement and monitoring has many purposes. Quality indicators make it possible to document the quality of care; make comparisons (benchmarking) over time between healthcare institutions; make judgments and set priorities; support accountability, regulation and credibility; support quality improvement; and support patient choice of care services (41). They give a reliable reflection of the quality of the care provided. By comparing the delivered care with the recommended care in CPGs, identification of suboptimal care can guide improvement of the quality of care.

Three types of quality indicators are distinguished, referring to the process and structure of medical care and the outcome of delivered care (Table 2).

Process indicators assess what the provider did for the patient and how well this was done. Process measures are direct measures of the quality of care, provided that an association has been demonstrated between a given process and outcome. For example, the proportion of survivors treated with greater than or equal to 35 Gy radiotherapy to a volume exposing the heart who have received an echocardiogram within two years after completion of therapy. Structure indicators relate to the presence or amount of staff, clients, money, beds, supplies, and buildings. An example related to childhood cancer survivorship care may be the proportion of pediatric oncology centers with a long-term follow-up clinic to provide survivorship care. From the survivor or patient perspective, as well as that of the insurer or payer, the ultimate consideration is the desired outcome (40). Outcome indicators are valid as performance indicators to the extent that outcomes, such as mortality, morbidity, or hospitalization, reflect the quality of specific care (42). For instance, the proportion of survivors treated with greater than or equal to 35 Gy radiotherapy to a volume exposing the heart who have developed clinical heart failure before the age of 45 years. Quality indicators can be operationalized with the support of review criteria and standards of care (i.e., CPGs). A review criterion is a clearly defined statement referring to the actual provision of care to individuals or populations of patients from a case-to-case basis (43). It should be precise and unambiguous, to allow for reliable and valid retrospective review. Reliability means that the indicator can be measured similarly in different situations and by different observers, whereas validity implies that the indicator is related to the outcome of interest. Some types of indicators, such as blood pressure or kidney function, are easier to quantify than others. In the transition from evidence-based to value-based healthcare, more emphasis has been put on patient-centered aspects of healthcare, such as health-related quality of life or patient satisfaction.

At present, there have been no efforts for the development of quality indicators in childhood cancer survivorship care. Several quality indicators have been developed for adult cancer care through combined evidence- and consensus-based processes (44-48). One of the more extensive and comprehensive endeavors is the Quality Oncology Practice Initiative, launched by the American Society of Clinical Oncology in 1997, which

currently encompasses 120 quality measures for cancer care. However, only seven of these indicators relate to survivorship, of which only four are applicable to childhood cancer survivors: 1) completion of a chemotherapy treatment summary within 3 months of the end of chemotherapy, 2) discussion of infertility risks prior to chemotherapy, 3) discussion of fertility preservation options, and 4) queries about smoking status including appropriate interventions (49). A wide range of relevant topics for childhood cancer survivors are therefore not addressed and assessed systematically. Nevertheless, it is promising that the use of quality indicators in adult cancer care has a positive effect on provided care (50, 51). For example, clinics that have adopted the Quality Oncology Practice Initiative measures for cancer care improved their performance over time. Specifically, those measures that address new clinical methods, such as giving antinausea and antivomiting medication when administering highly emetogenic chemotherapy, demonstrated rapidly increasing performance rates. However, for other clinically relevant measures such as assessing smoking status and counselling for infertility risks and fertility preservation, the participating centers consistently performed poorly, indicating that measurement itself is not sufficient for improving clinical care (50). In a different study, compliance to a quality measure for removal of 12 regional lymph nodes at colon cancer resection showed improvement after introduction of a reporting program, and better risk-adjusted survival (51).

Because the evidence base for long-term follow-up recommendations in survivorship care is expanding, the evaluation of actual clinical quality of care becomes more important. Although there are currently no systematic quality evaluations in childhood cancer survivorship care, nor have there been efforts for development of quality indicator sets, it would be useful to initiate such collaborations, to encourage further improvement within clinics and enable benchmarking between clinics and countries. The shift from paper to electronic medical records and the increase in cancer and survivor registries will greatly increase their feasibility and cost-effectiveness. Survivor participation should be central to these initiatives, as their experiences are pivotal in the concept of value-based healthcare. However, it should be emphasized that single-center evaluations of care quality as well as multi-stakeholder approaches can identify gaps in the current quality of provided care and might spark new research initiatives, thereby initiating a new cycle in the quality of care improvement process.

SUMMARY

Physicians involved in the care of childhood cancer survivors, and survivors, should be aware of the health problems that survivors may experience and provide high-quality, long-term follow-up care based on CPGs. The cyclical pattern of evidence generation, implementation, and evaluation drives current healthcare practices and systems. CPGs are essential for healthcare providers to translate research findings into clinical practice, as well as for patients to make well-informed healthcare decisions. The development and use of quality indicators are important to evaluate the impact of CPGs on the quality of care and survivor health outcomes. International collaboration among clinicians, researchers, guideline developers, patients, and survivors is essential in bridging the gap between research and clinical practice and evaluation of the quality of care. In this way we can optimize care and thereby the health and quality of life of childhood cancer survivors.

Table 2. Examples of a recommendation, indicator, review criterion and standard (adapted from Campbell et al., 2002)

	Process	Structure	Outcome
Recommendation	Survivors treated with chest radiation ≥ 35 Gy should receive cardiomyopathy surveillance using echocardiography with assessment of left ventricular systolic function, to begin no later than 2 years after completion of therapy, repeated at 5 years after diagnosis and continued every 5 years thereafter (reference 27)	Every pediatric oncology center should have a long-term follow-up clinic (reference 52)	Survivors should receive cardiomyopathy surveillance to minimize the burden of cardiovascular disease (reference 27)
Indicator	Survivors treated with chest radiation ≥ 35 Gy receiving an echo of the heart within 2 years after completion of therapy	The presence of a long-term follow-up clinic for survivorship care at pediatric oncology centers	The cumulative incidence of clinical heart failure among survivors treated with chest radiation ≥ 35 Gy
	Indicator numerator: Survivors treated with chest radiation ≥ 35 Gy having received an echo of the heart within 2 years after completion of therapy	**Indicator numerator:** Presence of a long-term follow-up clinic for survivorship care at the pediatric oncology centers	**Indicator numerator:** Survivors treated with chest radiation ≥ 35 Gy with clinical heart failure at or before the age of 45 years
	Indicator denominator: All survivors treated with chest radiation ≥ 35 Gy Gy	**Indicator denominator:** All pediatric oncology centers	**Indicator denominator:** All survivors treated with chest radiation ≥ 35 Gy that attained the age of 45 years or older
Review criterion	Has this survivor treated with chest radiation ≥ 35 Gy received an echo of the heart at 2 years after completion of therapy?	Does this pediatric oncology center have a long-term follow-up clinic to provide survivorship care?	Has this survivor treated with chest radiation ≥ 35 Gy had clinical heart failure at or before the age of 45 years?

Table 2. Examples of a recommendation, indicator, review criterion and standard (adapted from Campbell et al., 2002) (continued)

	Process	Structure	Outcome
Standard	**Target standard:** 80% of survivors treated with chest radiation ≥ 35 Gy should receive an echo of the heart within 2 years after completion of cardiotoxic therapy	**Target standard:** 80% of the pediatric oncology centers should have a long-term follow-up clinic to provide survivorship care	**Target standard:** Cumulative incidence of clinical heart failure in survivors treated with chest radiation ≥ 35 Gy should be 3% or less at the age of 45 years
	Achieved standard (hypothetical): 50% of survivors treated with chest radiation ≥ 35 Gy has received an echo of the heart within 2 years after completion of cardiotoxic therapy	**Achieved standard:** 38% of survivors receive long-term follow-up care under the guidance of a cancer survivorship expert service or cancer center (reference 53)	**Achieved standard (hypothetical):** Cumulative incidence of clinical heart failure in survivors treated with chest radiation ≥ 35 Gy is 6% at the age of 45 years (reference 54)

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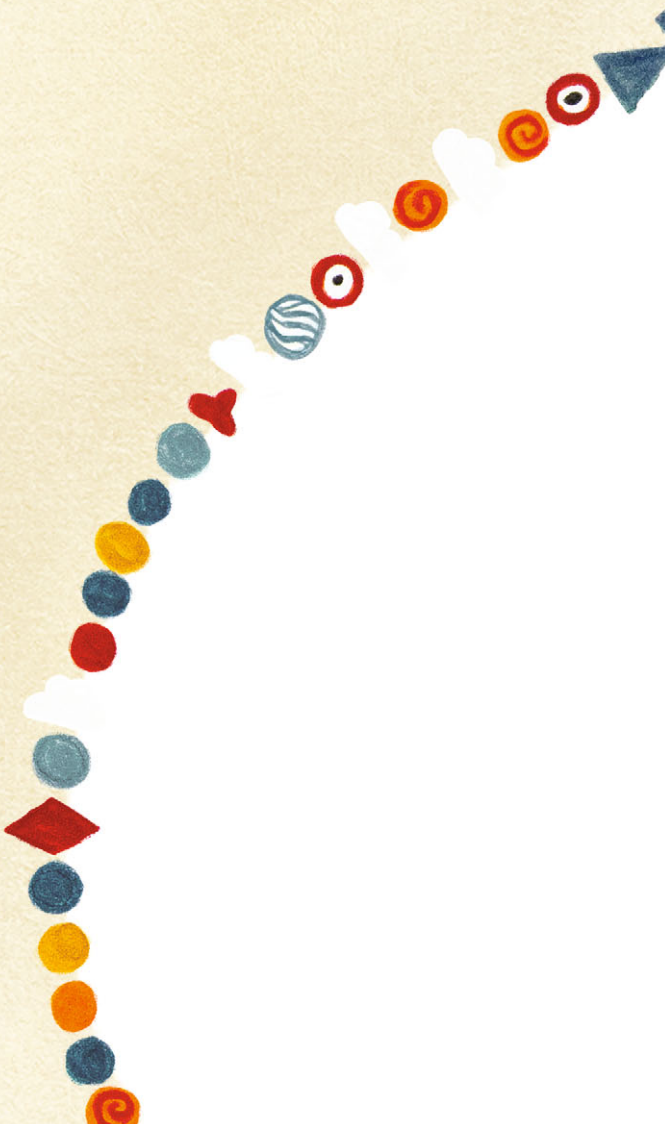

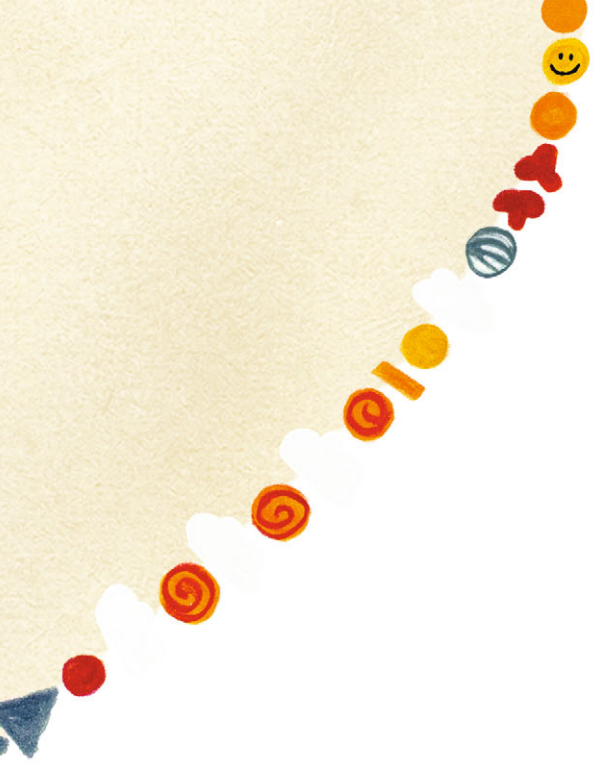

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A joint international consensus statement for measuring quality of survival for patients with childhood cancer

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ABSTRACT

The aim of treating childhood cancer remains to cure all. As survival rates improve, long-term health outcomes increasingly define quality of care. The International Childhood Cancer Outcome Project developed a set of core outcomes for most types of childhood cancers involving relevant international stakeholders (survivors; pediatric oncologists; other medical, nursing, or paramedical care providers; and psychosocial or neurocognitive care providers) to allow outcome-based evaluation of childhood cancer care. A survey among healthcare providers ($n = 87$) and online focus groups with survivors ($n = 22$) resulted in unique candidate outcome lists for 17 types of childhood cancer (five hematological malignancies, four central nervous system tumors, and eight solid tumors). In a two-round Delphi survey, 435 healthcare providers from 68 institutions internationally (response rates for round 1, 70-97%; round 2, 65-92%) contributed to the selection of four to eight physical core outcomes (for example, heart failure, subfertility, and subsequent neoplasms) and three aspects of quality of life (physical, psychosocial, and neurocognitive) per pediatric cancer subtype. Measurement instruments for the core outcomes consist of medical record abstraction, questionnaires, and linkage with existing registries. This International Childhood Cancer Core Outcome Set represents outcomes of value to patients, survivors, and healthcare providers and can be used to measure institutional progress and benchmark with against peers.

INTRODUCTION

Most children and adolescents receiving modern cancer therapy survive at least five years beyond diagnosis (1-3). Substantial reductions in mortality over the past decades have been reached through therapeutic progress and improved supportive care (4). Despite these promising results, survival rates remain poor for specific childhood, adolescent and young adult cancer types, such as diffuse intrinsic pontine glioma or infant acute lymphoblastic leukemia (2). In addition, if a cure is achieved, it is often compromised by adverse physical, psychosocial and neurocognitive effects that may significantly impact on quality of life (5-9). Prevention, identification and timely treatment of these adverse health outcomes among patients and survivors is one of the main pillars of supportive and follow-up care (10, 11).

Contemporary treatment regimens and follow-up strategies aim not only to achieve survival but also to optimize the quality of survival. Improved quality of care is evident when survival increases without a concurrent increase in adverse health outcomes, or when the occurrence of unfavorable health effects is reduced with similar or increased survival rates. We advocate that measurement of outcomes that are valued by patients, rather than monitoring processes and structures of care (such as complete and timely documentation or the availability of dedicated facilities or staff), should be used to define and promote high-quality care (12-14). Through measurement of these outcomes, institutions can gain insight about their progress in treating childhood cancer, or identify best practices by benchmarking with their peers. The rapid digitization of society and healthcare systems, and the implementation of electronic health records, have accelerated the routine measurement and collection of data in medical settings. Harmonization of which outcomes to measure, compare and improve remains essential in order to draw meaningful conclusions and make an impact on the quality of care.

Pediatric cancers, which include many rare subtypes with a substantial collective health burden, could particularly benefit from international standardization of outcome measures. Core sets of patient-relevant outcomes have recently been defined and implemented for a range of other populations and disease types, including several adult cancers (15-22). Similar initiatives are emerging in pediatrics (23) and within pediatric oncology, for example acute lymphoblastic leukemia and brain tumors (24-27). Although evidence-based surveillance guidelines are available to define optimum care for the individual with or survivor of childhood cancer (28, 29), metrics to evaluate the quality of care from diagnosis into survivorship have not been established. A well-defined core outcome set for common types of childhood cancer provides a much needed metric to assess quality of care during and after treatment through the evaluation of patient-relevant outcomes.

The International Childhood Cancer Outcome Project developed the International Childhood Cancer Core Outcome Set derived from the perspectives of childhood cancer survivors and international healthcare providers. This core set represents physical, psychosocial and neurocognitive outcomes for each of 17 common childhood cancer subtypes.

METHODS

The International Childhood Cancer Outcome Project was coordinated by a project group with representatives from the Princess Máxima Center for Pediatric Oncology in the Netherlands (the Princess Máxima Center) and St. Jude Children's Research Hospital in the United States (St. Jude), and survivor representatives. Project participants included childhood cancer survivors and a wide variety of healthcare providers internationally (Supplementary Table 1).

We initially focused on defining a unique core set of five to ten clinically relevant outcomes for each of 17 childhood cancer subtypes representing common hematological malignancies (acute lymphoblastic leukemia, acute myeloid leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, and Langerhans cell histiocytosis), central nervous system tumors (low grade glioma, high grade glioma, embryonal tumor of the central nervous system, and craniopharyngioma), and solid tumors (neuroblastoma, osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, nonrhabdomyosarcoma soft tissue sarcoma, liver tumor, kidney tumor, and extracranial germ cell tumor). Clinical relevance was defined as having a physical, psychosocial or neurocognitive influence on daily life and persisting for or developing two or more years after therapy. Acute toxicities and palliative outcomes were considered to be outside the scope of the project. Moreover, we decided that overall survival and cause-specific mortality should be a part of each core set; therefore, these factors were not included in the selection and prioritization process (30).

A mixed methods approach consisting of the following three steps was used (Figure 1): 1) preparation, 2) outcome selection, and 3) future implementation.

Step 1: preparation

As a starting point for the prioritization process, potentially relevant outcomes for each of the 17 childhood cancer types were collected at the Princess Máxima Center through a survey among healthcare providers and focus groups individuals who survived childhood cancer. Institutional approval for performing the focus groups was given by the Clinical Research Committee on 3 November 2020 with a waiver of further medical ethical review as the study was not considered to be subject to the Dutch Medical Research Involving Humans Act (WMO).

The clinical, nursing, and paramedic staff at the Princess Máxima Center nominated 90 healthcare providers based on their expertise in the field to participate in an online survey (97% response rate) (Supplementary Table 2). Together, they represented 17 professional backgrounds: pediatric oncologists; radiation oncologists; pain specialists; supportive care/symptom control/palliative care experts; late effects physicians; nurses; advanced nurse practitioners; physical therapists; psychologists; neuropsychologists; medical social workers; child life specialists; pediatric neurologists; pediatric neurosurgeons; pediatric surgeons; pediatric endocrinologists; and pediatric oncologists with additional expertise in allogeneic transplants. Participants were asked to identify five to ten clinically relevant outcomes in any domain for a specific childhood cancer type as an open-ended question.

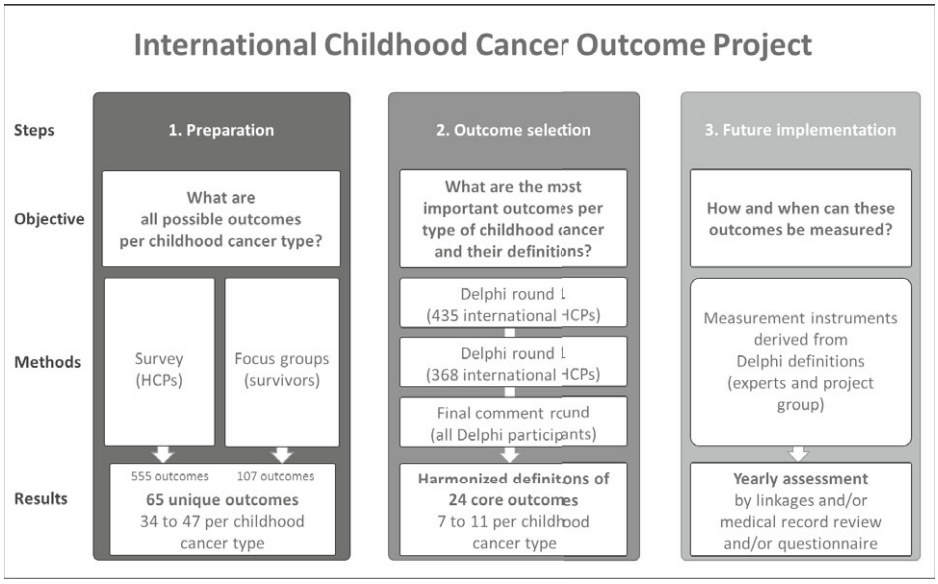


Figure 1. Overview of the International Childhood Cancer Outcome Project
The International Childhood Cancer Outcome Project consisted of three steps, from the starting point of 17 candidate outcome lists (step 1) to the selection of 17 core sets (step 2) with measurement instruments (step 3). Step 1, preparation, included a survey among healthcare providers from 17 professional backgrounds and focus groups of survivors. Step 2, outcome selection, included two Delphi rounds involving 435 (round 1) and 368 (round 2) international healthcare providers, finalized by a feedback round. Step 3, future implementation, included the selection of measurement instruments derived from the Delphi definitions by the project group, with consultation of topic experts. HCPs, healthcare providers.

Four online focus groups were organized for survivors: one each for adults (≥18 years) with a history of a childhood hematological malignancy (six participants), central nervous system tumor (six participants), or solid tumor (seven participants), and a separate focus group for adolescents (12-18 years; two participants diagnosed with brain tumors and one with osteosarcoma) (Supplementary Table 3). We hypothesized teenagers might experience different issues in daily life which would be more easily shared among peers. We did not organize focus groups for parents as the parent and survivor representatives included in the project group anticipated a risk of caregiver reporting bias compared with the self-reports of survivors, an observation supported by recent publications (31). Perspectives of younger patients and survivors were solicited during the adolescent focus group. Inclusion criteria consisted of being age 12 years or older; being a five-year survivor of a hematological malignancy, central nervous system tumor, or solid tumor; and providing signed informed consent by the participant (if age ≥16 years) or both participant and legal guardian (if age <16 years). The exclusion criterion was lack of Dutch language fluency. Participants were recruited through flyers at the late effects clinic, social media announcements, or nomination by their healthcare provider. We aimed for eight to ten participants per focus group to provide optimum data richness and conversational flow (32). The sessions were hosted digitally at the Princess Máxima Center in collaboration

with the Dutch Childhood Cancer Organization using videoconferencing software and online tools (that is, Mentimeter and Padlet).

Subsequently, the collected outcomes from the healthcare provider surveys and survivor focus groups were extracted and harmonized by two researchers (RLM and RJvK), with any discrepancies being resolved through discussion with a third party (LCMK) and with final agreement of the project group. These informed the unique candidate outcome lists that were established for each of the 17 childhood cancer types and served as the starting point for the outcome prioritization.

Step 2: outcome selection

To develop the core outcome set, including outcome definitions, we performed two Delphi rounds for 17 childhood cancer types. Both rounds were hosted electronically on the Welphi platform (www.welphi.com). Participants included healthcare providers at the Princess Máxima Center that participated in the healthcare provider survey (step 1), as well as staff at St. Jude Children's Research Hospital nominated by the project group, and leading international experts identified by working groups at the Princess Máxima Center and St. Jude Children's Research Hospital. All participants were categorized into three stakeholder groups (pediatric oncologists; other (medical, nursing, or paramedical) care providers; and psychosocial or neurocognitive care providers) (Supplementary Table 1). Survivors of childhood cancer did not participate in the Delphi rounds because survivor representatives expressed concerns that prioritizing outcomes on the individual level might be too complex and could cause psychological distress. However, the intermediate results and final core sets were reviewed and approved by the survivor representatives in the project group.

With the first Delphi round in March and April 2021, we aimed to condense the candidate outcome list to 15-20 outcomes per childhood cancer type and add missing outcomes. For each of the candidate outcomes, participants were asked to rate the prevalence and severity on a one to seven Likert scale (33). In addition, participants selected one most important outcome to include in the core set and could suggest new outcomes. Outcomes were moved forward to the second Delphi round if one or both of the following criteria were met: (i) a median severity of the outcome of ≥6.0 in at least one of the stakeholder groups, and median prevalence of the outcome being greater than or equal to the median prevalence score across all participants in that same stakeholder group; and/or (ii) top ranking, that is, ≥10% of participants within a stakeholder group considered the outcome the most important outcome to include in a core outcome set. If this resulted in a selection of less than 15 outcomes, the severity threshold would be decreased in steps of 0.5 until at least 15 outcomes were selected. New outcomes were added to the candidate outcome list if mentioned by two or more participants within the same type of childhood cancer.

All participants of the first Delphi round were also invited for the second Delphi round in May 2021, including nonresponders, provided they expressed an interest to participate. The results of the previous round were presented to the participants by e-mail. This second iteration aimed to prioritize approximately five outcomes per childhood cancer type and to refine the outcome definitions. Participants were asked to rate the importance of including each outcome in a core set of five outcomes on a one to seven Likert scale, and select the three most important outcomes per childhood cancer type (33).

Outcomes were prioritized by the following two criteria: (i) a median score of ≥6.0 or higher in at least one of the stakeholder groups, and being selected by ≥25% as one of the top three outcomes in that same stakeholder group; or (ii) median score of ≥6.0 among all participants. In order to establish the degree of consensus, three levels of agreement were defined according to these criteria: level A (both criteria fulfilled), B (only the first criterion fulfilled), and C (only the second criterion fulfilled). For the four central nervous system tumors (low grade glioma, high grade glioma, embryonal tumors of the central nervous system and craniopharyngioma), we observed that the psychosocial and neurocognitive outcomes were more highly prioritized than the physical outcomes. This would lead to exclusion of most of the latter outcomes if following the standard selection criteria. In order to improve the balance in these four Delphi surveys, we lowered the median score threshold for criterion i and ii to 5.0 for the physical outcomes in these surveys, while also including the psychosocial and neurocognitive outcomes based on the regular criteria. Outcomes with level A agreement, the highest level, were always included in the core set. Level B and C outcomes were included based on evidence presented in long-term follow-up guidelines and expert opinion within the project group. The final core sets and definitions were endorsed by the Delphi participants in an e-mail feedback round.

Draft definitions for each of the selected outcomes were developed by the project group, using the criteria for clinical relevance and a threshold where the patient experiences symptoms or an impact on daily life (for example, need to change lifestyle or use medication). Existing frameworks were used: preferably the Common Terminology Criteria for Adverse Events version 5 (34), supplemented by definitions used by the International Late Effects of Childhood Cancer Guideline Harmonization Group, Ponte di Legno Severe Toxicity Working Group, and World Health Organization. In both Delphi rounds, participants were asked to review the draft definitions. Definitions for the core outcomes were revised based on their feedback and presented in the final feedback round by e-mail.

Step 3: future implementation

The project group selected measurement instruments for each of the core outcomes, aiming to stay as close as possible to the endorsed Delphi definitions. Draft metrics were discussed and refined during three online project group meetings until full consensus was reached on final measurement instruments ready for implementation. For the physical core outcomes, two separate sets were created. One describes survey questions for symptomatic outcomes, that is, outcomes that have already resulted in a clinical diagnosis. The other set contains asymptomatic outcomes, that is, abnormalities on surveillance or diagnostic tests with or without a clinical diagnosis, using recommended surveillance strategies from the International Late Effects of Childhood Cancer Guideline Harmonization Group long-term follow-up guidelines (10). For the psychosocial and neurocognitive outcomes, internationally validated questionnaires were identified by expert consultation and mapped to the core outcomes. The objective was to determine the optimal coverage of these psychosocial and neurocognitive outcomes and alignment with other guidelines (26, 27). with minimal burden of completion on the parent (proxy), patient or survivor.

RESULTS

Step 1: preparation

A total of 555 outcomes were reported in the healthcare provider survey and 107 outcomes in the survivor focus groups. After combining these outcomes in the main groups and avoiding duplication, we included 65 unique outcomes in the candidate outcome lists for 17 separate childhood cancer types (34 to 47 outcomes per specific childhood cancer type) (Table 1).

Step 2: outcome selection

Response rates for the first round of the 17 surveys ranged from 70 to 97%, with a total of 435 surveys completed; response rates for the second round were between 65 to 92%, with a total of 368 surveys completed (Supplementary Table 4). Institutional approval for the Delphi surveys was waived by the Princess Máxima Center and St. Jude. Participants represented 68 institutions and 19 countries (Supplementary Table 5). Based on the selection criteria, a total of 53 outcomes were carried forward from the first to the second Delphi round, with 15 to 28 outcomes included in each of the 17 surveys, and physical, psychosocial and neurocognitive items represented across all childhood cancer types (Table 1). Eight outcome definitions were revised and definitions were developed for three newly added outcomes.

After the second Delphi round, a total of 24 unique outcomes were selected across all types of childhood cancer, in addition to overall survival and cause-specific mortality (Figure 2 and Table 2). This translates to 7 to 11 outcomes per childhood cancer type.

Level A agreement was found in 21 of the 24 outcomes (Supplementary Table 6), with three level B or C outcomes included based on expert opinion (that is, stroke and temperature dysregulation in craniopharyngioma, and reduced joint mobility in osteosarcoma and Ewing sarcoma). Three domains of quality of life were prioritized: physical, psychosocial and neurocognitive aspects. These resulted from a re-categorization of all psychosocial and neurocognitive outcomes and four physical outcomes (chronic pain, reduced levels of physical activity, sleep problems, and fatigue) after the second Delphi round. Three outcome definitions were modified. The core sets, including definitions, were accepted in the e-mail round (Table 3).

Step 3: future implementation

Measurement instruments were selected for each of the 24 physical, psychosocial and neurocognitive core outcomes (Table 4).

For the symptomatic physical core outcomes, 29 healthcare provider survey questions were formulated that capture each of the outcomes according to their Delphi definition, while allowing for outcomes to resolve using follow-up questions regarding year of diagnosis, current situation (active versus inactive) and year resolved, if applicable. For the asymptomatic physical core outcomes, an overview was created of surveillance tests recommended by the International Late Effects of Childhood Cancer Guideline Harmonization Group that have added value to capture outcomes in an early or asymptomatic stage (10). These can be extracted from medical records, if available.

Regarding the psychosocial and neurocognitive outcomes, we recommend self-report by the 23-item Pediatric Quality of Life Inventory (PedsQL) Generic questionnaire for all patients and survivors, with addition of the PedsQL Multidimensional Fatigue Scale with 18 items for those with a hematological malignancy or central nervous system tumor to capture general fatigue, cognitive fatigue, and sleep or rest fatigue (35, 36). Most psychosocial and neurocognitive items were captured by this approach, except for three: behavioral problems, independence or autonomy, and body image. Finally, for survival, we recommend performing a linkage with population registries to record overall survival and to review the medical record for the specific cause of death, depending on the available data sources in a country.

DISCUSSION

The International Childhood Cancer Outcome Project resulted in 17 core sets of 7 to 11 items per childhood cancer type, amounting to a total of 24 physical, psychosocial and neurocognitive outcomes for childhood cancer. We were able to define this set of important outcomes by an extensive two-round Delphi process including an international expert panel and survivors of childhood cancer. The core set can be used to evaluate the balance between survival and quality of survival for patients and survivors to measure progress within an organization, but also to benchmark with other institutions and identify best practices.

Strengths of this project include building on previous efforts within pediatric oncology (24-27), expanding the scope to most types of childhood cancer, and focusing on measures relevant to patients' and survivors' performance of activities in daily life. Moreover, the Delphi methodology allows equal contribution of all stakeholder types to the decision-making process, with substantial agreement in the prioritized outcomes (33). Another strength is that survivors were represented in the project group and consulted in the focus groups to ensure the final core sets reflect outcomes of importance to patients and survivors (31, 37).

In this project, we prioritized clinically relevant outcomes for children diagnosed with or having survived cancer, harmonized outcome definitions, and formulated measurement instruments. A next step will be to implement this core outcome indicator set in clinical practice. Measuring and evaluating these outcomes will be a powerful tool to advance quality of care. By focusing not just on survival but also on the outcomes most valued by patients, survivors, and their healthcare providers, the delicate balance between surviving and living with the consequences of cancer and its treatment becomes visible and actionable. It allows institutions to measure the impact of their treatment strategies in terms of improved survival, reduced adverse health outcomes or a combination of the two, thereby pinpointing current care needs and opportunities for future innovations. In addition, institutions adopting the same core set may participate in benchmarking initiatives to identify best practices across healthcare organizations to further improve the quality of care.

Importantly, the occurrence of early and late adverse health outcomes is not only dependent on the quality of care, but also relies on case-mix variables that describe differences between hospital populations, such as cancer subtype and stage, sex, age, genetic susceptibility, comorbidities, and other demographic or clinical traits. Therefore,

such data should be precisely documented and accounted for when benchmarking with other institutions (38). Moreover, the outcomes should preferably be measured prospectively to improve reliability and completeness compared to retrospective evaluation.

The International Childhood Cancer Core Outcome Set most likely cannot be immediately and completely extracted from common electronic health records. However, the outcomes can be measured by medical record abstraction, concise questionnaires, and linkage with existing registries. To facilitate and harmonize its implementation, we developed an overview of suggested measurement instruments. Regarding psychosocial and neurocognitive outcomes, we recommend using the established PedsQL Generic and Fatigue modules for survivors of 2 to 18 years of age. This decision aimed to balance the instrument's coverage of core outcomes, availability in different languages, validation across age ranges, and response burden. The PedsQL is considered a legacy instrument that is used widely in childhood cancer care and research, permitting comparisons with historical data, and is free to use for clinical work. Some institutions use this measure for follow-up until age 30 years, allowing for longitudinal assessments since diagnosis, including during the transition from acute to short- and long-term follow-up care. Although the PedsQL measures health-related quality of life on a more general level, it does not capture specific conditions such as anxiety, depression, posttraumatic stress, or suicidal ideation in detail. However, these types of psychopathology are less common in survivors of childhood cancer (39-42). The Patient-Reported Outcomes Measurement Information System (PROMIS) tools represent a favorable alternative, as they permit computerized adaptive testing, feature a relatively easy to interpret scoring system and include item banks that are increasingly becoming the international standard (43-45). However, because PROMIS measures are currently unavailable in many languages and only adopted by a few pediatric oncology centers worldwide, we recommend using the PedsQL as the primary measure to evaluate psychosocial and neurocognitive outcomes in this project. Evidently, more focused evaluations of specific physical, psychosocial or neurocognitive sequelae, preferably according to evidence-based clinical guidelines, remain important those at higher risk of developing adverse effects (10, 46).

The core set should be interpreted while acknowledging that an outcome prioritized on the aggregated level might not seem relevant for the individual, or alternatively, highly relevant outcomes on the individual level might not be part of the core set. Nevertheless, a concise set of relevant outcomes provides benefits in terms of feasibility (47-49). Furthermore, the 17 types of childhood cancer represented do not include all types of childhood cancer. This resulted partly from the relevance for the participating centers (for example, retinoblastoma is not treated at the Princess Máxima Center) or the infrequency of certain childhood cancer types (for example, thyroid carcinoma). Lastly, the candidate outcome lists which served as the starting point of the prioritization process were based on outcome collection efforts in the Netherlands. This might have induced sampling bias and limited generalizability. However, this risk is limited due to the possibility to put forth new outcomes during the Delphi process.

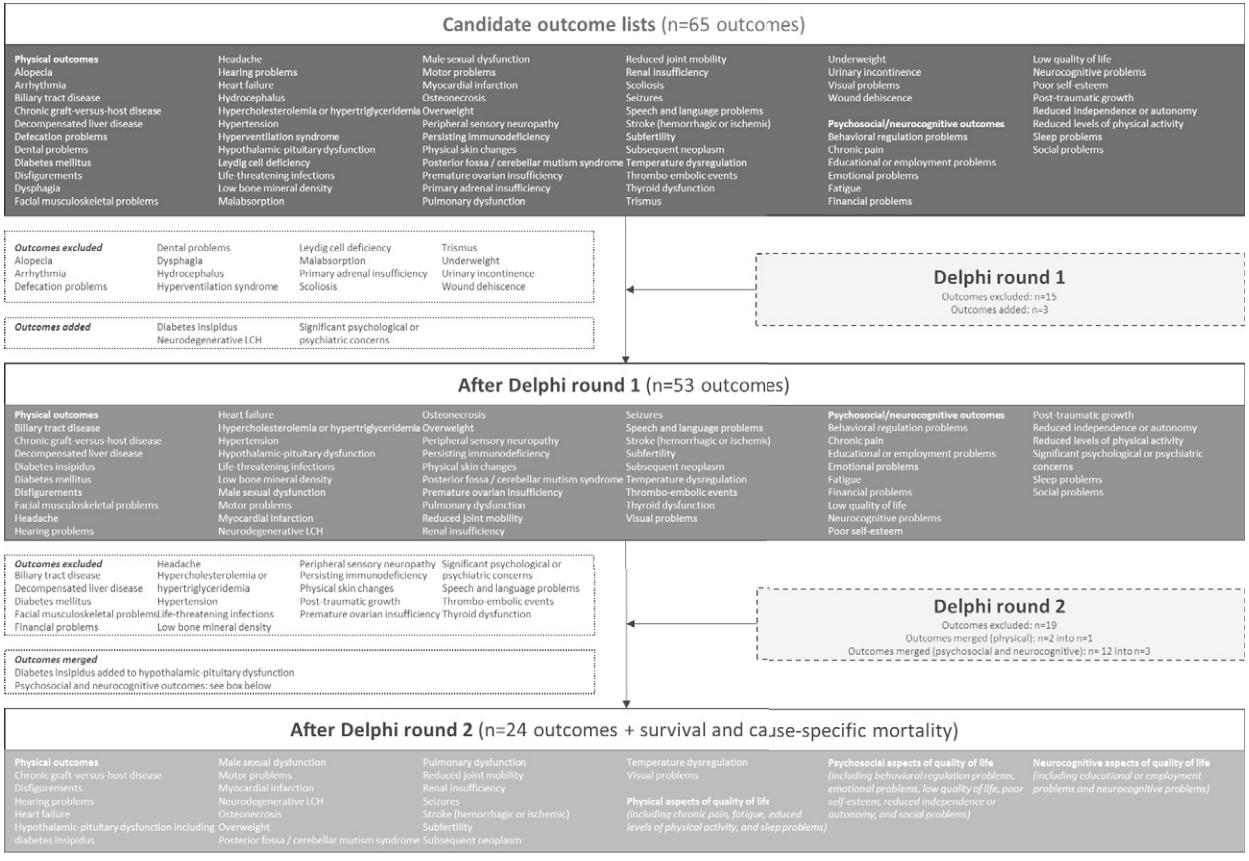
The successful development of the International Childhood Cancer Core Outcome Set is only the starting point of the implementation of outcome-based evaluation of quality of care. Apart from the involvement of survivor representatives and diverse healthcare providers throughout the project, additional elements including leadership, engagement,

a high quality database, balance between patient- and provider-report, and frequent communication of results are also crucial facilitators for the adoption of these core sets in clinical practice and the subsequent initiation of quality improvement efforts (47, 49, 50).

ACKNOWLEDGEMENTS

We thank the survivors that participated in the focus groups to share their experiences with life after childhood cancer. We also thank Willemijn Plieger for her valuable contribution to the preparation, conduct and interpretation of the focus groups.

Table 1. Overview of outcome selection from candidate outcome lists to final core sets



LCH, Langerhans cell histiocytosis.

Figure 2. International Childhood Cancer Core Outcome Set
These three circles represents the core outcomes included in the International Childhood Cancer Core Outcome Set, presented separately for central nervous system tumors, hematological malignancies and solid tumors. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; GvHD, graft-versus-host disease; HGG, high grade glioma; Hodgkin, Hodgkin lymphoma; HP, hypothalamic–pituitary; LCH, Langerhans cell histiocytosis; LGG, low grade glioma; non-Hodgkin, non-Hodgkin lymphoma; NRSTS, nonrhabdomyosarcoma soft tissue sarcoma; QoL, quality of life; RMS, rhabdomyosarcoma; SMN, subsequent malignant neoplasm (including meningioma).

Table 2. Overview of the 17 core outcome sets

	Acute lymphoblastic leukemia	Acute myeloid leukemia	Hodgkin lymphoma	Non-Hodgkin lymphoma	Langerhans cell histiocytosis	Low grade glioma	High grade glioma	Embryonal tumor of the CNS	Craniopharyngioma	Neuroblastoma	Osteosarcoma	Ewing sarcoma	Rhabdomyosarcoma	Nonrhabdomyosarcoma STS	Liver tumor	Kidney tumor	Extracranial germ cell tumor
Physical outcomes																	
Overweight	■	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■
Subsequent neoplasm	■	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■
Subfertility	■	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■
Heart failure	■	■	■	■						■	■	■	■	■	■	■	■
Chronic graft-versus-host disease	■	■															
Hypothalamic-pituitary dysfunction[a]					■	■	■	■	■								
Motor problems						■	■	■	■								
Hearing problems								■		■					■		■
Disfigurements												■	■	■			
Visual problems						■			■								
Reduced joint mobility											■	■					
Renal insufficiency															■	■	
Osteonecrosis	■																
Myocardial infarction			■														
Neurodegenerative LCH					■												
Pulmonary dysfunction					■												
Seizures							■										
Posterior fossa syndrome[b]								■									
Stroke (hemorrhagic or ischemic)									■								
Temperature dysregulation									■								
Male sexual dysfunction																	■
Psychosocial and neurocognitive outcomes																	
Physical aspects of quality of life[c]	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Psychosocial aspects of quality of life[d]	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Neurocognitive aspects of quality of life[e]	■	■	■	■	■	■	■	■	■								
Survival																	
Overall survival	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Cause-specific mortality	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■

Core outcomes for each childhood cancer type are marked in green, with overall survival and cause-specific mortality to be measured for everyone. CNS, central nervous system; STS, soft tissue sarcoma.

[a] Including diabetes insipidus.

[b] Posterior fossa syndrome/cerebellar mutism syndrome.

[c] Including chronic pain, reduced levels of physical activity, sleep problems and fatigue.

[d] Including low quality of life, social problems, behavioral regulation problems, emotional problems, poor self-esteem, and reduced independence or autonomy with age-appropriate daily living tasks.

[e] Including neurocognitive problems and educational or employment problems.

Table 3. Final outcome definitions accepted by the Delphi participants

Chronic graft-versus-host disease	Chronic graft-versus-host disease with a global severity score[a] of moderate or severe.
Disfigurements	Amputation and other physical disfigurements limiting instrumental or self-care ADL.
Hearing problems	Hearing problems, including hearing loss or deafness requiring a hearing aid or cochlear implant, or tinnitus with severe symptoms limiting instrumental or self-care ADL.
Heart failure	Heart failure, with symptoms at rest or with moderate activity or exertion, and/or with resting ejection fraction <40%.
Hypothalamic-pituitary dysfunction	Hypothalamic-pituitary dysfunction, with one or more of these abnormalities: ACTH deficiency with medical intervention indicated, GH deficiency confirmed by a stimulation test, TSH deficiency with medical intervention indicated, LH/FSH deficiency with medical intervention indicated, ADH deficiency (central diabetes insipidus) with medical intervention indicated, or precocious puberty with Tanner stage B2 before age 8 (girls) or testicular volume >4 cc before age 9 (boys).
Male sexual dysfunction	Male sexual dysfunction, including the presence or anorgasmia, decreased libido, anejeculation, retrograde ejaculation or erectile dysfunction requiring medical or other intervention.
Motor problems	Paralytic, neuropathic (e.g. twitching, muscle cramps, muscle weakness), or movement (e.g. ataxia, spasticity, disbalance) disorders limiting instrumental or self-care ADL, requiring walking aids or a wheelchair, or requiring urgent intervention.
Myocardial infarction	Myocardial infarction, including abnormal cardiac enzymes and ECG changes consistent with infarction.
Neurodegenerative LCH	Neurodegenerative LCH, including LCH-associated abnormal CNS imaging (LACI) and/or LCH-associated abnormal CNS symptoms (LACS).
Osteonecrosis	Osteonecrosis requiring medical or operative intervention.
Overweight	- Age 0 to 5 years: weight-for-height > 2 SD above WHO Child Growth Standards median. - Age 5 to 18 years: BMI-for-age > 1 SD above WHO Child Growth Standards median. - Age 18 years or older: BMI of ≥ 25 kg/m^2.

Table 3. Final outcome definitions accepted by the Delphi participants (continued)

Posterior fossa syndrome[b] (cerebellar mutism syndrome)	Posterior fossa syndrome (cerebellar mutism syndrome), characterized by 1) delayed onset mutism or reduced speech, and 2) emotional lability after cerebellar or fourth ventricle surgery.
Pulmonary dysfunction	Pulmonary dysfunction, including hypoxia requiring intermittent or continuous supplemental oxygen or limiting instrumental or self-care ADL.
Reduced joint mobility	Reduced mobility of the large joints (shoulder, elbow, hip, knee) limiting instrumental or self-care ADL.
Renal insufficiency	Chronic kidney disease, requiring medication, electrolyte supplementation, dialysis and/or or renal transplant.
Seizures	Seizures requiring medical or another intervention.
Stroke (hemorrhagic or ischemic)	Stroke, including intracranial hemorrhage requiring intervention or hospitalization or cerebrovascular ischemia requiring hospitalization.
Subfertility	Male or female subfertility, defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.
Subsequent neoplasm	Subsequent neoplasm which occurred as a new primary malignant neoplasm, and/or locally aggressive tumor (e.g. meningioma), either non-life threatening or acute life-threatening.
Temperature dysregulation	Temperature dysregulation, with a core temperature measured below <35o Celsius/95o Fahrenheit or requiring intervention such as specialized heat clothing.
Visual problems	Visual problems, including decreased vision with best corrected visual acuity of 0.1 or worse in the affected eye, or double vision or field of vision limitation, limiting instrumental or self-care ADL, e.g. a blind cane or a guide dog.

Table 3. Final outcome definitions accepted by the Delphi participants (continued)

Physical aspects of quality of life	Not applicable, grouped outcome measured by PedsQL Generic
Psychosocial aspects of quality of life	Not applicable, grouped outcome measured by PedsQL Generic
Neurocognitive aspects of quality of life	Not applicable, grouped outcome measured by PedsQL Fatigue

Activities of daily living (ADL) are defined according to the Common Terminology Criteria for Adverse Events version 5, with instrumental ADL referring to preparing meals, shopping for groceries or clothes, using the telephone, managing money, and self-care ADL referring to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden. ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; ADL, activities of daily living; BMI, body mass index; CNS, central nervous system; ECG, electrocardiogram; FSH, follicle stimulating hormone; LCH, Langerhans cell histiocytosis; LH, luteinizing hormone; GH, growth hormone; SD, standard deviations; TSH, thyroid stimulating hormone; WHO, World Health Organization.

[a] Definition of chronic graft-versus-host disease global severity score according to Lee SJ, Classification systems for chronic graft-versus-host disease. Blood. 2017;129(1):30-37.

[b] Definition of posterior fossa syndrome according to Gudrunardottir T et al., Consensus paper on post-operative pediatric cerebellar mutism syndrome: the Iceland Delphi results. Childs Nerv Syst. 2016;32(7):1195-203.

Table 4. Measurement instruments for the International Childhood Cancer Core Outcome Set

Core outcome	Measurement instrument
Measurement instruments for the symptomatic physical core outcomes	
Overweight[a]	Data extraction: height and weight
Subsequent neoplasm[a,b]	Date extraction: occurrence and type of subsequent neoplasm
Subfertility[c]	1 item: Has this person had a clinical diagnosis of subfertility, including a failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse?[d]
Heart failure[c]	1 item: Has this person had a clinical diagnosis of heart failure with resting ejection fraction (EF) <40%?[d]
Chronic graft-versus-host disease[c]	1 item: Has this person had a clinical diagnosis of chronic graft-versus-host disease with a global severity score of moderate or severe?[d,e]
Motor problems[c]	1 item: Has this person had a clinical diagnosis of paralysis, motor neuropathy (e.g. twitching, muscle cramps, muscle weakness) or a movement disorder (e.g. ataxia, spasticity) requiring support in instrumental or self-care ADL[f], requiring walking aids or a wheelchair, or requiring urgent intervention?[d]
Hypothalamic-pituitary dysfunction, including diabetes insipidus[c]	6 items: Has this person had a clinical diagnosis of ACTH deficiency requiring hydrocortisone medication?[d] Has this person had a clinical diagnosis of GH deficiency confirmed by a stimulation test?[d] Has this person had a clinical diagnosis of TSH deficiency requiring thyroid medication?[d] Has this person had a clinical diagnosis of LH/FSH deficiency requiring estradiol or testosterone medication?[d] Has this person had a clinical diagnosis of central precocious puberty with Tanner stage B2 before age 8 (girls) or testicular volume >4 cc before age 9 (boys)?[g] Has this person had a clinical diagnosis of ADH deficiency (central diabetes insipidus) requiring desmopressin medication?[d]
Measurement instruments for the symptomatic physical core outcomes	
Hearing problems[c]	2 items: Has this person had a clinical diagnosis of hearing loss or deafness, with an indication for a hearing aid or cochlear implant?[d] Has this person had a clinical diagnosis of tinnitus, with severe symptoms requiring support in instrumental or self-care ADL?[d,f]

Table 4. Measurement instruments for the International Childhood Cancer Core Outcome Set (continued)

Core outcome	Measurement instrument
Disfigurements[c]	1 item: Has this person had an amputation or other physical disfigurement, requiring support in instrumental or self-care ADL?[f,g]
Visual problems[c]	2 items: Has this person had a clinical diagnosis of visual problems, including a best corrected visual acuity of 0.1 or worse in one or both eyes?[d] Has this person had a clinical diagnosis of double vision or field of vision limitation, requiring support in instrumental or self-care ADL, for example a blind cane or a guide dog?[d,f]
Reduced joint mobility[c]	1 item: Has this person had a clinical diagnosis of reduced mobility of one or more of the large joints (shoulder, elbow, hip, knee), requiring support in instrumental of self-care ADL?[d,f]
Renal insufficiency[c]	2 items: Has this person had a clinical diagnosis of chronic kidney disease, requiring medication or electrolyte supplementation?[d] Has this person had a clinical diagnosis of chronic kidney disease, requiring dialysis and/or a renal transplant?[d]
Osteonecrosis[c]	2 items: Has this person had a clinical diagnosis of osteonecrosis, requiring medication (bisphosphonates, lipid lowering drugs, anticoagulants)?[d] Has this person had a clinical diagnosis of osteonecrosis requiring surgery?[d]
Myocardial infarction[c]	1 item: Has this person had a clinical diagnosis of myocardial infarction, including abnormal cardiac enzymes and ECG changes?[d]
Neurodegenerative LCH[c]	1 item: Has this person had a clinical diagnosis of neurodegenerative LCH, including LCH-associated abnormal CNS imaging (LACI) or LCH-associated abnormal symptoms (LACS)?[g]
Measurement instruments for the symptomatic physical core outcomes	
Pulmonary dysfunction[c]	2 items: Has this person had a clinical diagnosis of pulmonary dysfunction, requiring intermittent or continuous supplemental oxygen?[d] Has this person had a clinical diagnosis of pulmonary dysfunction requiring support in instrumental or self-care ADL?[d,f]
Seizures[c]	1 item: Has this person had a clinical diagnosis of seizures, requiring medication or another intervention?[d]

Table 4. Measurement instruments for the International Childhood Cancer Core Outcome Set (continued)

Core outcome	Measurement instrument
Posterior fossa syndrome[c,h]	1 item: Has this person had a clinical diagnosis of posterior fossa syndrome (cerebellar mutism syndrome), requiring support in instrumental or self-care ADL?[d,f]
Stroke (hemorrhagic or ischemic)[c]	1 item: Has this person had a clinical diagnosis of stroke (intracranial hemorrhage or cerebrovascular ischemia) requiring an intervention or hospitalization?[d]
Temperature dysregulation[c]	1 item: Has this person had a clinical diagnosis of temperature dysregulation with a core temperature measured below <35° C or 95° F or requiring intervention such as specialized heat clothing?[d]
Male sexual dysfunction[c]	1 item: Has this person had a clinical diagnosis of any type of male sexual dysfunction (anorgasmia, decreased libido, anejeculation, retrograde ejaculation or erectile dysfunction) requiring medication or another intervention?[d]
Measurement instruments for the asymptomatic physical core outcomes	
Subfertility[a]	Data extraction: sperm count (males), FSH (males and females) (if available)
Heart failure[a]	Data extraction: LV systolic function on ultrasound (if available)
Hearing problems[a]	Data extraction: audiometry (if available)
Renal insufficiency[a]	Data extraction: eGFR (if available)
Measurement instruments for the psychosocial and neurocognitive outcomes	
Physical aspects of QoL[i]	8 items: PedsQL Generic (Dimension: Physical Functioning) 12 items: PedsQL Fatigue (Dimensions: General Fatigue and Sleep/Rest Fatigue)
Psychosocial aspects of QoL[i]	10 items: PedsQL Generic (Dimensions: Emotional Functioning and Social Functioning)
Neurocognitive aspects of QoL[i]	5 items: PedsQL Generic (Dimension: School Functioning) 6 items: PedsQL Fatigue (Dimension: Cognitive Fatigue)
Measurement instruments for survival	

Table 4. Measurement instruments for the International Childhood Cancer Core Outcome Set (continued)

Core outcome	Measurement instrument
Overall survival[b]	Data extraction: last follow-up (survival) or date of death (mortality)
Cause-specific mortality[a,b]	Data extraction: cause of death[j]

Measurement instruments to capture the International Childhood Cancer Core Outcome Set, using medical record abstraction, questionnaires, or linkage with existing registries. ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; ADL, activities of daily living; CNS, central nervous system; eGFR, estimated glomerular filtration rate; FSH, follicle stimulating hormone; GH, growth hormone; LCH, Langerhans cell histiocytosis; LH, luteinizing hormone; LV, left ventricular; PedsQL, Pediatric Quality of Life Inventory; QoL, quality of life; TSH, thyroid stimulating hormone.

[a] Suggested data source: medical record.

[b] Suggested data source: existing registry (for example, cancer registry, population registry).

[c] Suggested data source: healthcare provider survey.

[d] Considered to be an outcome that may vary over time, requiring three follow-up questions about year of diagnosis, current situation (active/inactive) and year resolved if currently inactive.

[e] Global severity score according to Lee SJ, Classification systems for chronic graft-versus-host disease. Blood. 2017;129(1):30-37.

[f] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden. These definitions are adopted from the Common Terminology Criteria for Adverse Events version 5.

[g] Considered to be a permanent outcome, requiring one follow-up question about year of diagnosis.
Definition according to Gudrunardottir T et al., Consensus paper on post-operative pediatric cerebellar mutism. Childs Nerv Syst. 2016;32:1195-1203.
"Post-operative pediatric cerebellar mutism syndrome is characterized by delayed onset mutism/reduced speech and emotional lability after cerebellar or 4th ventricle tumor surgery in children. Additional common features include hypotonia and oropharyngeal dysfunction/dysphagia. It may frequently be accompanied by the cerebellar motor syndrome, cerebellar cognitive affective syndrome and brain stem dysfunction including long tract signs and cranial neuropathies. The mutism is always transient, but recovery from cerebellar mutism syndrome may be prolonged."

[i] Suggested data source: self-report or parent-report by patient or survivor (depending on age and ability).

[j] Suggested to be measured according to Kilsdonk E et al., Late mortality in childhood cancer survivors according to pediatric cancer diagnosis and treatment era in the Dutch LATER cohort. Cancer Invest 2022;40(5):413-24.

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Supplementary Table 1. Overview of project stakeholders participating in the healthcare provider survey, survivor focus groups and Delphi survey

	Princess Máxima Center for Pediatric Oncology	St. Jude Children's Research Hospital	Other institutions
Survey to inform candidate outcome list	Pediatric oncologists Radiation oncologists Pain specialists Supportive care/symptom control/palliative care experts Late effects physicians Nurses Advanced nurse practitioners Physical therapists Psychologists Neuropsychologists Medical social workers Child life specialists Pediatric neurologists Pediatric neurosurgeons Pediatric surgeons Pediatric endocrinologists Allogeneic transplant experts	Not applicable	Not applicable
Focus groups to inform candidate outcome list	5-year childhood cancer survivors with a hematological malignancy, central nervous system tumor, or solid tumor	Not applicable	Not applicable

Delphi survey	*Stakeholder group: pediatric oncologist* Pediatric oncologists *Stakeholder group: other (medical, nursing, or paramedical) healthcare providers* Radiation oncologists Pain specialists Supportive care/symptom control/palliative care experts Late effects physicians Nurses Advanced nurse practitioners Physical therapists Pediatric neurologists Pediatric neurosurgeons Pediatric surgeons Pediatric endocrinologists Allogeneic transplant experts *Stakeholder group: psychosocial and neurocognitive care providers* Psychologists Neuropsychologists Medical social workers Child life specialists	*Stakeholder group: pediatric oncologist* Pediatric oncologists *Stakeholder group: other (medical, nursing, or paramedical) healthcare providers* Radiation oncologists Pain specialists Supportive care/symptom control/palliative care experts Late effects physicians Nurses Advanced nurse practitioners Physical therapists Pediatric neurologists Pediatric neurosurgeons Pediatric surgeons Pediatric endocrinologists Allogeneic transplant experts *Stakeholder group: psychosocial and neurocognitive care providers* Psychologists Neuropsychologists Medical social workers Child life specialists	*Stakeholder group: pediatric oncologist* Pediatric oncologists *Stakeholder group: other (medical, nursing, or paramedical) healthcare providers* Supportive care/symptom control/palliative care experts Late effects physicians *Stakeholder group: psychosocial and neurocognitive care providers* Psychologists Neuropsychologists

Overview of the project participants, including survivors and healthcare providers from 17 professional backgrounds divided into three stakeholder groups.

Supplementary Table 2. Types of healthcare providers participating in the healthcare provider survey (part of step 1)

	Hematological malignancies						**Central nervous system tumors**					**Solid tumors**								
Type of healthcare provider	*Hematological malignancies (general)*	*Acute lymphoblastic leukemia*	*Acute myeloid leukemia*	*Hodgkin lymphoma*	*Non-Hodgkin lymphoma*	*Langerhans cell histiocytosis*	*Central nervous system malignancies (general)*	*Low grade glioma*	*High grade glioma*	*Embryonal tumors of the central nervous system*	*Craniopharyngioma*	*Solid tumors (general)*	*Neuroblastoma*	*Osteosarcoma*	*Ewing sarcoma*	*Rhabdomyosarcoma*	*Non-rhabdomyosarcoma soft tissue sarcomas*	*Liver tumor*	*Kidney tumor*	*Extracranial germ cell tumor*
Pediatric oncologist		2	1	2	2	1		2	1	2	1		1	1	1	1	1	1	1	1
Radiation oncologist	2						2					2								
Pain specialist	1						1					1								
Supportive care/symptom control/palliative care	3						3					3								
Late effects physician	1						1					1								

Nurse	4				2				2			
Advanced nurse practitioner	1				1				1			
Physical therapist	2				1				1			
Allogeneic transplant expert	4											
Pediatric neurologist						1	1	1	1			
Pediatric neurosurgeon						1	1	1	1			
Pediatric endocrinologist									1			
Pediatric surgeon									1			
Psychologist	2				1				2			
Neuropsychologist					3							
Medical social worker	1				1				1			
Child health	2				1				1			

The different survey topics are shown at the top of the table, with the type of healthcare provider participating on the left. Numbers in the cells indicate the number of healthcare providers with a specific background participating in each survey. The surveys were open in September 2020.

Supplementary Table 3. Characteristics of survivors participating in the focus groups (part of step 1)

	Focus group: hematological malignancies	Focus group: central nervous system tumors	Focus group: solid tumors	Focus group: children and adolescents
No. of participants	6	6	7	3
Age: mean (range)	31.0 (27-39)	27.8 (20-34)	35.6 (18-51)	14.3 (13-16)
Sex: n female (%)	6 (100)	3 (50)	5 (71)	1 (33)
Diagnosis	ALL (*n* = 2) AML (*n* = 2) Hodgkin (*n* = 2)	Germinoma (*n* = 2) Ependymoma (*n* = 1) Medulloblastoma (*n* = 1) Pilocytic astrocytoma (*n* = 1) PNET (*n* = 1)	Osteosarcoma (*n* = 2) Rhabdomyosarcoma (*n* = 2) Ewing sarcoma (*n* = 1) Small cell carcinoma of the ovary (*n* = 1) Wilms tumor (*n* = 1)	Brain tumor, unspecified (*n* = 2) Osteosarcoma (*n* = 1)
Year of diagnosis: mean (range)	1998 (1993-2005)	2000 (1987-2012)	1993 (1978-2016)	2009 (2007-2013)
Received LTFU: n (%)	5 (83)	5 (83)	6 (86)	2 (67)
Year of latest LTFU: mean (range)	2020 (2019-2021)	2019 (2016-2021)	2019 (2018-2020)	2020 (2020-2020)

Focus groups were held in December 2020 and January 2021. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; Hodgkin, Hodgkin lymphoma; LTFU, long-term follow-up; PNET, primitive neuro-ectodermal tumor.

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2)

Acute lymphoblastic leukemia	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
First Delphi round				
Responders (%)	34 (97%)	9 (100%)	16 (94%)	9 (100%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 9)	Advanced nurse practitioner (*n* = 2) Allogeneic transplant expert (*n* = 2) Late effects physician (*n* = 4) Nurse (*n* = 2) Pain specialist (*n* = 1) Physical therapist (*n* = 2) Radiation oncologist (*n* = 1) Supportive care/symptom control/ palliative care expert (*n* = 2)	Child life (*n* = 1) Medical social worker (*n* = 2) (Neuro)psychologist (*n* = 6)
Countries	*See right*	Belgium (*n* = 1) Denmark (*n* = 1) Germany (*n* = 1) The Netherlands (*n* = 2) United Kingdom (*n* = 1) United States of America (*n* = 3)	Croatia (*n* = 1) The Netherlands (*n* = 8) United States of America (*n* = 7)	Canada (*n* = 1) The Netherlands (*n* = 5) United Kingdom (*n* = 1) United States of America (*n* = 2)

Attrition: There was 1 non-responder in round 1, who did not express an interest to participate in round 2 (OTH *n* = 1). The number of invited stakeholders was reduced from 35 in round 1 to 34 in round 2.

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Acute lymphoblastic leukemia	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
Second Delphi round				
Responders (%)	29 (85%)	8 (89%)	15 (94%)	6 (67%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 8)	Advanced nurse practitioner (*n* = 2) Allogeneic transplant expert (*n* = 2) Late effects physician (*n* = 4) Nurse (*n* = 2) Physical therapist (*n* = 2) Radiation oncologist (*n* = 1) Supportive care/symptom control/ palliative care experts (*n* = 2)	Medical social worker (*n* = 1) (Neuro)psychologist (*n* = 5)
Countries	*See right*	Belgium (*n* = 1) Denmark (*n* = 1) Germany (*n* = 1) The Netherlands (*n* = 2) United Kingdom (*n* = 1) United States of America (*n* = 2)	Croatia (*n* = 1) The Netherlands (*n* = 7) United States of America (*n* = 7)	Canada (*n* = 1) The Netherlands (*n* = 2) United Kingdom (*n* = 1) United States of America (*n* = 2)

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Acute myeloid leukemia	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
First Delphi round				
Responders (%)	24 (89%)	4 (67%)	13 (100%)	7 (88%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 4)	Advanced nurse practitioner (*n* = 1) Allogeneic transplant expert (*n* = 2) Late effects physician (*n* = 4) Nurse (*n* = 1) Pain specialist (*n* = 1) Physical therapist (*n* = 2) Supportive care/symptom control/ palliative care expert (*n* = 2)	Child life (*n* = 1) Medical social worker (*n* = 2) (Neuro)psychologist (*n* = 4)
Countries	*See right*	The Netherlands (*n* = 2) United States of America (*n* = 2)	Belgium (*n* = 1) The Netherlands (*n* = 6) United States of America (*n* = 6)	The Netherlands (*n* = 4) United States of America (*n* = 3)

Attrition: There were 3 non-responders in round 1, 2 of which did not express an interest to participate in round 2 (ONC *n* = 1, PSY *n* = 1). The number of invited stakeholders was reduced from 27 in round 1 to 25 in round 2.

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Acute myeloid leukemia	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
Second Delphi round				
Responders (%)	23 (92%)	5 (100%)	13 (100%)	5 (71%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 5)	Advanced nurse practitioner (*n* = 1) Allogeneic transplant expert (*n* = 2) Late effects physician (*n* = 4) Nurse (*n* = 1) Pain specialist (*n* = 1) Physical therapist (*n* = 2) Supportive care/symptom control/ palliative care expert (*n* = 2)	Child life (*n* = 1) Medical social worker (*n* = 1) (Neuro)psychologist (*n* = 3)
Countries	*See right*	The Netherlands (*n* = 2) United States of America (*n* = 3)	Belgium (*n* = 1) The Netherlands (*n* = 6) United States of America (*n* = 6)	The Netherlands (*n* = 3) United States of America (*n* = 2)

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Hodgkin lymphoma	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
First Delphi round				
Responders (%)	30 (91%)	8 (89%)	16 (89%)	6 (100%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 8)	Advanced nurse practitioner (*n* = 2) Allogeneic transplant expert (*n* = 1) Late effects physician (*n* = 4) Nurse (*n* = 2) Pain specialist (*n* = 1) Physical therapist (*n* = 2) Radiation oncologist (*n* = 2) Supportive care/symptom control/ palliative care expert (*n* = 2)	Medical social worker (*n* = 2) (Neuro)psychologist (*n* = 4)
Countries	*See right*	Czech Republic (*n* = 1) France (*n* = 1) Germany (*n* = 1) The Netherlands (*n* = 2) United States of America (*n* = 3)	Slovenia (*n* = 1) The Netherlands (*n* = 7) United States of America (*n* = 8)	Australia (*n* = 1) The Netherlands (*n* = 3) United States of America (*n* = 2)

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Hodgkin lymphoma	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
Attrition: There were 3 non-responders in round 1, all of which did not express an interest to participate in round 2 (ONC *n* = 1, OTH *n* = 2). The number of invited stakeholders was reduced from 33 in round 1 to 30 in round 2.				
Second Delphi round				
Responders (%)	25 (83%)	6 (75%)	14 (88%)	5 (83%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 6)	Advanced nurse practitioner (*n* = 2) Allogeneic transplant expert (*n* = 1) Late effects physician (*n* = 3) Nurse (*n* = 2) Pain specialist (*n* = 1) Physical therapist (*n* = 1) Radiation oncologist (*n* = 2) Supportive care/symptom control/ palliative care expert (*n* = 2)	Medical social worker (*n* = 1) (Neuro)psychologist (*n* = 4)
Countries	*See right*	Czech Republic (*n* = 1) Germany (*n* = 1) The Netherlands (*n* = 1) United States of America (*n* = 3)	Slovenia (*n* = 1) The Netherlands (*n* = 7) United States of America (*n* = 6)	Australia (*n* = 1) The Netherlands (*n* = 2) United States of America (*n* = 2)

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Non-Hodgkin lymphoma	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
First Delphi round				
Responders (%)	27 (90%)	7 (88%)	14 (93%)	6 (86%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 7)	Advanced nurse practitioner (*n* = 1) Allogeneic transplant expert (*n* = 1) Late effects physician (*n* = 4) Nurse (*n* = 2) Pain specialist (*n* = 1) Physical therapist (*n* = 2) Supportive care/symptom control/ palliative care expert (*n* = 3)	Child life (*n* = 1) Medical social worker (*n* = 2) (Neuro)psychologist (*n* = 3)
Countries	*See right*	Austria (*n* = 1) Germany (*n* = 1) The Netherlands (*n* = 2) United Kingdom (*n* = 1) United States of America (*n* = 2)	Belgium (*n* = 1) Finland (*n* = 1) The Netherlands (*n* = 6) United Kingdom (*n* = 1) United States of America (*n* = 5)	The Netherlands (*n* = 3) United States of America (*n* = 3)

Attrition: There were 3 non-responders in round 1, 2 of which did not express an interest to participate in round 2 (OTH *n* = 1, PSY *n* = 1). The number of invited stakeholders was reduced from 30 in round 1 to 28 in round 2.

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Non-Hodgkin lymphoma	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
Second Delphi round				
Responders (%)	25 (89%)	7 (88%)	14 (100%)	4 (67%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 7)	Advanced nurse practitioner (*n* = 1) Allogeneic transplant expert (*n* = 1) Late effects physician (*n* = 4) Nurse (*n* = 2) Pain specialist (*n* = 1) Physical therapist (*n* = 2) Supportive care/symptom control/ palliative care expert (*n* = 3)	Medical social worker (*n* = 1) (Neuro)psychologist (*n* = 3)
Countries	*See right*	Austria (*n* = 1) Germany (*n* = 1) The Netherlands (*n* = 1) United Kingdom (*n* = 1) United States of America (*n* = 3)	Belgium (*n* = 1) Finland (*n* = 1) The Netherlands (*n* = 6) United Kingdom (*n* = 1) United States of America (*n* = 5)	The Netherlands (*n* = 1) United States of America (*n* = 3)

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Langerhans cell histiocytosis	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
First Delphi round				
Responders (%)	21 (88%)	7 (78%)	9 (90%)	5 (100%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 7)	Advanced nurse practitioner (*n* = 1) Late effects physician (*n* = 3) Nurse (*n* = 1) Pain specialist (*n* = 1) Physical therapist (*n* = 2) Supportive care/symptom control/ palliative care expert (*n* = 1)	Child life (*n* = 1) Medical social worker (*n* = 2) (Neuro)psychologist (*n* = 2)
Countries	*See right*	Austria (*n* = 1) France (*n* = 1) Greece (*n* = 1) Italy (*n* = 1) The Netherlands (*n* = 1) United Kingdom (*n* = 1) United States of America (*n* = 1)	Switzerland (*n* = 1) The Netherlands (*n* = 4) United States of America (*n* = 4)	The Netherlands (*n* = 4) United States of America (*n* = 1)

Attrition: There were 3 non-responders in round 1, 1 of which did not express an interest to participate in round 2 (OTH *n* = 1). The number of invited stakeholders was reduced from 24 in round 1 to 23 in round 2.

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Langerhans cell histiocytosis	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
Second Delphi round				
Responders (%)	19 (83%)	6 (67%)	9 (100%)	4 (80%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 6)	Advanced nurse practitioner (*n* = 1) Late effects physician (*n* = 3) Nurse (*n* = 1) Pain specialist (*n* = 1) Physical therapist (*n* = 2) Supportive care/symptom control/ palliative care expert (*n* = 1)	Child life (*n* = 1) Medical social worker (*n* = 1) (Neuro)psychologist (*n* = 2)
Countries	*See right*	Greece (*n* = 1) Italy (*n* = 1) Switzerland (*n* = 1) The Netherlands (*n* = 1) United Kingdom (*n* = 1) United States of America (*n* = 1)	Switzerland (*n* = 1) The Netherlands (*n* = 4) United States of America (*n* = 4)	The Netherlands (*n* = 3) United States of America (*n* = 1)

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Low grade glioma	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
First Delphi round				
Responders (%)	31 (89%)	9 (100%)	16 (89%)	6 (75%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 9)	Advanced nurse practitioner (*n* = 2) Late effects physician (*n* = 3) Nurse (*n* = 1) Pain specialist (*n* = 1) Pediatric neurologist (*n* = 2) Pediatric neurosurgeon (*n* = 2) Physical therapist (*n* = 2) Radiation oncologist (*n* = 1) Supportive care/symptom control/ palliative care expert (*n* = 2)	Child life (*n* = 1) Medical social worker (*n* = 2) (Neuro)psychologist (*n* = 3)
Countries	*See right*	Austria (*n* = 1) Canada (*n* = 1) Denmark (*n* = 1) Germany (*n* = 1) The Netherlands (*n* = 2) United States of America (*n* = 3)	Sweden (*n* = 1) The Netherlands (*n* = 8) United States of America (*n* = 7)	The Netherlands (*n* = 4) United States of America (*n* = 2)

Attrition: There were 4 non-responders in round 1, all of which did not express an interest to participate in round 2 (OTH *n* = 2, PSY *n* = 2). The number of invited stakeholders was reduced from 35 in round 1 to 31 in round 2.

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Low grade glioma	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
Second Delphi round				
Responders (%)	25 (81%)	7 (78%)	13 (81%)	5 (83%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 7)	Advanced nurse practitioner (*n* = 1) Late effects physician (*n* = 3) Nurse (*n* = 1) Pediatric neurologist (*n* = 2) Pediatric neurosurgeon (*n* = 1) Physical therapist (*n* = 2) Radiation oncologist (*n* = 1) Supportive care/symptom control/ palliative care expert (*n* = 2)	Medical social worker (*n* = 2) (Neuro)psychologist (*n* = 3)
Countries	*See right*	Canada (*n* = 1) Denmark (*n* = 1) The Netherlands (*n* = 2) United States of America (*n* = 3)	Sweden (*n* = 1) The Netherlands (*n* = 6) United States of America (*n* = 6)	The Netherlands (*n* = 3) United States of America (*n* = 2)

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

High grade glioma	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
First Delphi round				
Responders (%)	28 (85%)	7 (88%)	16 (94%)	5 (63%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 7)	Advanced nurse practitioner (*n* = 2) Late effects physician (*n* = 3) Pain specialist (*n* = 1) Pediatric neurologist (*n* = 2) Pediatric neurosurgeon (*n* = 2) Physical therapist (*n* = 2) Radiation oncologist (*n* = 2) Supportive care/symptom control/ palliative care expert (*n* = 2)	Medical social worker (*n* = 2) (Neuro)psychologist (*n* = 3)
Countries	*See right*	Germany (*n* = 1) The Netherlands (*n* = 2) United Kingdom (*n* = 1) United States of America (*n* = 3)	The Netherlands (*n* = 8) United States of America (*n* = 8)	Belgium (*n* = 1) The Netherlands (*n* = 2) United States of America (*n* = 2)

Attrition: There were 5 non-responders in round 1, 4 of which did not express an interest to participate in round 2 (OTH *n* = 1, PSY *n* = 3). The number of invited stakeholders was reduced from 33 in round 1 to 29 in round 2.

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

High grade glioma	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
Second Delphi round				
Responders (%)	23 (79%)	7 (88%)	12 (75%)	4 (80%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 7)	Advanced nurse practitioner (*n* = 1) Late effects physician (*n* = 2) Pediatric neurologist (*n* = 2) Pediatric neurosurgeon (*n* = 1) Physical therapist (*n* = 2) Radiation oncologist (*n* = 2) Supportive care/symptom control/ palliative care expert (*n* = 2)	Medical social worker (*n* = 1) (Neuro)psychologist (*n* = 3)
Countries	*See right*	Germany (*n* = 1) The Netherlands (*n* = 2) United States of America (*n* = 4)	The Netherlands (=6) United States of America (*n* = 6)	Belgium (*n* = 1) The Netherlands (*n* = 1) United States of America (*n* = 1)

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2)

Embryonal tumors of the CNS	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
First Delphi round				
Responders (%)	28 (85%)	4 (67%)	15 (88%)	9 (90%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 4)	Advanced nurse practitioner (*n* = 2) Late effects physician (*n* = 3) Nurse (*n* = 1) Pain specialist (*n* = 1) Pediatric neurologist (*n* = 2) Physical therapist (*n* = 2) Radiation oncologist (*n* = 2) Supportive care/symptom control/ palliative care expert (*n* = 2)	Medical social worker (*n* = 2) (Neuro)psychologist (*n* = 7)
Countries	*See right*	Germany (*n* = 1) The Netherlands (*n* = 1) United Kingdom (*n* = 1) United States of America (*n* = 1)	Switzerland (*n* = 1) The Netherlands (*n* = 8) United States of America (*n* = 6)	Canada (*n* = 1) Germany (*n* = 1) Sweden (*n* = 1) The Netherlands (*n* = 3) United States of America (*n* = 3)

Attrition: There were 5 non-responders in round 1, 2 of which did not express an interest to participate in round 2 (OTH *n* = 1, PSY *n* = 1). The number of invited stakeholders was reduced from 33 in round 1 to 31 in round 2.

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Embryonal tumors of the CNS	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
Second Delphi round				
Responders (%)	27 (87%)	5 (83%)	13 (81%)	9 (100%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 5)	Advanced nurse practitioner (*n* = 1) Late effects physician (*n* = 3) Nurse (*n* = 1) Pediatric neurologist (*n* = 2) Pediatric neurosurgeon (*n* = 1) Physical therapist (*n* = 2) Radiation oncologist (*n* = 1) Supportive care/symptom control/ palliative care expert (*n* = 2)	Medical social worker (*n* = 2) (Neuro)psychologist (*n* = 7)
Countries	*See right*	Germany (*n* = 1) The Netherlands (*n* = 2) United Kingdom (*n* = 1) United States of America (*n* = 1)	Switzerland (*n* = 1) The Netherlands (*n* = 7) United States of America (*n* = 5)	Canada (*n* = 1) Germany (*n* = 1) Sweden (*n* = 1) The Netherlands (*n* = 3) United States of America (*n* = 3)

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Craniopharyngioma	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
First Delphi round				
Responders (%)	27 (82%)	7 (100%)	15 (83%)	5 (63%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 7)	Advanced nurse practitioner (*n* = 2) Late effects physician (*n* = 2) Pain specialist (*n* = 1) Pediatric endocrinologist (*n* = 2) Pediatric neurologist (*n* = 1) Pediatric neurosurgeon (*n* = 2) Physical therapist (*n* = 2) Radiation oncologist (*n* = 1) Supportive care/symptom control/ palliative care expert (*n* = 2)	Medical social worker (*n* = 1) (Neuro)psychologist (*n* = 4)
Countries	*See right*	Germany (*n* = 1) Switzerland (*n* = 1) The Netherlands (*n* = 2) United Kingdom (*n* = 2) United States of America (*n* = 1)	The Netherlands (*n* = 7) United States of America (*n* = 8)	Germany (*n* = 1) The Netherlands (*n* = 1) United Kingdom (*n* = 1) United States of America (*n* = 2)

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Craniopharyngioma	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
Attrition: There were 6 non-responders in round 1, all of which did not express an interest to participate in round 2 (OTH *n* = 3, PSY *n* = 3). The number of invited stakeholders was reduced from 33 in round 1 to 27 in round 2.				
Second Delphi round				
Responders (%)	23 (85%)	6 (86%)	12 (80%)	5 (100%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 6)	Advanced nurse practitioner (*n* = 1) Late effects physician (*n* = 2) Pediatric endocrinologist (*n* = 2) Pediatric neurologist (*n* = 1) Pediatric neurosurgeon (*n* = 1) Physical therapist (*n* = 2) Radiation oncologist (*n* = 1) Supportive care/symptom control/ palliative care expert (*n* = 2)	Medical social worker (*n* = 1) (Neuro)psychologist (*n* = 4)
Countries	*See right*	Germany (*n* = 1) Switzerland (*n* = 1) The Netherlands (*n* = 2) United Kingdom (*n* = 1) United States of America (*n* = 1)	The Netherlands (*n* = 5) United States of America (*n* = 7)	Germany (*n* = 1) The Netherlands (*n* = 1) United Kingdom (*n* = 1) United States of America (*n* = 2)

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Neuroblastoma	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
First Delphi round				
Responders (%)	21 (70%)	4 (50%)	12 (75%)	5 (83%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 4)	Advanced nurse practitioner (*n* = 2) Late effects physician (*n* = 3) Nurse (*n* = 1) Pain specialist (*n* = 1) Physical therapist (*n* = 2) Radiation oncologist (*n* = 1) Supportive care/symptom control/ palliative care expert (*n* = 1) Surgeon (*n* = 1)	Child life (*n* = 1) Medical social worker (*n* = 1) (Neuro)psychologist (*n* = 3)
Countries	*See right*	France (*n* = 1) The Netherlands (*n* = 1) United States of America (*n* = 2)	Belgium (*n* = 1) Italy (*n* = 1) The Netherlands (*n* = 6) United States of America (*n* = 4)	The Netherlands (*n* = 3) United States of America (*n* = 2)

Attrition: There were 9 non-responders in round 1, 8 of which did not express an interest to participate in round 2 (ONC *n* = 3, OTH *n* = 4, PSY *n* = 1). The number of invited stakeholders was reduced from 30 in round 1 to 22 in round 2.

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Neuroblastoma	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
Second Delphi round				
Responders (%)	17 (77%)	4 (80%)	10 (83%)	3 (60%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 4)	Advanced nurse practitioner (*n* = 2) Late effects physician (*n* = 3) Nurse (*n* = 1) Physical therapist (*n* = 2) Radiation oncologist (*n* = 1) Supportive care/symptom control/ palliative care expert (*n* = 1)	Medical social worker (*n* = 1) (Neuro)psychologist (*n* = 2)
Countries	*See right*	France (*n* = 1) The Netherlands (*n* = 1) United States of America (*n* = 2)	Belgium (*n* = 1) Italy (*n* = 1) The Netherlands (*n* = 4) United States of America (*n* = 4)	The Netherlands (*n* = 1) United States of America (*n* = 2)

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Osteosarcoma	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
First Delphi round				
Responders (%)	29 (94%)	6 (100%)	16 (89%)	7 (100%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 6)	Advanced nurse practitioner (*n* = 2) Late effects physician (*n* = 3) Nurse (*n* = 2) Orthopedic surgeon (*n* = 1) Pain specialist (*n* = 1) Physical therapist (*n* = 2) Radiation oncologist (*n* = 2) Supportive care/symptom control/ palliative care expert (*n* = 2) Surgeon (*n* = 1)	Child life (*n* = 2) Medical social worker (*n* = 1) (Neuro)psychologist (*n* = 4)
Countries	*See right*	The Netherlands (*n* = 2) United Kingdom (*n* = 1) United States of America (*n* = 3)	The Netherlands (*n* = 7) United States of America (*n* = 9)	The Netherlands (*n* = 4) United States of America (*n* = 3)

Attrition: There were 2 non-responders in round 1, both of which did not express an interest to participate in round 2 (OTH *n* = 2). The number of invited stakeholders was reduced from 31 in round 1 to 29 in round 2.

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Osteosarcoma	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
Second Delphi round				
Responders (%)	25 (86%)	6 (100%)	15 (94%)	4 (57%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 6)	Advanced nurse practitioner (*n* = 2) Late effects physician (*n* = 3) Nurse (*n* = 2) Pain specialist (*n* = 1) Physical therapist (*n* = 2) Radiation oncologist (*n* = 2) Supportive care/symptom control/ palliative care expert (*n* = 2) Surgeon (*n* = 1)	Child life (*n* = 1) Medical social worker (*n* = 1) (Neuro)psychologist (*n* = 2)
Countries	*See right*	The Netherlands (*n* = 2) United Kingdom (*n* = 1) United States of America (*n* = 3)	The Netherlands (*n* = 7) United States of America (*n* = 8)	The Netherlands (*n* = 1) United States of America (*n* = 3)

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Ewing sarcoma	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
First Delphi round				
Responders (%)	23 (79%)	6 (75%)	11 (79%)	6 (86%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 6)	Advanced nurse practitioner (*n* = 1) Late effects physician (*n* = 2) Nurse (*n* = 1) Pain specialist (*n* = 1) Physical therapist (*n* = 2) Radiation oncologist (*n* = 1) Supportive care/symptom control/ palliative care expert (*n* = 2) Surgeon (*n* = 1)	Child life (*n* = 2) Medical social worker (*n* = 1) (Neuro)psychologist (*n* = 3)
Countries	*See right*	The Netherlands (*n* = 2) United Kingdom (*n* = 1) United States of America (*n* = 3)	The Netherlands (*n* = 5) United States of America (*n* = 6)	Australia (*n* = 1) The Netherlands (*n* = 3) United States of America (*n* = 2)

Attrition: There were 6 non-responders in round 1, all of which did not express an interest to participate in round 2 (ONC *n* = 2, OTH *n* = 3, PSY *n* = 1). The number of invited stakeholders was reduced from 29 in round 1 to 23 in round 2.

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Ewing sarcoma	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
Second Delphi round				
Responders (%)	20 (87%)	5 (83%)	11 (100%)	4 (67%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 5)	Advanced nurse practitioner (*n* = 1) Late effects physician (*n* = 2) Nurse (*n* = 1) Pain specialist (*n* = 1) Physical therapist (*n* = 2) Radiation oncologist (*n* = 1) Supportive care/symptom control/ palliative care expert (*n* = 2) Surgeon (*n* = 1)	Child life (*n* = 1) Medical social worker (*n* = 1) (Neuro)psychologist (*n* = 2)
Countries	*See right*	The Netherlands (*n* = 2) United States of America (*n* = 3)	The Netherlands (*n* = 5) United States of America (*n* = 6)	Australia (*n* = 1) The Netherlands (*n* = 1) United States of America (*n* = 2)

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Rhabdomyosarcoma	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
First Delphi round				
Responders (%)	23 (85%)	6 (86%)	12 (86%)	5 (83%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 6)	Advanced nurse practitioner (*n* = 2) Late effects physician (*n* = 3) Nurse (*n* = 1) Pain specialist (*n* = 1) Physical therapist (*n* = 2) Radiation oncologist (*n* = 1) Supportive care/symptom control/ palliative care expert (*n* = 2)	Child life (*n* = 1) Medical social worker (*n* = 1) (Neuro)psychologist (*n* = 3)
Countries	*See right*	The Netherlands (*n* = 2) United Kingdom (*n* = 1) United States of America (*n* = 3)	Czech Republic (*n* = 1) The Netherlands (*n* = 6) United States of America (*n* = 5)	The Netherlands (*n* = 3) United Kingdom (*n* = 1) United States of America (*n* = 1)

Attrition: There were 4 non-responders in round 1, 2 of which did not express an interest to participate in round 2 (OTH *n* = 1, PSY *n* = 1). The number of invited stakeholders was reduced from 27 in round 1 to 25 in round 1. A neurocognitive expert was moved from the PSY stakeholder group in round 1 to the ONC stakeholder group in round 2, because of a professional background as pediatric oncologist.

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Rhabdomyosarcoma	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
Second Delphi round				
Responders (%)	19 (76%)	7 (88%)	10 (77%)	2 (50%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 7)	Advanced nurse practitioner (*n* = 1) Late effects physician (*n* = 3) Nurse (*n* = 1) Physical therapist (*n* = 2) Radiation oncologist (*n* = 1) Supportive care/symptom control/ palliative care expert (*n* = 2)	Medical social worker (*n* = 1) (Neuro)psychologist (*n* = 1)
Countries	*See right*	Italy (*n* = 1) The Netherlands (*n* = 2) United Kingdom (*n* = 2) United States of America (*n* = 2)	Czech Republic (*n* = 1) The Netherlands (*n* = 4) United States of America (*n* = 5)	The Netherlands (*n* = 1) United States of America (*n* = 1)

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Non-rhabdomyosarcoma STS	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
First Delphi round				
Responders (%)	25 (89%)	7 (88%)	13 (93%)	5 (83%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 7)	Advanced nurse practitioner (*n* = 2) Late effects physician (*n* = 3) Nurse (*n* = 1) Pain specialist (*n* = 1) Physical therapist (*n* = 2) Radiation oncologist (*n* = 1) Supportive care/symptom control/ palliative care expert (*n* = 2) Surgeon (*n* = 1)	Child health (*n* = 1) Medical social worker (*n* = 1) (Neuro)psychologist (*n* = 3)
Countries	*See right*	France (*n* = 1) Italy (*n* = 1) The Netherlands (*n* = 1) United States of America (*n* = 4)	The Netherlands (*n* = 7) United States of America (*n* = 6)	The Netherlands (*n* = 3) United Kingdom (*n* = 1) United States of America (*n* = 1)

Attrition: There were 3 non-responders in round 1, 2 of which did not express an interest to participate in round 2 (OTH *n* = 1, PSY *n* = 1). The number of invited stakeholders was reduced from 28 in round 1 to 26 in round 2. A neurocognitive expert was moved from the PSY stakeholder group in round 1 to the ONC stakeholder group in round 2, because of a professional background as pediatric oncologist.

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Non-rhabdomyosarcoma STS	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
Second Delphi round				
Responders (%)	18 (69%)	7 (78%)	9 (69%)	2 (50%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 7)	Advanced nurse practitioner (*n* = 1) Late effects physician (*n* = 3) Nurse (*n* = 1) Physical therapist (*n* = 2) Supportive care/symptom control/ palliative care expert (*n* = 2)	Medical social worker (*n* = 1) (Neuro)psychologist (*n* = 1)
Countries	*See right*	France (*n* = 1) Italy (*n* = 1) The Netherlands (*n* = 1) United Kingdom (*n* = 1) United States of America (*n* = 3)	The Netherlands (*n* = 4) United States of America (*n* = 5)	The Netherlands (*n* = 1) United States of America (*n* = 1)

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Liver tumor	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
First Delphi round				
Responders (%)	20 (91%)	7 (100%)	9 (82%)	4 (100%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 7)	Advanced nurse practitioner (*n* = 1) Late effects physician (*n* = 3) Nurse (*n* = 1) Pain specialist (*n* = 1) Physical therapist (*n* = 2) Surgeon (*n* = 1)	Child life (*n* = 1) Medical social worker (*n* = 1) (Neuro)psychologist (*n* = 2)
Countries	*See right*	France (*n* = 1) The Netherlands (*n* = 2) United Kingdom (*n* = 1) United States of America (*n* = 3)	The Netherlands (*n* = 5) United States of America (*n* = 4)	The Netherlands (*n* = 4)

Attrition: There were 2 non-responders in round 1, both of which did not express an interest to participate in round 2 (OTH *n* = 2). The number of invited stakeholders was reduced from 22 in round 1 to 20 in round 2.

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Liver tumor	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
Second Delphi round				
Responders (%)	13 (65%)	5 (71%)	6 (67%)	2 (50%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 5)	Advanced nurse practitioner (*n* = 1) Late effects physician (*n* = 2) Nurse (*n* = 1) Physical therapist (*n* = 2)	Medical social worker (*n* = 1) (Neuro)psychologist (*n* = 1)
Countries	*See right*	The Netherlands (*n* = 2) United Kingdom (*n* = 1) United States of America (*n* = 2)	The Netherlands (*n* = 3) United States of America (*n* = 3)	The Netherlands (*n* = 2)

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Kidney tumor	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
First Delphi round				
Responders (%)	24 (80%)	8 (100%)	11 (73%)	5 (71%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 8)	Advanced nurse practitioner (*n* = 1) Late effects physician (*n* = 2) Nurse (*n* = 2) Pain specialist (*n* = 1) Physical therapist (*n* = 2) Radiation oncologist (*n* = 1) Supportive care/symptom control/ palliative care expert (*n* = 1) Surgeon (*n* = 1)	Child life (*n* = 1) Medical social worker (*n* = 2) (Neuro)psychologist (*n* = 2)
Countries	*See right*	Germany (*n* = 1) Poland (*n* = 1) The Netherlands (*n* = 2) United States of America (*n* = 4)	The Netherlands (*n* = 6) United States of America (*n* = 5)	The Netherlands (*n* = 3) United States of America (*n* = 2)

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Kidney tumor	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
Attrition: There were 6 non-responders in round 1, 5 of which did not express an interest to participate in round 2 (OTH *n* = 4, PSY *n* = 1). The number of invited stakeholders was reduced from 30 in round 1 to 25 in round 2.				
Second Delphi round				
Responders (%)	19 (76%)	7 (88%)	8 (73%)	4 (67%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 7)	Late effects physician (*n* = 2) Nurse (*n* = 2) Physical therapist (*n* = 2) Radiation oncologist (*n* = 1) Supportive care/symptom control/ palliative care expert (*n* = 1)	Medical social worker (*n* = 2) (Neuro)psychologist (*n* = 2)
Countries	*See right*	Germany (*n* = 1) Poland (*n* = 1) The Netherlands (*n* = 2) United States of America (*n* = 3)	The Netherlands (*n* = 3) United States of America (*n* = 5)	The Netherlands (*n* = 1) United Kingdom (*n* = 1) United States of America (*n* = 2)

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Extracranial germ cell tumor	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
First Delphi round				
Responders (%)	20 (83%)	6 (86%)	10 (91%)	4 (67%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 6)	Advanced nurse practitioner (*n* = 2) Late effects physician (*n* = 2) Nurse (*n* = 1) Pain specialist (*n* = 1) Physical therapist (*n* = 2) Supportive care/symptom control/ palliative care expert (*n* = 1) Surgeon (*n* = 1)	Child life (*n* = 1) Medical social worker (*n* = 2) (Neuro)psychologist (*n* = 1)
Countries	*See right*	France (*n* = 1) Germany (*n* = 1) The Netherlands (*n* = 2) United States of America (*n* = 2)	The Netherlands (*n* = 7) United States of America (*n* = 3)	The Netherlands (*n* = 2) United States of America (*n* = 2)

Attrition: There were 4 non-responders in round 1, 3 of which did not express an interest to participate in round 2 (OTH *n* = 1, PSY *n* = 2). The number of invited stakeholders was reduced from 24 in round 1 to 21 in round 2.

Supplementary Table 4. Participants and response rates in each of the 17 Delphi surveys (part of step 2) (continued)

Extracranial germ cell tumor	Overall	Stakeholder group: ONC	Stakeholder group: OTH	Stakeholder group: PSY
Second Delphi round				
Responders (%)	18 (86%)	6 (86%)	9 (90%)	3 (75%)
Stakeholder types	*See right*	Pediatric oncologist (*n* = 6)	Advanced nurse practitioner (*n* = 2) Late effects physician (*n* = 2) Nurse (*n* = 1) Physical therapist (*n* = 2) Supportive care/symptom control/ palliative care expert (*n* = 1) Surgeon (*n* = 1)	Medical social worker (*n* = 2) (Neuro)psychologist (*n* = 1)
Countries	*See right*	France (*n* = 1) Germany (*n* = 1) The Netherlands (*n* = 2) United States of America (*n* = 2)	The Netherlands (*n* = 6) United States of America (*n* = 3)	The Netherlands (*n* = 1) United States of America (*n* = 2)

CNS, central nervous system; ONC, pediatric oncologists; OTH, other (medical, nursing, or paramedical) healthcare providers; PSY, psychosocial and neurocognitive care providers; STS, soft tissue sarcoma.

Supplementary Table 5. Institutions represented by the participants in the 17 Delphi surveys (part of step 2)

Institution	Country
Agia Sofia Children's Hospital	Greece
Alberta Children's Hospital	Canada
Birmingham Children's Hospital	United Kingdom
Children's Healthcare of Atlanta	United States of America
Children's Hospital for Wales	United Kingdom
Children's National Hospital	United States of America
Cincinnati Children's Hospital	United States of America
Clinical Hospital Center Rijeka	Croatia
Columbia University Irving Medical Center	United States of America
Dana-Farber/Boston Children's Cancer and Blood Disorders Center	United States of America
Dana-Farber Cancer Institute	United States of America
Faculty of Medicine and University of Turku	Finland
Great North Children's Hospital	United Kingdom
Great Ormond Street Hospital	United Kingdom
Hôpital Armand Trousseau	France
Hopp Children's Cancer Center Heidelberg (KiTZ)	Germany
Hospital for Sick Children	Canada
Inselspital	Switzerland
Institut Curie	France
Institut d'hématologie et d'oncologie pédiatrique (IHOP)	France
Institut Gustave Roussy	France
Institute of Oncology	Slovenia
Istituto Giannina Gaslini	Italy
Istituto Tumori	Italy
Justus-Liebig-University of Giessen	Germany
Kantonsspital Aarau	Switzerland
Maine Children's Cancer Program	United States of America
MD Anderson Cancer Center	United States of America
Medical University of Vienna	Austria
Memorial Sloan Kettering Cancer Center	United States of America
Memorial Sloan Kettering Kids	United States of America
National Cancer Institute	United States of America
Nemours Al DuPont Hospital for Children	United States of America
Nottingham Children's Hospital	United Kingdom
Princess Máxima Center for Pediatric Oncology	The Netherlands

Supplementary Table 5. Institutions represented by the participants in the 17 Delphi surveys (part of step 2) (continued)

Institution	Country
Rigshospitalet	Denmark
Royal Manchester Children's Hospital	United Kingdom
Saarland University	Germany
Seattle Children's Hospital	United States of America
Skåne University Hospital	Sweden
Stanford Cancer Center	United States of America
Sydney Children's Hospital	Australia
St. Anna's Kinderspital	Austria
St. Jude Children's Research Hospital	United States of America
Texas Children's Hospital	United States of America
The Capital Region of Denmark	Denmark
The Royal Marsden	United Kingdom
University Clinic Bonn	Germany
University Clinic Heidelberg	Germany
University Clinic Münster	Germany
University College London Hospitals	United Kingdom
University Hospital Brno	Czech Republic
University Hospital in Motol	Czech Republic
University Hospital Oldenburg	Germany
University Hospitals Bristol	United Kingdom
University Hospitals Gent	Belgium
University Hospitals Leuven	Belgium
University Medical Center Göttingen	Germany
University Medical Center Hamburg-Eppendorf	Germany
University of California, San Francisco	United States of America
University of Glasgow	United Kingdom
University of Oklahoma Health Sciences Center	United States of America
University of Padua	Italy
University of Utah Health	United States of America
University of York	United Kingdom
Vanderbilt University Medical Center	United States of America
Watford General Hospital	United Kingdom
Wroclaw Medical University	Poland

Supplementary Table 6. Prioritized outcomes in the first and second round of the 17 Delphi surveys (part of step 2)

	Hematological malignancies				
	Acute lymphoblastic leukemia	**Acute myeloid leukemia**	**Hodgkin lymphoma**	**Non-Hodgkin lymphoma**	**Langerhans cell histiocytosis**
Physical outcomes					
Alopecia	NP1	NP1	NP1	NP1	NP1
Arrhythmia	NPC	NPC	NPC	NPC	NPC
Biliary tract disease	NPC	NPC	NPC	NPC	NPC
Posterior fossa / cerebellar mutism syndrome	NPC	NPC	NPC	NPC	NPC
Chronic graft-versus-host disease	C	A	NP1	NP2	NP1
Decompensated liver disease	NP1	NP1	NP1	NP1	NP2
Defecation problems	NPC	NPC	NPC	NPC	NPC
Dental problems	NPC	NPC	NPC	NPC	NPC
Diabetes insipidus	NPC	NPC	NPC	NPC	A*
Diabetes mellitus	NP2	NP1	NP1	NP1	NP1
Disfigurements	NP1	NP1	NP1	NP1	NP2
Dysphagia	NP1	NP1	NP1	NP1	NP1
Facial musculoskeletal problems	NPC	NPC	NPC	NPC	NPC
Headache	NPC	NPC	NPC	NPC	NPC
Hearing problems	NP1	NP1	NP1	NP1	NP2
Heart failure	A	A	A	A	NP1
Hydrocephalus	NPC	NPC	NPC	NPC	NPC
Hypercholesterolemia or hypertriglyceridemia	NP1	NP1	NP1	NP1	NP2
Hypertension	NP1	NP1	NP1	NP1	NP1
Hyperventilation syndrome	NPC	NPC	NPC	NPC	NPC
Hypothalamic-pituitary dysfunction	NP1	NP1	NP1	NP1	A
Leydig cell deficiency	NPC	NPC	NPC	NPC	NPC
Life-threatening infections	NP2	NP2	NP1	NP2	NP1
Low bone mineral density	NP1	NP1	NP1	NP1	NP2
Malabsorption	NP1	NP1	NP1	NP1	NP1

CNS tumors						Solid tumors					
Low grade glioma	High grade glioma	Embryonal tumors of the CNS	Craniopharyngioma	Neuroblastoma	Osteosarcoma	Ewing sarcoma	Rhabdomyosarcoma	Non-rhabdomyo-sarcoma STS	Liver tumor	Kidney tumor	Extracranial germ cell tumor
NP1	NP1	NP1	NP1	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC
NPC	NPC	NPC	NPC	NP1	NP1	NP1	NP1	NP1	NP1	NP1	NP1
NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NP2	NPC	NPC
NP1	NP1	A	NP1	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC
NPC	NPC	NPC	NPC	NP1	NP1	NP1	NP1	NP1	NP1	NP1	NP1
NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NP1	NPC
NPC	NPC	NPC	NPC	NP1	NP1	NP1	NP1	NP1	NP1	NP1	NP1
NPC	NPC	NPC	NPC	NPC	NPC	NPC	NP1	NPC	NPC	NPC	NPC
NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC
NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC
NP1	NP2	NP1	NP1	NP1	NP2	A	A	B	NP1	NP1	NP1
NP1	NP1	NP1	NP1	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC
NPC	NPC	NPC	NPC	NP1	NP1	NP1	NP2	NP1	NP1	NP1	NP1
NP1	NP2	NP1	NP1	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC
NP1	NP1	C	NP1	A	NP2	NP1	NP1	NP1	A	NP1	B
NP1	NP1	NP1	NP1	B	A	A	NP1	B	NP1	A	NP1
NP1	NP1	NP1	NP1	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC
NPC	NPC	NPC	NP1	NPC	NPC	NPC	NPC	NPC	NPC	NP2	NPC
NPC	NPC	NPC	NP1	NPC	NPC	NPC	NPC	NPC	NPC	NP2	NPC
NPC	NPC	NPC	NPC	NP1	NP1	NP1	NP1	NP1	NP1	NP1	NP1
A	C	C	A	NP1	NP1	NP1	NP2	NP1	NP1	NP1	NP1
NPC	NPC	NPC	NP1	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC
NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC
NPC	NPC	NPC	NPC	NP1	NP1	B	NP1	NP1	NP1	NP1	NP1
NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC

Supplementary Table 6. Prioritized outcomes in the first and second round of the 17 Delphi surveys (part of step 2) (continued)

	Hematological malignancies				
	Acute lymphoblastic leukemia	**Acute myeloid leukemia**	**Hodgkin lymphoma**	**Non-Hodgkin lymphoma**	**Langerhans cell histiocytosis**
Physical outcomes					
Male sexual dysfunction	NPC	NPC	NPC	NPC	NPC
Motor problems	NP2	NP1	NP1	NP1	NP2
Myocardial infarction	NP1	NP1	A	NP1	NP1
Neurodegenerative LCH	NPC	NPC	NPC	NPC	A*
Osteonecrosis	A	NP1	NP2	NP1	NP2
Overweight	NP2	NP1	B	NP2	NP2
Peripheral sensory neuropathy	NP1	NP1	NP1	NP1	NP2
Persisting immunodeficiency	NP1	NP1	NP1	NP2	NP1
Physical skin changes	NP1	NP1	NP1	NP1	NP2
Premature ovarian insufficiency	NP1	NP2	NP2	NP2	NP1
Primary adrenal insufficiency	NPC	NPC	NPC	NPC	NPC
Pulmonary dysfunction	NP2	NP1	NP2	NP2	A
Reduced joint mobility	NP1	NP1	NP1	NP2	NP2
Renal insufficiency	NP1	NP1	NP1	NP2	NP1
Scoliosis	NPC	NPC	NPC	NPC	NPC
Seizures	NP1	NPC	NPC	NPC	NPC
Speech and language problems	NPC	NPC	NPC	NPC	NPC
Stroke (hemorrhagic or ischemic)	NP2	NP2	NP1	NP1	NP1
Subfertility	C	A	A	B	NP1
Subsequent neoplasm	A	A	A	A	NP2
Temperature dysregulation	NPC	NPC	NPC	NPC	NPC
Thrombo-embolic events	NP1	NP1	NP2	NP2	NP1
Thyroid dysfunction	NP1	NP1	NP2	NP1	NP1
Trismus	NPC	NPC	NPC	NPC	NPC

CNS tumors						Solid tumors					
Low grade glioma	High grade glioma	Embryonal tumors of the CNS	Craniopharyngioma	Neuroblastoma	Osteosarcoma	Ewing sarcoma	Rhabdomyosarcoma	Non-rhabdomyo-sarcoma STS	Liver tumor	Kidney tumor	Extracranial germ cell tumor
NPC	NP1	NPC	NPC	NP2	NP2	NP2	NP1	NP1	NP1	NP2	A
A	A	C	C	NP1	C	NP2	NP2	NP2	NP2	NP1	NP1
NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC
NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC
NPC	NPC	NPC	NPC	NP1	NP2	NP1	NP1	NP1	NP1	NP1	NP1
C	NP1	NP2	A	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC
NP1	C	NP1	NP1	NP2	NP1	NP2	NP2	NP1	NP1	NP2	NP1
NPC	NPC	NPC	NPC	NP1	NP1	NP1	NP1	NP1	NP1	NP1	NP1
NPC	NP1	NPC	NPC	NP1	NP1	NP1	NP1	NP1	NP1	NP1	NP1
NPC	NPC	NPC	NPC	NP2	NP1	NP2	NP2	NP2	NP2	NP2	NP1
NPC	NPC	NPC	NP1	NP1	NP1	NP1	NP1	NP1	NP1	NP1	NP1
NPC	NPC	NPC	NPC	NP1	NP1	NP1	NP1	NP1	NP1	NP2	NP1
NP1	NP1	NP1	NP1	NP1	B	C	NP2	NP2	NP1	NP1	NP1
NPC	NPC	NPC	NPC	NP1	NP1	NP2	NP1	NP1	A	B	NP1
NPC	NPC	NPC	NPC	NP1	NP1	NP1	NP1	NP1	NP1	NP1	NP1
NP1	A	NP1	NP1	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC
NP2	NP2	NP1	NP1	NPC	NPC	NPC	NP1	NPC	NPC	NPC	NPC
NP1	NP1	NP1	C	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC
NP1	NP1	C	NP1	A	B	C	B	B	B	NP2	A
NP1	C	C	NP1	A	NP2	B	B	B	A	A	B
NPC	NPC	NPC	C	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC
NP1	NP1	NP1	NP1	NP1	NP1	NP1	NP1	NP1	NP1	NP1	NP1
NP1	NP1	NP1	NP1	NP1	NP1	NP1	NP1	NP1	NP1	NP1	NP1
NPC	NPC	NPC	NPC	NPC	NPC	NPC	NP1	NPC	NPC	NPC	NPC

Supplementary Table 6. Prioritized outcomes in the first and second round of the 17 Delphi surveys (part of step 2) (continued)

	Hematological malignancies				
	Acute lymphoblastic leukemia	**Acute myeloid leukemia**	**Hodgkin lymphoma**	**Non-Hodgkin lymphoma**	**Langerhans cell histiocytosis**
Physical outcomes					
Underweight	NP1	NP1	NP1	NP1	NP1
Urinary incontinence	NPC	NPC	NPC	NPC	NPC
Visual problems	NP1	NP1	NP1	NP1	NP1
Wound dehiscence	NPC	NPC	NPC	NPC	NPC
Quality of life outcomes: physical aspects					
Chronic pain	NP2	NP1	NP1	NP2	NP2
Fatigue	B	B	B	A	NP2
Reduced levels of physical activity	NPC	NPC	NPC	NP2*	NPC
Sleep problems	NP1	NP1	NP2	NP1	NP1
Quality of life outcomes: psychosocial aspects					
Behavioral regulation problems	NP2	NP2	NP2	NP2	C
Emotional problems	NP1	NP2	NP2	NP2	NP2
Financial problems	NP1	NP1	NP2	NP2	NP2
Low quality of life	A	A	NP2	NP2	NP2
Poor self-esteem	NP1	NP1	NP2	NP2	NP2
Post-traumatic growth	NP2	NP2	NP1	NP1	NP2
Reduced independence or autonomy**	NP2	NP2	NP2	NP1	NP2

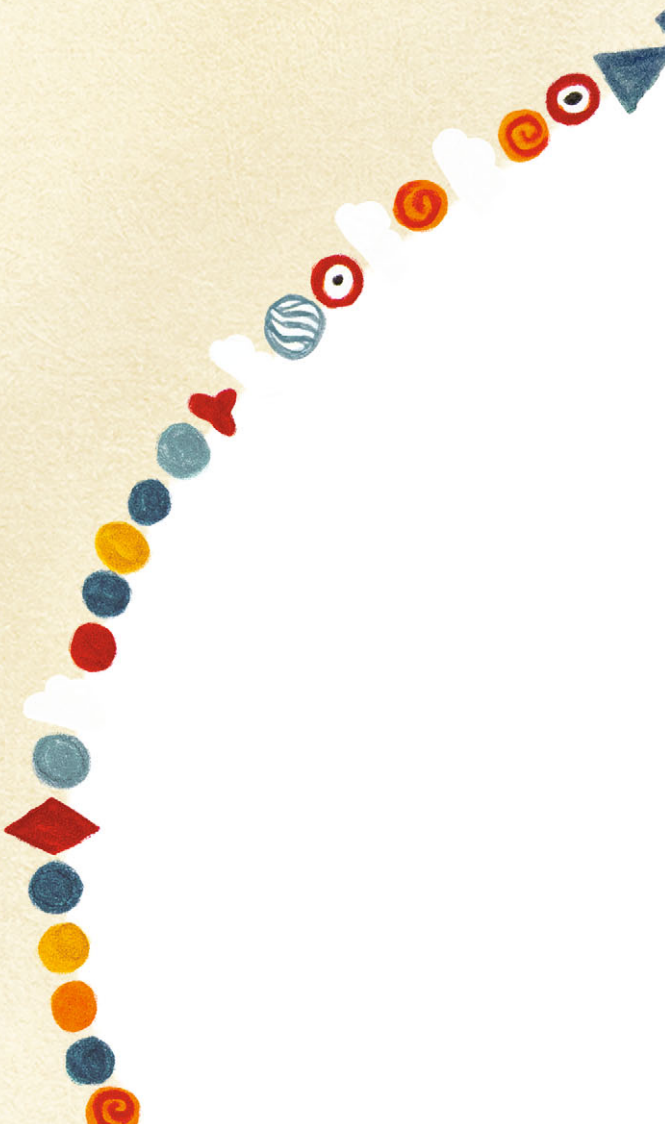
CNS tumors				Solid tumors							
Low grade glioma	High grade glioma	Embryonal tumors of the CNS	Craniopharyngioma	Neuroblastoma	Osteosarcoma	Ewing sarcoma	Rhabdomyosarcoma	Non-rhabdomyo-sarcoma STS	Liver tumor	Kidney tumor	Extracranial germ cell tumor
NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC
NPC	NPC	NPC	NPC	NP1	NP1	NP1	NP1	NP1	NP1	NP1	NP1
A	C	NP1	A	NP1	NP1	NP1	NP1	NP2	NP1	NP1	NP1
NPC	NP1	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC
NP1	NP1	NP2	NP1	NP2	A	A	NP1	A	B	NP1	NP2
C	NP2	C	A	NP2	NP2	NP2	NP2	NP2	NP2	B	NP2
C	C	C	C	NP2	C	A	NP1	NP2	B	NP2	B
NP1	NP2	NP1	C	NP1	NP2	NP2	NP1	NP1	NP1	NP2	NP2
NP1	NP2	NP2	C	B	NP1	NP2	B	NP2	NP1	NP2	NP2
NP2	C	NP1	NP2	NP2	NP2	NP1	NP2	NP2	NP2	B	B
NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC
B	A	B	C	NP2	NP2	NP2	NP2	B	NP2	NP1	NP2
NP2	NP2	NP2	NP2	NP1	NP2	B	NP2	NP2	NP2	NP2	NP2
NP2	NP1	NP1	NP1	NP1	NP1	NP2	NP2	NP1	NP1	NP2	NP2
NP2	A	A	C	NP2	NP2	A	NP1	NP2	NP1	NP2	NP1

Supplementary Table 6. Prioritized outcomes in the first and second round of the 17 Delphi surveys (part of step 2) (continued)

	Hematological malignancies				
	Acute lymphoblastic leukemia	**Acute myeloid leukemia**	**Hodgkin lymphoma**	**Non-Hodgkin lymphoma**	**Langerhans cell histiocytosis**
Quality of life outcomes: psychosocial aspects					
Significant psychological or psychiatric concerns	NPC	NPC	NPC	NPC	NPC
Social problems***	NP2	NP2	NP2	NP2	NP2
Quality of life outcomes: neurocognitive aspects					
Educational or employment problems	NP2	NP1	NP2	B	NP2
Neurocognitive problems	A	C	NP2	B	C

A indicates level A agreement, B indicates level B agreement, and C indicates level C agreement in the second Delphi round, with criteria for each level of agreement specified in the manuscript. NPC (**n**ot **p**rioritized in **c**andidate outcome list) indicates an outcome was not included in the survey's candidate outcome list. NP1 (**n**ot **p**rioritized in **1**st Delphi round) indicates an outcome was included in the candidate outcome list, but not prioritized in the first Delphi round. NP2 (**n**ot **p**rioritized in **2**nd Delphi round) indicates an outcome was included up to the first Delphi round, but not prioritized in the second Delphi round. Outcomes are named based on the final wording, which might have changed based on participant feedback during the Delphi surveys. *New outcome suggested in the first Delphi round. **Full outcome name: reduced independence or autonomy with age-appropriate daily living tasks. ***Full outcome name: Social problems, including difficulties with peers or relationships. CNS, central nervous system; LCH, Langerhans cell histiocytosis; NP1, not prioritized in the first Delphi round; NP2, not prioritized in the second Delphi round; NPC, not prioritized for candidate outcome list; STS, soft tissue sarcoma.

	CNS tumors				Solid tumors							
	Low grade glioma	**High grade glioma**	**Embryonal tumors of the CNS**	**Craniopharyngioma**	**Neuroblastoma**	**Osteosarcoma**	**Ewing sarcoma**	**Rhabdomyosarcoma**	**Non-rhabdomyo-sarcoma STS**	**Liver tumor**	**Kidney tumor**	**Extracranial germ cell tumor**
	NP2*	NP2*	NPC	NP2*	NPC	NPC	NPC	NPC	NPC	NPC	NPC	NPC
	NP2	B	A	A	NP2	NP2	NP2	NP1	B	NP2	NP2	B
	C	A	A	C	NP1	NP2	B	NP2	NP2	NP2	NP2	NP2
	A	A	A	C	NP2	NP1	NP1	NP2	NP1	NP2	NP2	NP2



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Summary and general discussion

Most children diagnosed with cancer will survive five or more years. This thesis aimed to contribute to the quality of their survival by developing a person-centered approach to survivorship care, providing a better understanding of their risk of pulmonary late effects after treatment with cyclophosphamide, and facilitating outcome-based evaluation to improve the quality of care. In this chapter, I will first highlight and reflect on the main findings of both parts of this thesis. This is followed by several recommendations for clinical practice, survivorship research, and care evaluation.

PART 1: LIFE AFTER CHILDHOOD CANCER AND THE IMPORTANCE OF SURVIVORSHIP CARE

The concept of cancer survivorship and models of care

Main findings

In **Chapter 2**, we explored the concept of cancer survivorship and described models to organize and provide long-term follow-up care. In summary, survivorship conceptually begins at the moment of diagnosis, and continues throughout treatment and thereafter, regardless of achieving remission or cure. Long-term survival is defined as five years or more after diagnosis. In this chapter, we specifically focused on the spectrum of endocrine late effects, their risk factors and recommended surveillance strategies. Well-known late endocrine toxicities of a childhood cancer diagnosis and treatment include hypothalamic-pituitary dysfunction, primary thyroid dysfunction, primary gonadal injury, metabolic syndrome, obesity, diabetes mellitus, and low bone mineral density. Evidence-based guidelines, including those by the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG), guide healthcare providers in deciding who should receive surveillance for these late effects, when it should be initiated, at which frequency it should be repeated, and how to proceed if abnormalities are identified. The model of care can vary greatly, not only depending on the healthcare system, but also on the preferences of the survivor and their healthcare provider. Most commonly, care is delivered by the cancer center, but alternatives are general practitioner-led or shared care, or supported self-management. Key elements include guidance by a multidisciplinary team at a cancer survivorship expert service or cancer center, as well as the provision of an individualized survivorship care plan with a summary of cancer treatment and personal recommendations based on clinical practice guidelines.

The PanCareFollowUp project

Main findings

Chapter 3 introduced the PanCareFollowUp project, initiated to improve the health and quality of life of childhood cancer survivors by facilitating the implementation of person-centered survivorship care across Europe. We described how the project is structured in eight work packages, focusing on the development and evaluation of the PanCareFollowUp Care Intervention, the development and evaluation of the PanCareFollowUp eHealth Lifestyle Intervention, dissemination of results, establishment of policy recommendations, management of the project, and ethics.

Reflection

Despite wide recognition of the importance of long-term follow-up to prevent late effects or detect them in an early stage, many adult survivors of childhood cancer still do not have access to such care (1-3). Similar challenges are faced around the world, and include a lack of personnel and funding, insufficient time, limited awareness among survivors and their healthcare providers, and high out-of-pocket expenses (4). PanCareFollowUp is an example of international collaboration to synergize efforts and expertise to reach the common goal of lifelong follow-up care for survivors. In analogy to previous PanCare projects, the work was efficiently divided among the fourteen project partners, representing ten European countries (5, 6). Milestones and deliverables ensured that project aims were met in time, and that inter-dependencies did not result in a delay of the work. The COVID-19 pandemic arose just before the Care and Lifestyle studies were planned to start recruitment. Globally, acute clinical care was prioritized over elective care and research, and many long-term follow-up clinics were temporarily closed (7). Despite this unanticipated challenge, there were only minor delays in interim project deadlines. Key aspects of this success were continued online meetings, a common understanding of the importance of the project and its specific goals, and regular review and mitigation of potential threats to the planning. Moreover, the study sites shared a strong feeling of responsibility and involvement, with some centers reinforcing their recruitment when others had to pause, also reflecting the differences in COVID-19 management across Europe.

The PanCareFollowUp Care Intervention

Main findings

In **Chapter 4**, we described the PanCareFollowUp Care Intervention which was developed by survivors, clinicians, and researchers. The aim was to empower survivors through knowledge about their treatment history, shared decision-making about surveillance options, and awareness about a healthy lifestyle and other beneficial choices within their influence. The three-step approach (including pre-visit preparation, a clinic visit and a follow-up call) was designed to allow flexible implementation in different healthcare systems, while maintaining key requirements such as a treatment summary and personalized surveillance recommendations (8). Core groups were leading in the development of the Survivor Questionnaire, Treatment Summary template, Survivorship Care Plan template, and information materials. Feedback rounds among the PanCareFollowUp Consortium and survivors external to the project helped to further refine and improve each of the components. For the purpose of the PanCareFollowUp Care Study, these documents were translated from English to Czech, Dutch, Italian and Swedish. Post-project updates of these materials are included in a Replication Manual which will be made freely available.

Reflection

The main aim of the PanCareFollowUp project was to improve access to long-term follow-up care. Therefore, the strengths and limitations of the PanCareFollowUp Care Intervention will be discussed in a structured way according to the Levesque framework for patient-centered access to healthcare (9). This model was previously applied to long-term follow-up care after childhood, adolescent and young adult cancer by McLoone and

colleagues, to identify supply- and demand-side factors that can be modified to optimize care pathways (4). The framework uses a multilevel perspective, including relevant factors for those providing (i.e., health systems, institutions, and healthcare providers) and receiving (i.e., individuals, households, communities and populations) care. Levesque and colleagues defined access as "the opportunity to identify healthcare needs, to seek healthcare services, to reach, to obtain or use healthcare services, and to actually have a need for services fulfilled". Based on published literature, they conceptualized five dimensions of accessibility of services: 1) Approachability; 2) Acceptability; 3) Availability and accommodation; 4) Affordability and 5) Appropriateness. Furthermore, they defined five dimensions of personal abilities that are required to turn accessibility into access: 1) Ability to perceive; 2) Ability to seek; 3) Ability to reach; 4) Ability to pay, and; 5) Ability to engage. The PanCareFollowUp Care Intervention will be appraised according to these five dimensions and abilities in the context of childhood cancer survivorship.

The first dimension (Approachability and Ability to perceive) includes aspects such as not knowing about the existence of long-term follow-up services, lack of knowledge about the initial treatment and potential late effects, or the notion that surveillance and survivorship care are only relevant for those with current health issues (10-14). A structured transition from pediatric to adult healthcare services, as increasingly implemented, will likely support awareness about a survivor's treatment history and potential late effects. Reaching those that were treated in the earlier eras, however, continues to be challenging. Survivors lost to follow-up can sometimes be retraced, but might also have moved, changed their contact details, or died (15). For those (re-) engaged in long-term follow-up, the PanCareFollowUp Care Intervention improves their understanding about their need for survivorship care by providing and discussing the survivor's Treatment Summary and Survivorship Care Plan in partnership between the survivor and the healthcare provider. Recent studies indicate that survivorship care plans result in a significantly improved health literacy among childhood cancer survivors and their parents as well as a higher attendance of subsequent follow-up care (16-19). Actively involving the survivor while respecting their narrative promotes conversations and care decisions which are aligned with the values and preferences of the survivor (20, 21). Notably, certain subgroups seem to benefit less or not at all from using a survivorship care plan (16, 17). It remains to be studied how to effectively reach all survivors, especially those with the highest need of long-term follow-up care. For example, game-based learning might be much more appealing among younger survivors of childhood cancer and showed a significant improvement in knowledge about late effects (22).

Supply-side factors represented in the second dimension (Acceptability and Ability to seek) include an underappreciation of survivorship issues by healthcare organizations, and thereby limited support in initiating and continuing long-term follow-up services for survivors in oncology-focused settings (1, 2, 23, 24). Meanwhile, primary care providers indicate a feeling of inexperience and insufficient knowledge regarding the management of late effects, in addition to limited time and financial resources to provide such care (25, 26). These issues require different approaches. The PanCareFollowUp Care Intervention, a cancer-center led care model, is expected to increase awareness and confidence among primary care providers through the shareable Survivorship Care Plan. Using this document, they can be informed about the delivery of survivor-related care and the availability of expertise centers and guidelines (14). In addition, primary care physicians

can take the lead on care within their field of expertise (e.g. cardiovascular risk or chronic kidney disease management), with the long-term follow-up clinic staying in charge of surveillance recommendations and guideline updates. However, acceptability on the healthcare provider and policy level demands further attention. For example, fellowships in childhood cancer survivorship might familiarize physicians with the concept of long-term follow-up (27). The results of the Care Study might also contribute to a better understanding of the benefits of person-centered survivorship care. This will support the integration of lifelong follow-up in the care pathway for any child with cancer. On the demand-side, attendance is better for those with higher health-related self-efficacy and those feeling ready to transition before they move from pediatric to adult healthcare settings (24, 28-30). In contrast, those with cognitive impairment are less likely to attend planned clinic visits, whereas these survivors may be at higher risk for other late effects and more in need of risk-based surveillance (31). Person-centered care, as integrated in the PanCareFollowUp Care Intervention, combines evidence-based surveillance with a holistic view. It acknowledges that the survivor may have physical, mental and social health needs and that these may depend on personal preferences and values (20). The approach consists of three main elements: 1) initiating a provider-survivor partnership by focusing on the survivor's perspective on life and health; 2) integrating this partnership through information sharing; and 3) safeguarding the partnership by considering and discussing the individual's preferences and values in care decisions (32). Using this empowering strategy which supports them to manage their own healthcare needs, less survivors might be lost to follow-up. Another important consideration is the reluctance of some survivors to engage with long-term follow-up care due to painful emotions or a fear of discovering late effects or a cancer recurrence (11, 33). The PanCareFollowUp Care Intervention specifically addresses worries and fears in the Survivorship Questionnaire. If issues emerge, these can be further explored during the clinic visit, with specialist referral for psychological or social support if needed. Acknowledgement and validation of their concerns may prevent disengagement from care. Recent work indicated that healthcare providers are conscious of the risk of increased distress due to a survivorship care plan, although survivors mostly reported positive effects (18, 34). Nonetheless, aspects such as the need for information and support, cognitive abilities, coping style and personal preferences warrant further exploration in future studies in order to optimally support a survivor's ability to seek care.

The third dimension (Availability, Accommodation and Ability to reach) underscores the importance of established long-term follow-up programs with survivorship expertise and close collaboration with other subspecialists (1, 30, 35, 36). The PanCareFollowUp Care Intervention very specifically addresses availability of care, as it provides institutions with many of the materials needed to initiate a long-term follow-up clinic. For survivors with potential access to a late effects clinic, a longer travel distance and restricted opening hours can be additional barriers to participate in follow-up care (33, 37). Other common obstacles relate to transportation, responsibilities regarding childcare or informal care, or work commitments (31, 33, 38). The PanCareFollowUp Care Intervention partly mediates these issues by efficiently planning potential surveillance tests on the day of the clinic visit, leveraging the information collected beforehand through the Treatment Summary and Survivor Questionnaire. Moreover, a post-visit phone call is used to finalize the Individualized Survivorship Care Plan, reducing the travel time. Other studies

suggested that leveraging virtual care services and delivering interventions remotely could facilitate attendance (39-41). Nevertheless, a recent study on a completely distance-delivered program indicated that survivors only recalled 1.9 of their average of 6.6 recommendations correctly, and 56% did not adhere to any of the recommendations after six months (42). However, similar numbers are found throughout the landscape of healthcare, with up to 70% non-compliance when lifestyle changes are required (43). This exemplifies the challenging nature of changing health behaviors and the importance of a person-centered approach. Including a clinic visit, as in the PanCareFollowUp Care Intervention, might be more effective than using telephone or videoconference meetings only. Another alternative would be to use other models which allow care provision closer to home, such as primary-led care. However, limited expertise on survivor-specific issues, as discussed in the first dimension, remains an influential barrier among primary care providers, with most survivors preferring follow-up by a medical oncologist (14, 44, 45).

The fourth dimension (Affordability and Ability to pay) includes financial factors on both the supply- and demand-side. Healthcare providers experience limitations due to insufficient funding and, partly related to this issue, staff shortages (2). On the survivor side, limited reimbursement and high out-of-pocket expenses can be important factors that affect their ability to pay, as well as the fear of losing insurance coverage after the detection of late effects (24, 37, 38, 46). These factors might be less influential in countries with universal health coverage. In addition, the "right to be forgotten", which has been implemented in several European countries including the Netherlands, may limit the adverse financial impact of being a childhood cancer survivor as it ensures eligibility for life insurance and mortgages regardless of a survivor's medical history (47). Although the PanCareFollowUp Care Intervention does not specifically address the financial impact, we did collect costs incurred by the healthcare provider and survivor as part of the Care Study. This will allow a comprehensive assessment of the costs associated with the person-centered care visit in relation to short-term and projected long-term effects.

Lastly, the fifth dimension (Appropriateness and Ability to engage) includes supply-side elements such as insufficient knowledge about and adherence to existing guidelines among healthcare providers, limited multidisciplinary care and poor coordination and continuity of care (23, 25, 26, 48). Several components of the PanCareFollowUp Care Intervention address these barriers. For example, the Survivorship Care Plan helps to educate healthcare providers about a survivor's treatment-related risks and communicates evidence-based recommendations to specialists and the primary care physician (19, 49, 50). In a Swedish study, a care plan helped improve the adherence to breast cancer screening guidelines among female childhood cancer survivors, leading to the detection of three novel cases (51). A promising perspective in this regard is the development of digital support tools that can generate and provide survivorship care plans using treatment information and the most recent guidelines. These instruments, such as the European Survivorship Passport (34) and US-based Passport for Care show significant improvement in guideline adherence (52, 53). However, their implementation is not straightforward and includes the consideration of many ethical, legal, social, economic and technological aspects (34, 54). Important factors regarding the ability to engage are independence and personal responsibility (37, 55). Similar to other chronic conditions, self-management skills are essential among survivors to understand their treatment-related risks, monitor symptoms, set goals, and seek care when needed (49,

56). With empowerment as a fundamental outcome, the person-centered approach in PanCareFollowUp Care may positively impact on the ability of survivors to engage in care.

The PanCareFollowUp Recommendations

Main findings

In **Chapter 5**, we presented the PanCareFollowUp Recommendations. We used a pragmatic methodology to develop recommendations for long-term follow-up care for relevant topics where no evidence-based IGHG guidelines existed. This included reviewing four existing national long-term follow-up guidelines for answers to six clinical questions: 1) Who needs surveillance?; 2) What surveillance modality should be used?; 3) At what age and time should surveillance be initiated?; 4) At what frequency should surveillance be performed?; 5) When should surveillance be discontinued?; and 6) What should be done when abnormalities are identified? For conditions that would benefit from prevention, we added an additional question: 7) What standard recommendations should be given to survivors at risk? If three out of four guidelines agreed, we adopted their recommendation, whereas topics with less or no concordance were discussed within the Working Group to reach agreement. The resulting 25 consensus-based recommendations describe strategies including awareness only (n = 6), awareness, history and/or physical examination (n = 9), or additional surveillance tests (n = 10), and complement the existing IGHG guidelines in anticipation of evidence-based guidance for these topics.

Reflection

Following their publication, these recommendations have not only been implemented at the four study sites of the PanCareFollowUp Care Study, but are currently being used in various European countries, including Germany and Austria (57). As anticipated, several IGHG guidelines have been published since, covering topics such as bone mineral density surveillance (58), dexrazoxane cardioprotection (59), and education and employment outcomes (60), while guidelines on cardiomyopathy surveillance and subsequent breast cancer have been updated (61, 62). An update of the PanCareFollowUp Recommendations by PanCare is expected in 2024. As many of the consensus-based topics presented in this chapter have not been addressed by the IGHG yet, our work remains relevant for current clinical practice in anticipation of evidence-based guidelines. A benefit of the pragmatic approach of the PanCareFollowUp Recommendations was the accelerated process of only nine months to develop 25 consensus-based recommendations. An average evidence-based guideline, by contrast, can take multiple years. A solution integrating evidence-based precision and condensed timelines might lie in the concept of living guidelines (63). Using automated searches, the process is optimized so individual recommendations can be updated once new relevant evidence is released and identified. Frequent, smaller updates may be more feasible and ensure the translation of the most recent evidence to clinical practice. Most living guidelines have been found to stay up-to-date, but the risk of exceeding the planned period of being updated still exists and remains dependent on the continued efforts of the guideline panel (64).

The PanCareFollowUp Care Study

Main findings

Chapter 6 introduced the protocol for the PanCareFollowUp Care Study, designed to evaluate the feasibility, effectiveness and costs of implementing the PanCareFollowUp Care Intervention. In this prospective cohort study, 800 survivors receive the PanCareFollowUp Care Interventions at four study sites in Belgium, the Czech Republic, Italy and Sweden. Follow-up is performed until six months after the clinic visit. The survivor-reported outcomes, survivor-reported experiences, clinical outcomes and feasibility outcomes will be described and analyzed with attention to the repeated measurements, the multicenter design, the use of multiple testing, and potentially relevant subgroups. Moreover, the health economic outcomes provide insight into the costs associated with implementation, as well as observed and modeled benefits. The data is managed centrally by one of the project partners. The Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM) framework has been used to assess the impact of the PanCareFollowUp Care Intervention throughout the project and after the study ended.

Reflection

Although long-term follow-up care is widely endorsed, evidence on the efficacy and cost-effectiveness is very limited. Survivors that attended follow-up demonstrated better awareness about their cancer diagnosis, treatment, and late effects, and had less hospitalizations than non-attendees (15, 65). There is also some evidence pointing toward the cost-effectiveness of specific surveillance strategies and interventions (66-69). However, at the start of the PanCareFollowUp project, the comprehensive approach of person-centered care had not been evaluated yet. Recently, a program aimed at childhood cancer survivors disengaged from cancer-related follow-up care was piloted in Australia (15). Recognizing similar challenges in initiating and providing survivorship care, the “Re-engage” program was developed as a distance-delivered, nurse-led intervention aiming to educate and empower survivors (15). Their target population is similar to that of the PanCareFollowUp Care Study, but the intervention is slightly different, as it completely relies on videoconferencing software and telephone calls, with recommended surveillance performed by specialists or primary care services after referral. However, their primary outcome is similar: health-related self-efficacy measured at baseline, one month and six months post-intervention, with initial reports indicating a significant increase due to the intervention. However, despite experiencing the program as beneficial, survivors did not show significant improvement on health behaviors, and demonstrated low recall of and adherence to individualized healthcare recommendations (15, 42). Perhaps a clinic visit, as included in the PanCareFollowUp Care Intervention, is more efficient to tailor the information to the needs of the survivor, thereby resulting in better adherence to recommendations and future follow-up (14). Analyses on the cost consequences were planned according to the Re-engage study protocol, but have not been published yet. Compared to Re-engage feasibility study, the PanCareFollowUp Care Study provides an equally comprehensive evaluation of person-centered follow-up care and its effects on empowering survivors. Moreover, it is analyzed in a larger study population (800 compared to 30 survivors). In addition, it will provide insight in variations according to healthcare system and country, which is relevant information in

the European context. Lastly, the cost-effectiveness evaluations will provide the much-needed knowledge about the costs associated with implementing person-centered follow-up care in relation to the expected benefits. Together, this information will be valuable to healthcare providers, managers and policy makers to efficiently allocate resources and improve access to long-term follow-up care for all survivors of childhood cancer in Europe.

The DCCSS-LATER 2 PULM sub-study

Main findings

In **Chapter 7**, we examined long-term pulmonary dysfunction in relation to cyclophosphamide exposure among childhood cancer survivors. In this Dutch Childhood Cancer Survivor Study (DCCSS)-LATER 2 PULM sub-study, 828 survivors that had been treated with cyclophosphamide and/or pulmonary toxic treatment, and controls, completed a questionnaire, a clinic visit and a pulmonary function test. Our primary outcomes included diffusion abnormalities, restrictive dysfunction, and obstruction measured by a pulmonary function test. Secondary outcomes were chronic cough or recurrent respiratory tract infections identified by a questionnaire, and shortness of breath or supplemental oxygen need observed during a clinic visit. Consistent with previous studies, diffusion and restriction abnormalities were most prevalent among those treated with pulmonary toxic treatment (70-72). We constructed several multivariable logistic and linear regression models to examine the association between cyclophosphamide and several pulmonary outcomes with adjustment for relevant confounders, such as pulmonary toxic treatment, age at diagnosis, attained age, clinically relevant cardiac dysfunction and smoking. The linear regression on total lung capacity z-score, indicative of restrictive dysfunction, showed a 0.3 point reduction after a cumulative cyclophosphamide dose of ≥10 g/m^2. However, this is a modest effect compared to the lower limit of normal for restrictive dysfunction at a TLC z-score of -1.65. Moreover, the logistic regression on diffusion impairment showed an odds ratio of 2.0 for those treated with a cumulative cyclophosphamide dose of 5,000-10,000 mg/m^2, but did not provide further evidence for a dose-response relationship. We concluded that there were no clinically relevant effects of cyclophosphamide on any of the primary or secondary outcomes.

Reflection

Our study was the first to be able to clearly distinguish between the adverse effects of cyclophosphamide and pulmonary toxic treatment. Strengths included the leverage of the DCCSS-LATER cohort (1963-2001) as a long-term population-based cohort and inclusion of a survivor control group. Moreover, we performed clinical evaluation of most outcomes, used contemporary reference equations for the pulmonary function tests, and had accurate data on diagnosis, treatment and relevant confounders (73, 74). In addition, multiple imputation helped to increase the accuracy and statistical power of our analyses (75). However, our findings should be interpreted in the context of a few limitations. Due to the study design, we could not account for the impact of lung complications during cancer treatment on long-term pulmonary health, nor could we evaluate longitudinal changes (76-78). Also, the use of pulmonary function tests performed according to surveillance guidelines for those exposed to pulmonary toxic treatment might have

produced selection bias, which means that the impact of pulmonary toxic chemotherapy, radiotherapy or surgery might be over- or underestimated. In summary, our results can be used to strengthen evidence-based pulmonary surveillance recommendations for many survivors of childhood cancer treated with cyclophosphamide, but without established pulmonary toxic treatment.

PART 2: EVALUATING THE QUALITY OF CARE FOR CHILDHOOD CANCER PATIENTS AND SURVIVORS

Clinical practice guidelines and quality indicators in pediatric oncology

Main findings

In **Chapter 8**, we described the importance of clinical practice guidelines and quality indicators in pediatric oncology. Through systematic reviews of clinical research, the most recent and relevant evidence is translated to clinical guidance. Quality indicators are an important tool in the evaluation of the quality of care that is provided. These measurable elements of clinical practice give insight about the processes (e.g., adherence to surveillance recommendations), structures (e.g., the availability of a long-term follow-up clinic) or outcomes (e.g., survival rates or low occurrence of adverse health outcomes) that are associated with high-quality care.

The International Childhood Cancer Core Outcome Set to measure quality of survival

Main findings

In **Chapter 9**, we presented the International Childhood Cancer Core Outcome Set. In close collaboration with parent and survivor representatives and healthcare providers worldwide, we prioritized the outcomes which are most relevant in defining quality of survival after childhood cancer. Using this metric, institutions can measure their own progress over time or benchmark with peers. This will benefit the quality of care in pediatric oncology. A total of 24 physical, psychosocial and neurocognitive outcomes were selected to capture quality of survival for 17 types of childhood cancer. Agreement was found on outcome definitions and measurement instruments, which include medical record abstraction, questionnaires (for patients, survivors and/or healthcare providers), or linkage with existing registries.

Reflection

The International Childhood Cancer Core Outcome Set integrated the perspectives of many stakeholders to provide a comprehensive but concise selection of outcomes. Using outcomes to evaluate the quality of care has increasingly gained attention since the introduction of value-based healthcare in 2010 (79). Porter defines value as “health outcomes achieved per dollar spent”, shifting the focus from the amount of work performed or the volume of services delivered to the results that are achieved. Other important elements of value-based healthcare include an emphasis on the patient perspective, recognition that relevant outcomes are condition-specific and multidimensional, and the promotion of standardized outcome measurement as a tool to better understand value and identify opportunities for improvement (80). In the Netherlands, the implementation of outcomes measurement was accelerated by the

2018-2022 program "Value-based healthcare" by the Dutch Association of Hospitals. It focused on three pillars: 1) learning and improving using outcome data; 2) learning and improving using patient experiences; and 3) promoting shared decision-making. One of its ambitions was to use value-based healthcare for at least 50% of the disease burden by the end of the program.

Core sets of outcomes for different conditions and populations are essential to harmonize outcome measurement and allow benchmarking between institutions. By the start of our project, these had been defined for several types of adult cancer, as well as for childhood acute lymphoblastic leukemia and brain tumors (81-91). However, our project was the first to cover most types of pediatric cancers, agree on harmonized definitions and measurement instruments across all included subtypes, and involve many different stakeholders including childhood cancer survivors in the decision-making process. Some of the lessons learned that were recently published by the International Consortium for Health Outcomes Measurement (85) were already integrated in our project, such as the use of the Delphi methodology to form consensus and the engagement of survivor representatives throughout the process (92). The physical, psychosocial and neurocognitive outcomes prioritized in the International Childhood Cancer Core Outcome Set cover several of the domains outlined by ICHOM. These include disutility of care (i.e., early and late adverse effects of cancer treatment), functioning and quality of life, and survival and disease control (92).

Agreement on the International Childhood Cancer Core Outcome Set is only the starting point toward outcome-based evaluation of care. The next step is integration of outcome measurement in clinical practice. Implementation requires the alignment and engagement of many stakeholders. Experiences with health outcomes measurement in other fields can inform about effective strategies in pediatric oncology. For example, continued patient involvement has been shown to be an important facilitator for successful implementation, in addition to a high quality database, frequent reporting and feedback, engagement and leadership (93). Nevertheless, despite the added value for understanding experiences and care pathways, patient engagement can also be challenging (94). Clarification about the role of patients, survivors and caregivers throughout the implementation process will help to involve them where needed most. Moreover, our strategy to define harmonized measurement instruments across the 17 types of childhood cancer will be advantageous to the standardization and comparability of results (92). Lastly, it would be worthwhile to explore the use of dashboards to display and evaluate outcomes, as end users describe them as "thrilling" and highly motivating to complete outcome registration (94).

RECOMMENDATIONS

Recommendations for clinical practice

Provide person-centered long-term follow-up care to empower survivors in managing their own healthcare needs and navigating the healthcare system.

Share and discuss a summary of treatment and personalized evidence-based surveillance recommendations with each survivor of childhood cancer by the end of their treatment, to improve awareness of their risk of late effects and their need for lifelong follow-up and to ensure they receive high-quality care.

Recommendations for clinical practice (continued)

Establish a structured transition process from pediatric to adult healthcare settings to support survivors in obtaining self-management skills and reduce the number lost to follow-up at this crucial moment.

Establish a structured transition process from pediatric to adult healthcare settings to support survivors in obtaining self-management skills and reduce the number lost to follow-up at this crucial moment.

Perform surveillance for late health problems of childhood cancer treatment, including pulmonary effects, according to published long-term follow-up guidelines.

Recommendations for survivorship research

Collaborate in multidisciplinary national or international research networks to effectively address relevant knowledge gaps while integrating different perspectives and types of expertise.

Include childhood cancer survivor representatives in the design, conduct and evaluation of research to ensure the results meet their needs.

Evaluate interventions aiming to improve access to long-term follow-up with attention for supply-side (i.e., health systems, institutions, and healthcare providers) and demand-side (i.e., individuals, households, communities and populations) factors, to correctly identify which dimensions are being targeted and to highlight which barriers and facilitators regarding the accessibility of healthcare and the abilities of survivors require further attention.

Study the effects of receiving a survivorship care plan on positive outcomes such as empowerment, health and quality of life, but also take into account the potential risk of increased anxiety and distress. Furthermore, explore the factors that can influence the effectiveness of providing a survivorship care plan in improving a survivor's health literacy and self-management skills, and use this knowledge to develop targeted strategies to support survivors in their abilities to seek and receive appropriate care.

Collect information on the costs associated with novel long-term follow-up strategies, so effective approaches can be evaluated on a health economic level and used to optimize care pathways.

Investigate the potential of living guideline tools to support and accelerate the development of new evidence-based guidelines and the update of existing recommendations.

Implement statistical methods to improve the accuracy and power of research in the presence of missing data, for example by performing multiple imputation, and consider causality relations between variables during the study design and analysis.

In future studies on long-term pulmonary health, focus on a better understanding of the significance of diffusion impairment and restrictive dysfunction, to differentiate between (subclinical) confirmed interstitial lung disease and microscopic damage to the lung tissue.

Recommendations for evaluation of care
Leverage known facilitators (e.g., continued patient involvement, high quality database, interactive dashboards, frequent reporting and feedback, engagement and leadership) to improve the successful implementation of outcome-based evaluation and provide insight into the progress in improving the quality of care at the Princess Máxima Center.
Involve other pediatric oncology centers in the implementation of the International Childhood Cancer Core Outcome Set to facilitate benchmarking and the identification of best practices to further improve the quality of care.

CONCLUSIONS

The research described in this thesis aimed to contribute to the health and wellbeing of childhood cancer survivors from diagnosis throughout their lives. We described the development and evaluation of a person-centered care model, provided a better understanding of the potentially pulmonary toxic effect of cyclophosphamide, and defined an international core outcome set to measure quality of survival. This work has resulted in several tools and recommendations which are currently being used or implemented to provide, improve and evaluate clinical care. Moreover, the results can be used to further strengthen surveillance guidelines and have given rise to new research questions. In the context of limited resources, future efforts should continue to involve childhood cancer survivors ensure that research and care are aligned to meet their needs.

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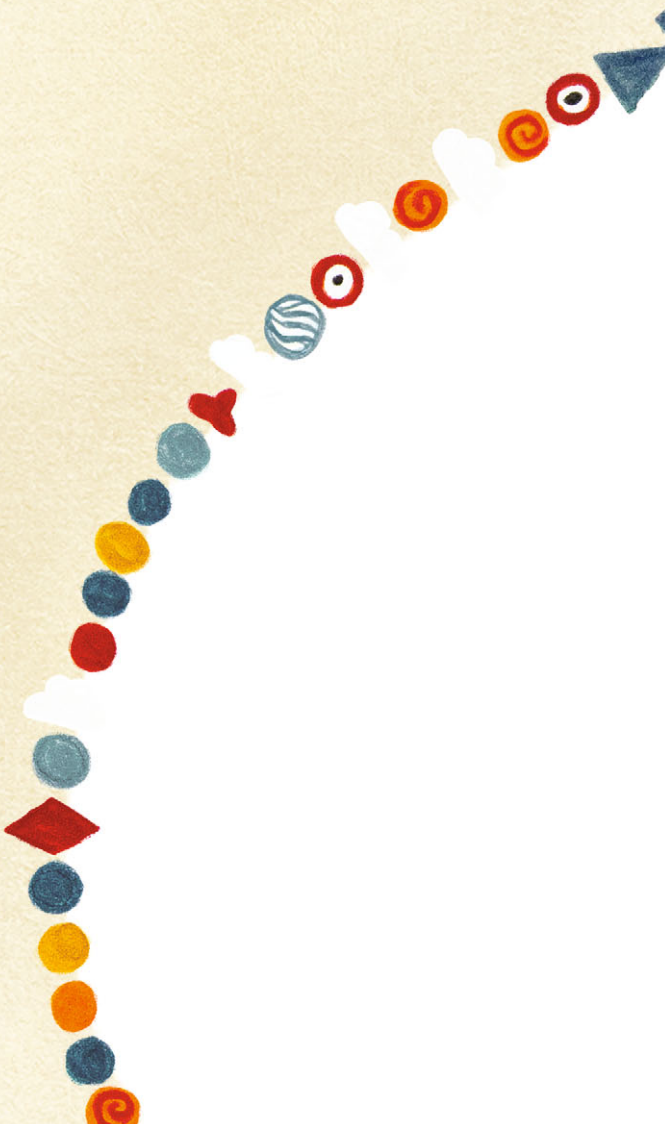


11

Nederlandse samenvatting

Ieder jaar wordt bij ongeveer zeshonderd kinderen in Nederland kanker vastgesteld. De kans op overleven na kinderkanker is in de afgelopen decennia sterk toegenomen door steeds betere behandelingen en ondersteunende zorg. Vijf jaar na de diagnose is nog meer dan 80% van de kinderen in leven. Helaas kunnen de kanker zelf, maar ook de behandelingen met bijvoorbeeld chemotherapie, bestraling, chirurgie en stamceltransplantaties bijwerkingen geven op de lange termijn. Deze fysieke en psychosociale late gevolgen, zoals hartfalen, verminderde vruchtbaarheid, tweede tumoren of vermoeidheid kunnen jaren later nog ontstaan en hebben een negatieve invloed op de kwaliteit van leven na kinderkanker.

Het is belangrijk om late effecten te voorkomen, waar mogelijk, of om deze zo vroeg mogelijk te ontdekken en te behandelen. Daarom wordt aangeraden om hier gedurende de rest van het leven gericht op te controleren. In Nederland heeft elke overlevende van kinderkanker (ook wel: survivor) toegang tot lange termijnzorg. Op Europees niveau bestaan hierin echter grote verschillen. Na het bereiken van de volwassen leeftijd worden de controles bij de kinderoncoloog vaak afgesloten, maar slechts een op de drie survivors van kinderkanker kan deze vervolgens voortzetten in de volwassen zorgsetting. Dit komt onder andere door een tekort aan tijd, onvoldoende zorgverleners, beperkte kennis over late effecten en ontoereikende financiële vergoedingen. Het Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer (PanCare) is in 2008 opgericht als samenwerking tussen professionals, survivors en hun families om de toegang tot en kwaliteit van lange termijnzorg in Europa te verbeteren. Vanuit dit oogpunt heeft PanCare meegewerkt aan verschillende Europese projecten, waaronder PanCareFollowUp. Het PanCareFollowUp Consortium bestaat uit veertien partijen uit tien Europese landen. Binnen het project is er onder andere gewerkt aan een persoonsgericht zorgmodel (de PanCareFollowUp Care Interventie) en een persoonsgerichte digitale zorginterventie voor het verbeteren van de leefstijl (de PanCareFollowUp eHealth Lifestyle Intervention). Persoonsgerichte zorg is afgestemd op de persoonlijke behoeften, wensen en voorkeuren van de survivor, in plaats van enkel zijn of haar medische toestand.

Evidence-based richtlijnen helpen om zorg te verlenen die is gebaseerd op de meest recente en betrouwbare wetenschappelijke inzichten. Ze beschrijven bijvoorbeeld na welke behandelingen voor kinderkanker er wel of geen onderzoek moet worden gedaan naar specifieke late effecten, hoe vaak er controle moet plaatsvinden en wat de vervolgstappen zijn als er afwijkingen worden gevonden. Aanvankelijk ontwikkelden verschillende landen hun eigen richtlijnen. Sinds 2010 wordt er binnen de International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) op internationaal niveau samengewerkt om evidence-based richtlijnen op te stellen voor het voorkomen, herkennen en behandelen van late effecten. Tot op heden zijn er 20 klinische praktijkrichtlijnen gepubliceerd. Voor een aantal belangrijke onderwerpen is de richtlijn echter nog in ontwikkeling, een proces dat vaak meerdere jaren duurt. In Europa speelt de PanCare Guidelines Group een rol in de ontwikkeling, implementatie en verspreiding van richtlijnen.

Onderzoek ligt aan de basis van evidence-based richtlijnen en helpt om inzicht te geven in het ontstaan van late effecten en effectieve behandelopties. Wereldwijd zijn er verschillende cohorten van mensen die als kind kanker hebben gehad. In Nederland heeft het Dutch Childhood Cancer Survivor Study (DCCSS)-LATER cohort (1963-2001) samen met de bijbehorende DCCSS-LATER studies deel 1 en 2 bijgedragen aan een

beter begrip van hartfalen, vruchtbaarheid, vermoeidheid, tweede tumoren, nierfalen, hoge bloeddruk, mondgezondheid, psychosociale gezondheid en mortaliteit bij survivors van kinderkanker. Een van de onderzoeksvragen betrof de lange termijn-invloed van cyclofosfamide op de longgezondheid. Binnen de DCCSS-LATER 2 PULM sub-studie is hier door middel van vragenlijstonderzoek, een poliklinisch bezoek en longfunctietesten in 828 deelnemers nauwkeurig naar gekeken.

De missie van het Prinses Máxima Centrum is om elk kind met kanker te genezen met optimale kwaliteit van leven. Hiervoor is zorg van de hoogste kwaliteit nodig. Inzicht in de genezingskans, maar ook in andere uitkomsten die de kwaliteit van overleven bepalen, is nodig om de voortgang in het bereiken van deze missie te kunnen beoordelen. Er bestond echter nog geen overeenstemming over de uitkomsten die van waarde zijn bij het evalueren van de kwaliteit van overleven en daarmee de kwaliteit van zorg. Bij het vaststellen van een set van belangrijkste uitkomsten is het van belang om de meningen en waarden van survivors van kinderkanker en verschillende zorgverleners mee te nemen, zodat er uitkomsten worden geprioriteerd die voor hen belangrijk zijn. Daarnaast is internationale samenwerking essentieel, omdat resultaten tussen verschillende centra alleen goed vergeleken kunnen worden als dezelfde uitkomsten op een vergelijkbare manier worden gemeten.

Dit proefschrift beoogt bij te dragen aan de kwaliteit van overleving na kinderkanker. Specifieke doelstellingen zijn: 1) het ontwikkelen van een persoonsgericht zorgmodel voor lange termijnzorg (PanCareFollowUp Care Intervention), inclusief richtlijnen voor de controles op late effecten en materialen voor de implementatie; 2) het opstellen van een studieprotocol om de haalbaarheid, effectiviteit en kosten van de implementatie van dit persoonsgerichte zorgmodel te evalueren in verschillende centra in Europa; 3) het bestuderen van de associatie tussen cyclofosfamide en lange termijnschade van de longen in Nederlandse survivors van kinderkanker; en 4) het vaststellen van een set van belangrijke uitkomsten voor 17 typen kinderkanker inclusief geharmoniseerde definities en meetinstrumenten.

DEEL 1: HET LEVEN NA KINDERKANKER EN HET BELANG VAN LANGE TERMIJNZORG

Het eerste deel van dit proefschrift geeft een introductie op het leven na kinderkanker en verschillende modellen voor lange termijnzorg, belicht verschillende aspecten van het PanCareFollowUp project en onderzoekt de potentiële longschadelijke effecten van cyclofosfamide.

In **hoofdstuk** 2 wordt beschreven dat het leven na kinderkanker al begint op het moment van de diagnose. Lange termijnsoverleving wordt gedefinieerd als vijf jaar of langer na diagnose. Het hoofdstuk richt zich specifiek op het spectrum van hormonale late effecten, ziekte- en behandelingsgerelateerde risicofactoren en aanbevolen diagnostische testen. Lange termijnzorg kan via verschillende zorgmodellen worden georganiseerd. Meestal wordt de zorg gecoördineerd vanuit een (kinder)oncologisch centrum, maar het kan ook worden aangeboden vanuit de huisarts, in samenwerking tussen huisarts en (kinder)oncologisch centrum, of als zelfmanagement door de survivor met ondersteuning vanuit een (kinder)oncologisch centrum waar nodig.

De opzet van het PanCareFollowUp project wordt gepresenteerd in **hoofdstuk 3**. PanCareFollowUp heeft als doel om de toegang tot lange termijnzorg in Europa te verbeteren. Acht werkgroepen hebben de verantwoordelijkheid over verschillende taken zoals de ontwikkeling en evaluatie van de PanCareFollowUp Care Intervention, ontwikkeling en evaluatie van de PanCareFollowUp eHealth Lifestyle Intervention, verspreiding van resultaten, opstellen van beleidsaanbevelingen, projectmanagement en ethiek.

In **hoofdstuk 4** wordt de ontwikkeling van de PanCareFollowUp Care Intervention beschreven. Dit persoonsgerichte zorgmodel is tot stand gekomen in samenwerking met survivors, zorgverleners en onderzoekers. Het bestaat uit drie stappen: 1) voorbereiding op het bezoek aan de polikliniek door de survivor (middels een voorbereidende vragenlijst) en door de zorgverlener (door het uitwerken van de behandelgeschiedenis); 2) een bezoek aan de polikliniek en 3) een telefoongesprek. Door deze strategie krijgen survivors een beter begrip van hun behandelgeschiedenis, kunnen zij samen met hun zorgverlener besluiten maken over hun lange termijnzorg en ontvangen zij voorlichting over het belang van een gezonde leefstijl. Hiermee worden zij in staat gesteld om regie te nemen over hun eigen gezondheid en zorgbehoeften. Als onderdeel van de PanCareFollowUp Care Intervention is er een voorbereidende vragenlijst voor de survivor (Survivor Questionnaire), een template voor de behandelsamenvatting (Treatment Summary) en een template voor het individueel zorgplan (Survivorship Care Plan) ontwikkeld. Ook is er informatie voor zorgverleners en survivors opgesteld.

Vervolgens worden in **hoofdstuk 5** de PanCareFollowUp Recommendations gepresenteerd. Voor onderwerpen waar nog geen IGHG richtlijn voor beschikbaar was, werd een pragmatische methodologie gebruikt om aanbevelingen te formuleren. Hiervoor werden vier bestaande nationale lange termijnzorg-richtlijnen gebruikt om zes klinische vragen te beantwoorden: 1) Wie heeft er een hoog risico?; 2) Welke diagnostiek zou moeten plaatsvinden?; 3) Wanneer moeten de controles worden gestart?; 4) In welke frequentie moeten de controles worden herhaald?; 5) Wanneer kunnen de controles worden afgerond?; en 6) Wat is de vervolgstap als er afwijkingen worden geconstateerd? Voor aandoeningen waarbij preventie een belangrijke rol speelt, werd er een aanvullende vraag gesteld: 7) Welke standaard aanbevelingen moeten worden gegeven aan survivors met een verhoogd risico op deze aandoening? Indien drie van de vier richtlijnen dezelfde aanbeveling beschreven, werd deze overgenomen. Bij onderwerpen waarbij er minder of geen overeenstemming bestond, werd er binnen de werkgroep overlegd. Dit resulteerde in 25 pragmatische aanbevelingen, gebaseerd op consensus, waarbij strategieën worden aanbevolen zoals bewustwording (n = 6), bewustwording, anamnese en lichamelijk onderzoek (n = 9) of aanvullende onderzoeken (n = 10). Deze aanbevelingen vormen een aanvulling op de huidige IGHG richtlijnen.

Hoofdstuk 6 beschrijft het protocol van de PanCareFollowUp Care Study. Deze studie is opgezet om de haalbaarheid, effectiviteit en kosten van de implementatie van de PanCareFollowUp Care Intervention te onderzoeken. In opzet worden 800 survivors van kinderkanker uitgenodigd om deel te nemen aan de PanCareFollowUp Care Intervention in vier centra in België, Tsjechië, Italië en Zweden. Zij worden vervolgd tot zes maanden na het bezoek aan de polikliniek. Verschillende gegevens worden verzameld, waaronder de ervaringen en het welbevinden van de survivor, klinische uitkomsten zoals het aantal nieuw ontdekte late effecten en informatie over de haalbaarheid en kosten van het

aanbieden van de PanCareFollowUp Care Intervention. De data wordt centraal beheerd door een van de projectpartners. Door middel van het Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM) framework wordt gedurende en na de studie beoordeeld welk effect de PanCareFollowUp Care Interventie heeft.

In **hoofdstuk 7** is gekeken naar de associatie tussen cyclofosfamide en late longproblemen. De behandeling tegen kinderkanker kan schadelijk zijn voor de longen en bijvoorbeeld leiden tot een kleinere longinhoud of verlittekening van het longweefsel. Voorbeelden van bekende longschadelijke behandelingen zijn bepaalde soorten chemotherapie (bleomycine, busulfan, carmustine en lomustine), bestraling van de longen (als specifiek veld of als onderdeel van totale lichaamsbestraling) of operatie aan de longen of borstkas. Indien iemand een van deze behandelingen heeft gekregen, wordt er aangeraden om de longfunctie te vervolgen. In de jaren '70 werd echter ook beschreven dat cyclofosfamide, een type chemotherapie dat regelmatig wordt gebruikt, schadelijk zou kunnen zijn voor de longen. In vervolgstudies kwam dit in wisselende mate naar voren. Binnen de DCCSS-LATER 2 PULM sub-studie werd daarom specifiek gekeken naar het potentiële longschadelijke effect van cyclofosfamide in survivors van kinderkanker. De primaire uitkomsten van deze studie waren afwijkingen op een longfunctietest: verminderde gaswisseling (diffusieprobleem), een verminderd longvolume (restrictie) of vernauwde luchtwegen met problemen bij het uitademen (obstructie). Daarnaast werd er gekeken naar het voorkomen van een chronische hoest, terugkerende luchtweginfecties, kortademigheid en zuurstofbehoefte. Wat betreft restrictieve dysfunctie hadden survivors die waren behandeld met een cumulatieve dosis cyclofosfamide van ≥10 g/m^2 een gemiddelde daling van 0.3 punten in de z-score van de totale longcapaciteit. Dit is echter een beperkt effect ten opzichte van de afkapwaarde voor de diagnose van restrictieve dysfunctie, die wordt gesteld op een z-score van -1.65. Ook hadden survivors die waren behandeld met een cumulatieve dosis cyclofosfamide van 5-10 g/m^2 een tweemaal zo hoge kans op het ontwikkelen van diffusieproblemen als survivors die geen cyclofosfamide hadden gehad. Doordat deze kans niet significant verhoogd was voor survivors met een nog hogere cumulatieve dosis cyclofosfamide waren er geen sterke aanwijzingen voor een dosis-respons relatie. Verder werden er geen significante bevindingen gedaan. Daarom concludeerden wij dat cyclofosfamide na correctie voor relevante confounders niet geassocieerd lijkt met klinisch relevante longschade op de langere termijn.

DEEL 2: EVALUATIE VAN DE KWALITEIT VAN ZORG VOOR KINDEREN MET KANKER EN SURVIVORS

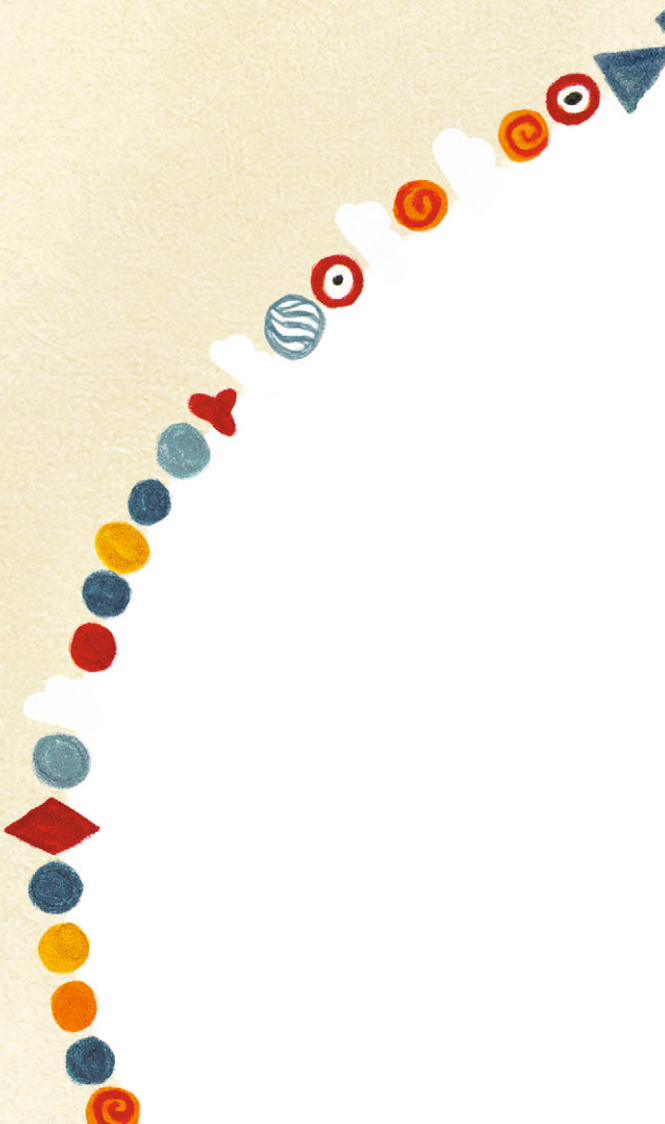
Het tweede deel van dit proefschrift richt zich op evaluatie van zorg en beschrijft de ontwikkeling van een set van belangrijkste uitkomsten om de kwaliteit van overleven na kinderkanker te beoordelen.

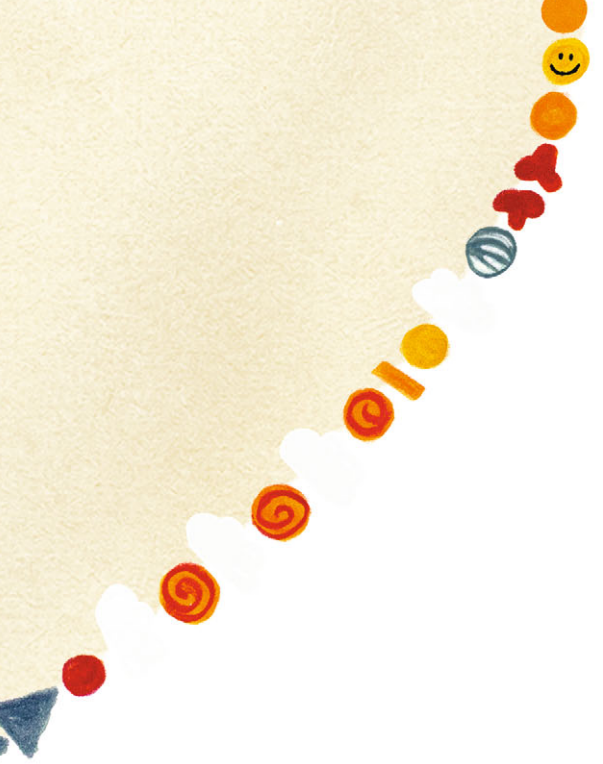
In **hoofdstuk 8** wordt het belang van klinische praktijkrichtlijnen en kwaliteitsindicatoren binnen de kinderoncologie beschreven. Door systematische beoordelingen van klinisch onderzoek worden de meest recente en relevante wetenschappelijke bevindingen vertaald naar klinische aanbevelingen in evidence-based richtlijnen. Kwaliteitsindicatoren zijn belangrijke hulpmiddelen bij het evalueren van de kwaliteit van zorg. Het zijn meetbare elementen van de klinische praktijk die inzicht

geven in processen (bijvoorbeeld navolging van aanbevelingen voor lange termijnzorg), structuren (bijvoorbeeld beschikbaarheid van een LATER poli) of uitkomsten (bijvoorbeeld overlevingskans of verminderd voorkomen van late effecten) die geassocieerd zijn met een hoge kwaliteit van zorg.

Tot slot toont **hoofdstuk 9** hoe er in samenwerking tussen onderzoekers, zorgverleners, survivors en ouders een set van belangrijkste uitkomsten is ontwikkeld die gebruikt kan worden om de kwaliteit van overleven te beschrijven. Hiervoor werden vragenlijsten afgenomen, focusgroepen gehouden en Delphi processen georganiseerd waarbij ruim 400 experts wereldwijd betrokken waren. De International Childhood Cancer Core Outcome Set bevat 24 fysieke, psychosociale en neurocognitieve uitkomsten die samen de kwaliteit van overleven voor 17 typen kinderkanker beschrijven. Er was overeenstemming over de uitkomstdefinities en meetinstrumenten, waarbij gekozen werd voor extractie van informatie uit het medisch dossier, vragenlijsten (voor patiënten, survivors en/of zorgverleners) of koppelingen met bestaande registraties. Met de International Childhood Cancer Core Outcome Set kunnen kinderoncologische centra inzicht krijgen in hun eigen voortgang over de tijd of hun resultaten benchmarken met andere instituten. Dit geeft aanknopingspunten om de kwaliteit van zorg steeds verder te verbeteren. Het samenstellen van deze set met belangrijkste uitkomsten vormt een belangrijke eerste stap. Vervolgens is het belangrijk om de uitkomstregistratie op een duurzame manier te implementeren. Hierbij kunnen lessen uit eerdere uitkomstimplementatietrajecten worden toegepast, zoals het belang van patiëntparticipatie, een goede database, regelmatige rapportage en feedback, betrokkenheid en leiderschap.

Samenvattend is het doel van dit proefschrift om bij te dragen aan de gezondheid en het welbevinden van allen die als kind kanker hebben gehad, vanaf hun diagnose en gedurende de rest van hun leven. Dit proefschrift heeft geresulteerd in meerdere hulpmiddelen en aanbevelingen die momenteel worden toegepast of geïmplementeerd in de praktijk. Ook kunnen de bevindingen worden gebruikt om de bewijskracht van klinische praktijkrichtlijnen te versterken en nieuwe onderzoeksvragen te formuleren. Het blijft van belang om survivors van kinderkanker te betrekken in de opzet van onderzoeken en interventies. Zo kunnen zorg en onderzoek optimaal op elkaar worden afgestemd om tegemoet te komen aan hun behoeften en hun vragen te beantwoorden.





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Appendices

CURRICULUM VITAE

Rebecca van Kalsbeek-Grootendorst was born on June 5, 1993, in Gouda, the Netherlands. She is the eldest of three siblings. From 1994 to 1997, she lived in Kuala Lumpur, Malaysia, after which her family relocated to IJsselstein, the Netherlands. During high school, Rebecca participated in the two-year Junior Med School program of the Erasmus Medical Center Rotterdam. After obtaining her pre-university education cum laude in 2011, she studied medicine at the Faculty of Medicine of Utrecht University and the University Medical Center Utrecht. During her studies, she was a member of student rowing association ORCA and Navigators Studentenvereniging Utrecht. She completed two interdisciplinary honours programs (Descartes College bachelor's honours program and Young Innovators master's honours program), received the Thomas More scholarship for honours students, and did several courses and internships abroad in Aarhus, Hong Kong and Berlin. Upon graduation in 2018, she worked as a resident (not in training) in pediatrics at Ziekenhuis Gelderse Vallei, Ede. In 2019, she started as a PhD candidate at the Princess Máxima Center for pediatric oncology, Utrecht, under the supervision of prof. dr. Leontien Kremer, prof. dr. Rob Pieters, dr. Renée Mulder, and dr. Heleen van der Pal. The results of her research are presented in this thesis. During her PhD, she participated in the TULIPS (Training Upcoming Leaders in Pediatric Sciences) PhD Curriculum 2020-2022. Her doctoral work was awarded with the Tom Voûte Young Investigator Award in 2023. In that same year, she obtained her postgraduate Epidemiology degree with cum laude distinction. Rebecca currently works as a resident (not in training) in pediatrics at the Wilhelmina Children's Hospital in Utrecht and lives in IJsselstein with her husband and two children.

PHD PORTFOLIO

Name: Rebecca J. van Kalsbeek-Grootendorst
Period: April 2019 to December 2023
Promotores: Prof. dr. Leontien C.M. Kremer and prof. dr. Rob Pieters
Copromotores: Dr. Renée L. Mulder and dr. Heleen J.H. van der Pal
Institution: Princess Máxima Center for pediatric oncology, Utrecht, the Netherlands

PhD training	Year
Courses	
Storytelling	2019
Introduction to Epidemiology	2019
Introduction to Statistics	2019
Study Design in Etiologic Research	2019
Classical Methods in Data Analysis	2020
Scientific Poster Presentations	2020
Modern Methods in Data Analysis	2020
Writing Research Proposals	2020
Pharmacoepidemiology and Drug Safety	2020
Clinical Epidemiology	2020
Systematic Reviews and Meta-Analysis of Prognosis Research	2020
Research Ethics: An Introduction	2020
Mixed Models	2020
Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers (BROK)	2020
Systematic Reviews of Diagnostic Studies	2021
Advanced Topics in Causal Research	2021
Advanced Diagnostic Research	2021
Psychological Flexibility	2021
Adobe Illustrator	2021
Survival Analysis	2022
Prognostic Research	2022
Systematic Reviews of Intervention Research	2022
Clinical Trials and Drug Risk Assessment	2022

PhD training	Year
Courses (continued)	
Supervising Research of MSc Students	2023
Presenting Your Research Confidently	2023
Herregistratie Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers (BROK)	2023
Seminars and symposia	
Weekly Princess Máxima Center research seminars	2019-2023
Monthly research group meetings	2019-2023
Monthly Dutch Childhood Cancer Survivor Study meetings	2019-2023
Princess Máxima Center Research Retreat, Doorwerth, the Netherlands (oral presentation)	2019
UMC Utrecht Symposium on Patient Participation, online	2020
TULIPS Jonge Onderzoekers Dag, online	2020
TULIPS Starting Weekend, Utrecht, the Netherlands	2020
Accelerate 1st Educational Webinar – Drug Development, online	2021
ZInvolle Registratie (ZIRE) Webinar, online	2021
TULIPS Grant Writing and Presenting Weekend, Egmond aan Zee, the Netherlands	2021
TULIPS End Weekend, Utrecht, the Netherlands	2022
TULIPS Jonge Onderzoekers Dag, Amsterdam, the Netherlands	2022
LATER Meet-Up, Utrecht, the Netherlands (oral presentation)	2023
TULIPS alumni event, Utrecht, the Netherlands	2023
Butterfly Summer School, Utrecht, the Netherlands (oral presentation)	2023
Conferences	
North American Symposium on Late Complications after Childhood Cancer (NASLCCC), Atlanta, USA	2019
E-Rare Strategic Workshop by the European Joint Programme on Rare Diseases, Gdańsk, Poland (oral presentation)	2019
24th PanCare meeting, Basel, Switzerland (oral presentation)	2019
International Consortium for Health Outcomes Measurement (ICHOM) Online Conference Series, online	2020
25th PanCare meeting, online (oral presentation)	2020
SIOP Europe 2nd Annual Meeting, online (oral presentation)	2021
International Consortium for Health Outcomes Measurement (ICHOM) Virtual Learning Series, online	2021

PhD training	Year
Conferences (continued)	
International Symposium on Late Complications after Childhood Cancer (ISLCCC), Utrecht, the Netherlands	2022
28th PanCare meeting, Budapest, Hungary (oral presentation)	2022
1st International Pediatric Cardio-Oncology Conference, Cincinnati, USA (oral presentation)	2022
29th PanCare meeting, Ghent, Belgium (oral presentation)	2023
55th Congress of the International Society of Paediatric Oncology (SIOP), Ottawa, Canada (poster presentation)	2023
Supervision	
Bachelor student University College Utrecht, Utrecht University	2021
Master student Care Ethics and Policy, University of Humanistic Studies	2022
Master student Medical Informatics, University of Amsterdam	2023
Other	
Support in the coordination of the PanCareFollowUp project	2019-2020
Training Upcoming Leaders in Pediatric Science (TULIPS) PhD Curriculum	2020-2022
Senior buddy for first-year PhD student	2022
Slimme Gasten – presenting research at a primary school	2022
Tom Voûte Young Investigator Award (€2500)	2023
Interview Nederlands Tijdschrift voor Oncologie	2024

DANKWOORD

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Rebecca van Kalsbeek-Grootendorst
24 februari 2024, IJsselstein