CHAPTER 1

GENERAL INTRODUCTION
1.1 GENERAL INTRODUCTION

“There is no cure for leukemia; treatment is directed at prolonging life and relieving symptoms. [...] Without any treatment the average duration of life is approximately four to five months. When transfusions and antibiotics are given, the life expectancy increases to eight months; with a combination of folic acid antagonists, 6-M.P., and steroids given in sequence children live an average of one year.” - Handbook of Pediatrics, Silver et al., 1961.[1]

It is hard to imagine that these lines were published less than 60 years ago. In fact, in the 1961 “Handbook of Pediatrics” the chapter “Neoplastic diseases” only comprised 12 of the total of 576 pages and contained various prognosis paragraphs similar to the one quoted above. Nevertheless, the first signs of the upcoming treatment regimens that would improve survival rates dramatically are already emerging: folic acid antagonists, 6-mercaptopurine and steroids are currently still used in the treatment of acute lymphoblastic leukemia.

In the 60 years since the handbook was published, cure rates have improved to the point that currently four out five children diagnosed with cancer in high-income countries will be cured.[2] Nowadays it is almost hard to imagine that the quote above is about acute lymphoblastic leukemia, as this is one of the types of childhood cancer with the most dramatic improvement in survival rates (see Figure 1.1). This shows how much this field of medicine has changed over the last decades.

![Figure 1.1. Overall survival of children diagnosed with acute lymphoblastic leukemia who were enrolled in Children’s Cancer Group and Children’s Oncology Group clinical trials, 1968 to 2009. Source: Hunger et al.[3] Reproduced with permission from New England Journal of Medicine, Copyright Massachusetts Medical Society.](image-url)
A major factor in the increase in survival rates is the introduction of multimodal, intensive treatment strategies comprising chemotherapy, radiotherapy, and/or surgery.[2] However these intensive treatments come at a price, as they are associated with several side effects, ranging from mild to potentially life-threatening. Children undergoing anti-cancer therapy suffer from these side effects, which reduce quality of life. In addition, there is a portion of children that die due to these side effects. Supportive care is the care focusing on preventing and treating the side effects of anti-cancer therapy.

There should be a focus on improving supportive care. Because with the ongoing improvement of childhood cancer survival rates, it is not only important if a child survives cancer (although this naturally remains the main concern), but also, and increasingly so, how a child survives cancer. To improve supportive care, and thus reduce treatment-related morbidity and mortality, development and implementation of evidence-based guidelines is of the utmost importance, as this contributes to informed treatment decisions and uniform care.

1.2 CHILDHOOD CANCER

INCIDENCE AND SURVIVAL

Each year approximately 550 children in the Netherlands are diagnosed with cancer. This is in line with the European incidence rate, which is 14 per 100,000 children (aged 0-14 years).[4] Even though the aforementioned major advances have been made in the treatment of childhood cancer, it remains an important cause of death in children in high-income countries. For instance, in 2015 in the Netherlands, neoplasms were responsible for 43 out of 158 deaths (27%) in children aged one to 10 years, and was therefore the primary cause of death in this age group.[5] In children aged 10-18 years external causes were the primary cause of death, followed by neoplasms with 23% of deaths. For children younger than one year, cancer is only the cause of death in 1% of all deaths, with the majority of deaths being due to conditions originating in the perinatal period and congenital anomalies.

Cancer in children differs to great extent to cancer in adults. For one, a child is growing and developing, which might affect treatment options and choices. In addition, the distribution of cancer types is substantially different in children as compared to adults. [2] Adults mainly suffer from solid malignancies, with carcinomas being the predominant type. In children however, carcinomas only account for 1.5% of all malignancies. Hematological malignancies, with leukemia occurring most frequently, have the highest incidence in childhood cancer, covering nearly half of all diagnosed malignancies in
children. Tumors of the central nervous system are also relatively common (23% of all malignancies), as are embryonal tumors (25% of all malignancies). The distribution of the types of cancer is highly dependent of age. For example, retinoblastoma accounts for almost one in 10 cancer diagnoses under the age of one year, but occurs rarely above the age of four years.

All tumor types have different treatment regimens, which are often designed as trial protocols that are adhered to in a national or international manner. In this way, with each protocol update a new treatment approach or adjustment that builds upon the previous findings can be trialed. Treatment protocols can comprise one or more treatment modalities, which are mostly chemotherapy, radiotherapy, surgery and/or immunotherapy. The duration of treatment depends on the type of tumor and various other factors (such as gene variations), and ranges from very short, for example one surgical procedure for some types of germ cell tumors, to very long, for example three years of chemotherapeutical treatment for some types of leukemia.

Although the overall survival in high-income countries has surpassed 80%, there is still great variation in the prognosis of different types of cancer. There are tumor types with an excellent prognosis, such as acute lymphoblastic leukemia (see Figure 1.1). Nevertheless there are also tumors that remain very difficult to treat, such as stage 4 neuroblastoma (10-year overall survival of 38%) or diffuse intrinsic pontine glioma (currently incurable).[6]

TREATMENT-RELATED MORBIDITY AND MORTALITY

Children who undergo treatment for cancer can be confronted with an array of side effects, as each treatment modality has its own side effects profile. Chemotherapy can lead to early toxicities such as nausea and vomiting, neuropathic pain, and/or bone marrow suppression (which on its turn increases the risk of serious infections).[7] But also late effects of chemotherapy occur, such as cardiotoxicity or infertility.[8] Each chemotherapeutic drug has its own profile of side effects, of which the severity can differ from individual to individual. Another widely used treatment modality, radiotherapy, is also associated with both early toxicities (e.g. skin blistering) and late toxicities (e.g. cognitive decline), depending on area and dose of irradiation.[9] Novel treatment modalities are naturally aimed at improving survival, but might also be aimed at decreasing these side effects. For instance, early cognitive outcomes in children irradiated to the brain using proton radiation therapy, a relatively novel treatment modality, show superior results as compared to traditional (photon) radiation therapy.[10]

Morbidity is naturally not limited to the direct somatic toxicities. In fact, when parents were asked what they believed their children found the most bothersome
cancer treatment-related adverse effects, the most prevalent symptoms were mood swings, fatigue, and disappointment at missing activities with friends/peers.[11] All these treatment-related adverse effects can severely decrease quality of life of a child and his/her family.

In addition, as the side effects of cancer treatment can be very severe, there is a portion of children that die due to these adverse effects. As the anti-cancer treatments are becoming more and more intensive and the total number of children that die from cancer is decreasing, preventing treatment-related deaths is crucial to further increase survival rates.[12]

1.3 SUPPORTIVE CARE IN CHILDHOOD CANCER

Supportive care is aimed at reducing side effects of childhood cancer treatment in the broadest sense. The Canadian clinician B. Page was among the first to define supportive care in 1994 and did this in both a comprehensive and comprehensible manner: “[..] In other words, supportive care is anything one does for the patient that is not aimed directly at curing his disease but rather is focused at helping the patient and family get through the illness in the best possible condition.”.[13]

Thus, supportive care is an extremely broad field, ranging from topics as medication for reducing nausea and vomiting to distraction techniques for reducing procedural pain, and from providing psychosocial support for a child and his/her family to treating graft-versus-host disease, and so on.

Optimal supportive care is of the utmost importance as it has the potential to reduce or even prevent early and late adverse effects of anti-cancer treatment, hereby increasing quality of life and potentially even reducing mortality.

1.4 EVIDENCE-BASED MEDICINE

In 2007 the BMJ, one of the most important and influential peer-reviewed medical journals, let readers vote on the world’s greatest medical milestones since the mid-19th century.[14] Sanitation was the clear winner, but at number seven of these most important advances was “evidence-based medicine”.

The term evidence-based medicine (EBM) was introduced to a wide audience in a 1992 publication by Gordon Guyatt from the Canadian McMaster University, still one of the driving forces behind EBM developments today.[15] Guyatt was part of a medical movement that gained momentum in the 1980s, and that argued that medical decisions
should be based on the best available scientific knowledge and good arguments. This was inspired by a feeling that medical decisions were too often based on seniority, individual physician habits or successful marketing of pharmaceutical companies.

Since the introduction of EBM, the definition has expanded, stating that healthcare practice should be “based on integrating knowledge gained from the best available research evidence, clinical expertise, and patients’ values and circumstances.”[16] Several methods to facilitate EBM have been introduced, of which systematic reviews and meta-analyses are among the most important. The body of medical scientific literature is expanding at a speed impossible to keep up with as an individual practitioner. In fact, the MEDLINE database, one of the largest databases with biomedical literature in the world, indexed over 750,000 citations per year in the last 10 years.[17] This corresponds to nearly 90 new medical papers being published every hour. Focusing on childhood cancer, a relatively small clinical area, a simple MEDLINE search for studies published in the last five years using “child AND cancer” resulted in 37,433 citations.[18] This still corresponds to over 20 new childhood cancer studies published per day, an unattainable rate to keep up with for an individual clinician.

Systematic reviews aim to summarize and critically appraise the available scientific knowledge for a clinical question and are therefore a welcome aid for clinicians who practice EBM. In 1993, an international network was formed that aimed to produce high-quality systematic reviews in a collaborative manner.[19] This network was entitled The Cochrane Collaboration, in memory of Archibald Cochrane, a Scottish epidemiologist that is regarded as one of the founders of EBM and an early advocate for the importance of randomized clinical trials. Presently, The Cochrane Collaboration is the largest international organization involved in medical evidence syntheses and its methods are considered as the standard reference for high-quality systematic reviews. Within the field of childhood cancer, Cochrane Childhood Cancer plays an important role in identifying, appraising, and synthesizing the available evidence on relevant clinical questions. The editorial base of Cochrane Childhood Cancer is located in the Princess Máxima Center for Pediatric Oncology in Utrecht, the Netherlands.

Conclusions from a systematic review can be used to develop evidence-based guidelines. These guidelines recommend on care by combining the best available scientific knowledge (systematic review conclusions) with other factors such as a treatment’s acceptability, feasibility, and resource use. When using these guidelines for clinical-decision making, patient relevant factors such as personal wishes and values naturally also play an important role.
EBM thus stimulated the connection between science and practice by asking structurized clinical questions and developing evidence-based guidelines, and is pivotal to improving care and clinical outcomes. A striking example of this importance is the estimation that if research into preventing and treating AIDS had not been put into practice, currently more than 50% of hospital beds in the US would be filled with AIDS patients.[16] This makes EBM so crucial, as without it new insights would not be implemented in practice and patients would not benefit from the medical scientific advances.

1.5 CLINICAL PRACTICE GUIDELINES

DEFINITION

As there are multiple interpretations of how an evidence-based guideline should be composed, and more importantly when it is considered truly based on evidence, there was a need for a more precise term and definition. In 2011 the Institute of Medicine (IoM) published a document entitled “Clinical Practice Guidelines We Can Trust”, in which the term Clinical Practice Guidelines (CPG) is defined as: “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.”[20]

There are various crucial factors in this definition. First; ‘intended to optimize patient care’. Although this seems logical and perhaps even at first sight somewhat condescending, it is important to stress this. Optimizing patient care should always be the underlying main motivator of guideline development. Second; ‘systematic review of evidence’. The CPG should be informed by a thorough and systematic evaluation and appraisal of the existing literature. This comprises searching multiple databases, using a priori developed comprehensive search strategies and search filters, with the results appraised by multiple independent, trained appraisers. Third and final; ‘assessment of the benefits and harms of alternative care options’. Naturally it is important to review the treatment option the CPG is focusing on, but this should always be put in the contemporary context. For example, are there more effective treatments? Are there treatments that are evenly effective but more patient friendly or more cost-effective? Guideline panels should not be fixated at merely studying the treatment they are focusing on, but also assess alternative care options in a systematic and transparent manner.

Although the definition is quite comprehensive, there are various other factors that are considered important parts of CPGs that lack in the IoM definition. Bulkier, but also more comprehensive, the definition of CPGs could be rephrased to: “Statements that
include recommendations intended to optimize patient care that are 1) informed by a protocol-driven systematic review of evidence, 2) formulated by a representative panel of professionals and patient representatives, and 3) include an assessment of the benefits, harms, and other relevant outcomes of the care option and alternative care options.”.

**EFFECTS OF CPGS**

An important effect of CPGs is the reduction of practice variation, as uncertainty about the most effective treatment has been found to be one of the most important causes of practice variations.[21] Variation in practice implies one of the centers is not advising the most effective treatment. Furthermore, being advised a specific treatment in one hospital and a completely other treatment in another hospital can also be confusing and frustrating for patients and their families. Thus in addition to contributing to uniform care, CPGs might also increase the confidence of patients in the provided care.

Reduction of practice variations is important, as it has been shown to be related to better health outcomes. For instance, in a study in children with asthma, variations in practice were associated with worse outcomes as compared to outcomes in children receiving uniform care.[22] With the care for children with cancer in the Netherlands being centralized in 2018 in the new Princess Máxima Center for Pediatric Oncology (Utrecht), care for all these children is coordinated from one center. This creates a unique opportunity to implement CPGs and reduce practice variations (see Figure 1.2).

**Figure 1.2.** With the Dutch situation changing from seven primary pediatric oncology hospitals to one primary pediatric oncology hospital and several shared care centers, there is a unique opportunity to facilitate uniform care, by going from the ‘classic’ situation (all centers use their internally developed protocols, see left panel) to the ‘desired’ situation (the Princess Máxima Center for Pediatric Oncology endorses supportive care CPGs and disseminates these to the shared care centers, see right panel).
It has repeatedly been shown that care in line with recommendations from CPGs has improved patient outcomes, in addition to facilitating a more efficient care delivery. [23,24] For instance, multiple studies have shown that guideline-consistent anti-emetic care was associated with a significant reduction of chemotherapy-induced nausea and vomiting in adults.[25,26] The effect of guideline-consistent care can go even further, as it was found that adherence to a CPG in relation to initiating antibiotic therapy in adult low-risk febrile neutropenia was associated with decreased mortality.[27] The effect of guideline adherence on outcomes in supportive care in children with cancer is an area of research that deserves attention but is yet to be explored.

Besides contributing to better health outcomes and uniform care, CPGs have additional benefits. They help clinicians to absorb the rapidly changing scientific state-of-art in a clinical relevant matter, they can improve the knowledge and awareness of patients (through educational materials), they can contribute to changes in public policy, and they expose gaps of evidence for which future studies need to be initiated.[24]

EXISTING GUIDELINES IN SUPPORTIVE CARE IN CHILDHOOD CANCER
Currently the number of CPGs focused on topics in childhood cancer supportive care is limited. Thankfully, for some important topics there are already recent CPGs available. These topics comprise for instance nausea and vomiting, febrile neutropenia, mucositis and fatigue.[7,28-33] Nevertheless, there are numerous important supportive care topics for which evidence-based guidance is lacking. As the field of supportive care is very broad, it is important to first develop CPGs for topics for which there is a high clinical demand for guidance.

An important recent development is the initiation of the International Pediatric Oncology Guidelines in Supportive Care Network (iPOG Network).[34] This is an international, multidisciplinary network of healthcare professionals with an interest in childhood cancer supportive care guideline development. By using international collaboration, the effort that the development of a CPG takes can be shared, and by informing one another on current projects, duplication of work is prevented. In addition, the iPOG network plays a role in educating and supporting individuals or organizations that aim to developed childhood cancer supportive care guidelines.
1.6 DEVELOPMENT OF CPGS

Throughout the years, there have been various methods to developing an evidence-based guideline. In an effort to create uniform, sensible, and transparent methods for developing CPGs, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group was formed in 2000.[35] This working group specifically focused on developing an approach to grade quality of evidence (or: certainty of effect estimate) and strength of recommendations. Currently, the GRADE approach is the world-leading standard for CPG development. Various organizations also provide local guidance to guideline development (often incorporating the GRADE approach), such as the Dutch National Health Care Institute with the AQUA directory on quality standards.[36]

There are various phases in the development of a CPG, which will briefly be discussed: 1) startup, 2) clinical questions, 3) evidence search and selection, 4) data extraction and quality appraisal, 5) summarizing evidence, 6) formulating recommendations, 7) writing the CPG. An overview of the complete process can be found in Figure 1.3.

In phase one, the startup phase, the topic is selected and a comprehensive guideline development panel (with multiple working groups if applicable) is composed. Also a systematic search is carried out to identify existing, relevant guidelines. If multiple guidelines on the desired topic are identified, the quality should be assessed and concordances and discordances between recommendations should be evaluated. In the case of concordant recommendations, it should be determined if there is sufficient supporting evidence to support these recommendations. For the discordant recommendations (and naturally for topics for which there is a lack of recommendations), clinical questions can be composed.

During phase two, clinical questions are composed by the complete guideline development panel. These should be composed using the PICO structure, an acronym that stands for Patient (who is your target population?), Intervention (which treatment do you want to study?), Control (which treatment do you want to compare it to?), and Outcomes (on which benefits and harms do you want information?). It is important to decide beforehand on the hierarchy of outcomes. In accordance to GRADE, outcomes can be critical for decision making, important but not critical for decision making, or not important for decision making.[37] This is scored by all panel members on a 9-point scale. Deciding this hierarchy a priori will facilitate the process of formulation of recommendations later on in the process.
When the PICO(s) are finalized, electronic search strategies can be designed. It is becoming increasingly popular to have these search strategies peer reviewed for correctness and applicability, e.g. by a librarian or a medical information specialist. In addition, at this point the eligibility criteria for the study should be determined.

Hereafter, in phase three, the literature search is performed and the selection of relevant citations can commence. This should be done by at least two independent reviewers, whereby discrepancies should be discussed and solved by consensus or by use of a third party arbiter. Usually, this selection is performed in multiple rounds depending on number of citations, for instance first selection based upon titles and abstracts, then based on full-text articles. It is advised to pilot the selection process to identify sub-optimally defined criteria or other chances for optimization.

Phase four is performed in a similar dual, independent fashion as phase 3. In this phase the data is extracted from the relevant studies, and the studies are evaluated for their methodological quality. For the data extraction a purpose-build data extraction form should be used (and piloted), that facilitates unambiguous extraction of relevant data. The quality appraisal should be performed by using an appropriate and established instrument for the specific study type. A well-known example is the Cochrane Risk of Bias Tool for evaluating the quality of randomized controlled trials (RCTs).

When the study qualities are determined, the quality of the body of evidence per outcome can be summarized using the GRADE system.[35] For this purpose all the included studies per outcome are combined and the quality of the body of evidence is graded as high, moderate, low, or very low. The classification is dependent upon multiple factors: the initial study design (e.g. RCTs start as high quality, observational studies as low quality), factors that require upgrading (dose response effect, large magnitude of effect), and factors that require downgrading (study limitations, inconsistency, indirectness, imprecision, or publication bias).

In phase five all findings are summarized in Summary of Findings tables, including conclusions of evidence with an overall level of evidence (corresponding to the lowest level of evidence of included critical outcomes). The Summary of Findings tables facilitate guideline development panel members to have a structured and comprehensive overview of the information needed to base recommendations upon. These tables are discussed and finalized in accordance with the entire panel.

In phase six the guideline development panel will discuss the evidence and formulate recommendations. These recommendations can be classified as strong or weak and can be for or against an intervention. Strong recommendations, phrased as “we recommend…”, imply that most informed patients would want to have that treatment,
and most clinicians would want to prescribe that treatment. Weak recommendations, phrased as “we suggest…”, imply that a large portion of informed patients would want that treatment, but also many would not, and puts more focus on identifying individual patient needs to base a joint decision upon.

In 2016 the GRADE working group introduced Evidence-to-decision (EtD) tables, which facilitate the process of discussing the important factors for basing a recommendation upon.[38,39] The EtD framework comprises 11 questions in six domains, i.e. problem, benefits and harms, resource use, equity, acceptability, and feasibility. After discussing and answering the questions, the panel then decides on the balance of desirable and undesirable consequences on a 5-point scale. After this a recommendation strength is chosen and the recommendation is formulated. This is supplemented with a short justification, subgroup considerations, implementation considerations, monitoring and evaluation considerations, and future research priorities. This systematic and transparent approach to formulating recommendations not only helps the guideline development panel, it also makes their choices and considerations insightful for users of the CPG.

When the formulations are finalized the CPG can be written (phase seven). The final document should be reviewed and agreed upon by all guideline development panel members, and can then be send out for external review by stakeholders.

IMPLEMENTATION
As bringing a CPG development to a successful end is a lot of work, it might be tempting to then breathe a sigh of relief and shift focus to another project. This would however be a mistake, as the recommendations of a finalized CPG still have to be made aware to clinicians and patients. It has proven to be challenging to implement a CPG successfully.
Various factors have been identified that are potential barriers to successful guideline implementation, for instance unfamiliarity with guidelines, reluctance of physicians to change their approach, and practical barriers (e.g. availability of recommended treatment).[41,42]

Multiple studies have evaluated the effectiveness of implementation strategies, which proved to be a difficult concept to measure.[41,43] Although there is no gold standard yet for implementation, there are various interventions identified that increase the chance of a successful CPG implementation. Besides interventions specifically tailored to the guideline recommendations (e.g. making the recommended treatment more easily available), these comprised use of computerized decision-making systems, formal training, active engagement of clinicians, and, perhaps most importantly, use of multifaceted implementation strategies combining the aforementioned interventions. [41,43,44]

A method to evaluate the implementation of guidelines, is to use indicators. Indicators are measurable items that can evaluate structure of care (settings in which care occurs), process of care (processes that belong to giving and receiving care), and
outcome of care (states of health or events that follow care).[45] The aim of developing and implementing indicators is to monitor, evaluate, and improve the quality of patient care and care deliverance.

Recently, interest in indicators is growing. Several sets of indicators to evaluate quality of care in multiple subdomains of adult oncology have been published and implemented.[46-48] Also the effect of implementing indicators to improve quality of care has been studied, for which it was found that feedback reports are among the most effective implementation strategies.[49] In childhood cancer supportive care, development and implementation of indicators is an underexposed area of research that should be explored, as it has the potential to improve quality of care.

1.7 AIMS AND OUTLINE OF THIS THESIS

The aim of the research described in this thesis is to improve childhood cancer supportive care, by developing and implementing supportive care CPGs for topics for which there is a high need for guidance. The research can be divided in three parts: preparation, development, and implementation.

PART I. PREPARATION FOR GUIDELINE DEVELOPMENT

Firstly, we wanted to explore for which supportive care topics there was a high clinical need for guidance. Thus in Chapter 2 we asked a multidisciplinary group of professionals to prioritize topics for guideline development. This was done in a two-round Delphi survey where side effects were first scored for prevalence, severity, and adequate treatment options, and subsequently for importance to develop a CPG.

We also wanted to explore the views of patients and parents on supportive care, use of guidelines, and shared decision making. Therefore, in Chapter 3 we report on a qualitative study in which we held traditional focus group meetings with parents and online asynchronous focus group meetings with children aged 12-18 years.

In Chapter 4 we explored the current state of supportive care practice in the Netherlands, focusing on concordances and discordances between supportive care practice in the then primary pediatric oncology hospitals. We also evaluated if current practice was in line with recommendations from existing supportive care CPGs. The preparation phase culminated in a plea (Chapter 5) for the development and implementation of CPGs for childhood cancer supportive care, in which we argue why these guidelines are desperately needed.
PART II. DEVELOPMENT OF CLINICAL PRACTICE GUIDELINES

In Chapter 6 we present the methodology for the development of a CPG we developed from scratch, focused on assessment and management of pain in children with cancer. In this chapter also the overall results of the inclusion and appraisal of evidence are discussed. As this CPG is very extensive, encompassing 22 clinical questions that we aimed to answer, we opted to publish this guideline in three parts. In Chapter 7, one of these parts is presented, i.e. the part that focused on the pharmacological, physical, and psychological treatment of procedure-related pain and distress in children with cancer. The other two parts focused on assessment of pain in children with cancer, and pharmacological, physical, and psychological treatment of tumor- and toxicity-related pain in children with cancer.

Another approach to develop a CPG is to use an existing high-quality evidence synthesis and update its findings, whereafter these can be discussed by the guideline development panel and recommendations can be formulated. In Chapter 8 we present such an approach, that we used to develop a CPG in which we provided recommendations on the infusion duration of anthracycline chemotherapy agents in children with cancer.

PART III. IMPLEMENTATION OF CLINICAL PRACTICE GUIDELINES

To evaluate how guidelines can be implemented we explored various approaches. In Chapter 9 we aimed to put an existing CPG for pediatric palliative care more firmly into practice, as it was previously proved to be underused. We did this by developing and piloting a functional individualized pediatric palliative care plan that covers physical, psychological, spiritual and social functioning, and puts great emphasis on the recommendations from the CPG, advance care planning and patients’ and parents’ preferences and desires.

In Chapter 10 we explored how we could develop and use indicators to measure the current state of care, more specifically to evaluate the implementation of a nationally endorsed febrile neutropenia guideline, and to produce baseline measurements on local quality of febrile neutropenia care.

Not all topics lend itself for indicator development, as sometimes there is not sufficient information available to define these indicators upon. Therefore, in Chapter 11 we tried to define grounds for indicators for treatment-related mortality by exploring in a cohort of over 1750 children with cancer how many children died, how many deaths were treatment-related, and if we could identify risk factors for treatment-related death.

In Chapter 12 the findings of all studies are summarized and discussed, and future perspectives are presented.
1.8 REFERENCES


[34] International Pediatric Oncology Guidelines in Supportive Care Network (iPOG Network) [Internet]. [cited 2018 Aug 14]. Available from: http://www.sickkids.ca/Research/iPOG/


PART 1

PREPARATION FOR GUIDELINE DEVELOPMENT