Master Thesis

Health Economics, Policy and Law

HEALTH-RELATED QUALITY OF LIFE WHEN DEALING WITH ACUTE LYMPHOBLASTIC LEUKAEMIA

A LITERATURE AND EXPLORATIVE STUDY OF FACTORS ASSOCIATED WITH HEALTH-RELATED QUALITY OF LIFE

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Preface

In the context of accomplishing the Master's degree of the study Health Economics, Policy and Law, this thesis concerning health-related quality of life in patients with adult acute lymphoblastic leukaemia is established. The subject of this thesis was offered by the faculty to the Master students. This research is part of the promotion research of Annemieke Leunis (MSc), researcher at the Institute of Policy and Management Health. The uniqueness of this topic and motivation of Annemieke Leunis made me choose this subject.

I especially want to thank my supervisor Annemieke Leunis. Her accompaniment and dedication during the research period were very helpful. Even in the period that the process did not expire fluently, she kept her patience and supported me to finish this thesis. I want to thank the respondents for returning the questionnaires and the Department of Haematology of the Erasmus University for their collaboration and permission for this research, which made the explorative study possible. Special thanks go to my family, partner and friends, who supported me during the whole process of writing this thesis.

Goes, May 2013

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Abbreviations

ALL	Acute Lymphoblastic Leukaemia
CNS	Central Nervous System
CRT	Cranial Radiotherapy
EORTC	European Organisation for Research and Treatment of Cancer
EPQ-R	Eysenck Personality Questionnaire Revised
ESAS	Edmonton Symptom Assessment Scale
FACIT-fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
Fact-an	Functional Assessment of Cancer Therapy-Anaemia
FAS	Fatigue Assessment Scale
GHD	Growth Hormone Deficiency
GHQ-28	General Health Questionnaire
GHT	Growth Hormone Treatment
HRQoL	Health-Related Quality of Life
HUI	Health Utility Index
MRD	Minimal Residual Disease
PCQL-32	Paediatric Cancer Quality of Life-32
PedsQL	Paediatric Quality of Life Inventory
SCL-90	Symptom Checklist-90
SCT	Stem Cell Transplantation
SF-12	Short Form-12
SF-36	Short Form-36
STAI	The State-Trait Anxiety Inventory
WHO	World Health Organization

Abstract

Introduction: In the past a diagnosis of acute lymphoblastic leukaemia (ALL) meant a certain fatality. However, over the last decades the five-year survival rate in treatment for adults has increased to approximately 45%. During and after treatment patients are confronted with possible physical, emotional, and behavioural side effects. The aim of this study was to investigate the health-related quality of life (HRQoL) and factors associated with the HRQoL of ALL patients.

Methods: Based on two theoretical models (Wilson & Cleary 1995; Holland 2002) a HRQoL model was developed, so a comparison could be made with both the literature review and the explorative study. The literature review in PubMed was performed to reproduce studies considering HRQoL of ALL patients. The explorative study was based on a paper questionnaire, including validated generic and disease specific questionnaires. Respondents were selected at the Erasmus Medical Centre based on inclusion in HOVON studies. Non-parametric tests were performed to find variables associated with a change in HRQoL.

Results: Twelve studies met the criteria for the literature review. Three studies described the HRQoL of the ALL population and nine studies compared the HRQoL of the ALL population with an ALL-free population. Overall when treatment has been finished, the study population had a similar or better HRQoL than the ALL-free population. Comparison with a norm population gave a higher HRQoL than comparison with a control population. The study population had a worse HRQoL during treatment when compared to the ALL-free population. Studies with an older population had a better score than studies with a younger population. Most studies in the literature review did not detect factors associated with changes in HRQoL. Nineteen respondents returned their questionnaire for the explorative study. Significant differences ($p<0.05$) with the Dutch norm population were found for physical functioning, role functioning, social functioning, fatigue, dyspnoea, and financial difficulties. Factors significantly associated ($p<0.05$) with a lower HRQoL within the ALL population were employment status, concurrent illnesses, marital status, coping with the disease, treatment, religion, fatigue, and a patient-physician relationship.

Conclusion: The HRQoL model was not verified by the literature review, while the explorative study showed some significant associations between the independent variables in the conceptual model and the HRQoL. This conceptual model was possibly applicable to ALL patients based on the results of the explorative study, but should be studied more in-depth in future research. The different outcomes of both types of studies were hard to compare, as these populations were diagnosed at a different age. The small study population in the explorative study might cause the lack of significant effects on HRQoL. Better or similar scores than the general population in the literature review might be caused by the survivors' subjective perceptions, causing a response shift. The small effects found in this study require in-depth investigation in larger groups. It should be attempted to focus more on factors associated with a worse HRQoL, so patients receive the optimal treatment and support. Long and very long-term effects should be investigated by following patients for more than twenty years after diagnosis. Preventing and minimising late effects of the disease will improve the HRQoL in survivors of ALL, particularly in those who were declared disabled, experienced concurrent illnesses, were not able to cope with the disease, and experienced fatigue.

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Introduction

Acute lymphoblastic leukaemia (ALL) is a complex malignant disease, affecting haematopoietic cells of the bone marrow. The normal process of maturation and differentiation of cells in the bone marrow is affected by the malignant proliferation of lymphoblasts. This process leads to replacement of normal bone marrow tissue with cancerous cells (Plasschaert et al. 2004). In the past, a diagnosis of ALL meant a certain fatality (Coebergh et al. 2006). However, the success rate in treatment of ALL has increased since 1960. For adults the five-year survival rate increased from 15-20% in 1960 to approximately 45% in 1990. The five-year survival rate for children even increased from 40-50% in 1960 to above 80% in 1990 (Pui et al. 2004; Gatta et al. 2003; 2005; Gustafsson et al. 2000; IKNL 2012). In the Netherlands the total incidence of adult ALL in 2010 was 207 patients (IKNL 2012).

Although the outlook for survival gets better, facing a life threatening health status can have a great impact on patients. During and after treatment the patients are confronted with possible side effects. These side effects are for example nausea and vomiting, mucositis, fatigue, bleeding, and infection (Viele 2003). The toxic nature of the treatment can cause long-term adverse effects including impaired intellectual function, neuroendocrine abnormalities, cardiotoxicity, impaired reproductive capacity, and secondary malignancy (Bhatia 2003). Beside these physical effects, emotional and behavioural problems may arise (Eiser et al. 2005).

Recognition of adverse ALL treatment effects has resulted in an increased interest in health-related quality of life (HRQoL). This concept is generally understood as a multidimensional construct. This construct concerns an individual's perception of the impact the illness and treatment can have on his/her health, wellbeing or functioning in relation to physical, psychological, and social aspects of life (Eiser & Morse 2001; Varni et al. 2005).

HRQoL is now considered as an important outcome measure for patients with cancer (or other diseases). Beside the interests in long term HRQoL it is also important during courses of treatment (Savage et al. 2009). As already noted, due to the higher survival rate the ALL population dealing with the side effects of ALL-treatment increases steadily. Therefore it becomes important to know what the HRQoL of these patients is and which factors are associated with a change in HRQoL. For gathering more insight in the HRQoL of ALL patients and factors related to a change in HRQoL the main question in this thesis is:

"Which factors are related to HRQoL of Dutch adult ALL patients and how do they affect HRQoL?"

To answer this question a literature review was performed of studies regarding HRQoL of ALL survivors. These studies focused on childhood ALL as none studies were found regarding adult ALL. Secondly a pilot study under Dutch adult ALL patients was performed to explore the HRQoL of a small population of adult ALL survivors. Chapter 1 gives background information of ALL. In this chapter the biology, epidemiology, and treatment of ALL are described. Furthermore the term HRQoL is explained and a HRQoL model is given based on two theoretical models. Methods of the study are described in chapter 2. In chapter 3 the results of the literature review and explorative study are given. In the discussion, the literature study and explorative study are reviewed. Furthermore recommendations for future research are given in this part.

1. Background Information

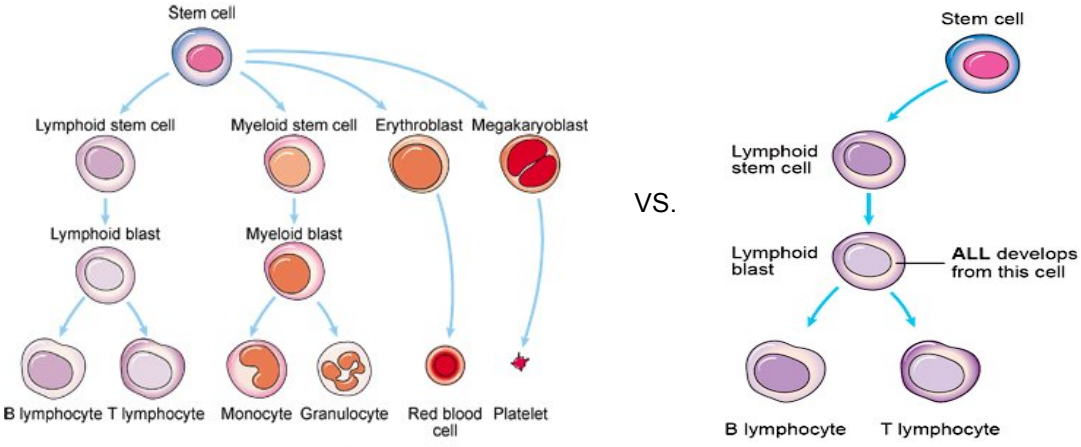
In the first paragraph the biology, epidemiology, treatment, and the prognostic factors and side effects of ALL are described. The second paragraph explains the term HRQoL. In this paragraph the definition of HRQoL, questionnaires to measure HRQoL, and variables that are associated with HRQoL are given. The chapter ends with a conceptual model of HRQoL as a fundament for this study.

1.1 Acute lymphoblastic leukaemia

Biology of acute lymphoblastic leukaemia

Leukaemia is a cancer of the white blood cells and bone marrow. There are several types and subtypes of leukaemia depending on the nature of the disease (acute or chronic) and the type of blood cells affected. ALL is one of these subtypes. A specific type of white blood cells which are called lymphocytes, are affected by ALL which can develop from any lymphoid cell blocked at a particular stage of development. It can also develop from primitive cells with multilineage potential. In healthy patients, bone marrow cells (called blasts) develop into several different types of blood cells with specific functions in the human body. The different cells are white blood cells, red blood cells, and platelets. White blood cells, or leukocytes, are cells of the immune system. These cells are involved in defending the body against both infectious diseases and foreign materials. Red blood cells deliver oxygen to the body tissues via the blood flow through the circulatory system. Platelets circulate in the blood and are involved in haemostasis, leading to the formation of blood clots. In patients with ALL the body produces too many white cells. However, these white cells do not mature and will not be able to work properly. Figure 1 shows the normal blood production and from which point ALL develops (Pui et al. 1993; Pui 1995).

Figure 1 Normal blood production vs. ALL (CancerReasearchUK 2012).



When the body produces many immature white cells, the risk of infection is higher and the bone marrow gets full with too many white blood cells. As a consequence there is not enough space for other types of blood cells, and the number of red blood cells and platelets will decrease. The abnormal white blood cells can also accumulate in parts of the lymphatic system and in the liver (CancerResearchUK 2012). The most common presenting symptoms of ALL are not exclusively symptoms of ALL, as many symptoms of ALL are vague (Rogalsky et al. 1986; Bleyer 1988). Too

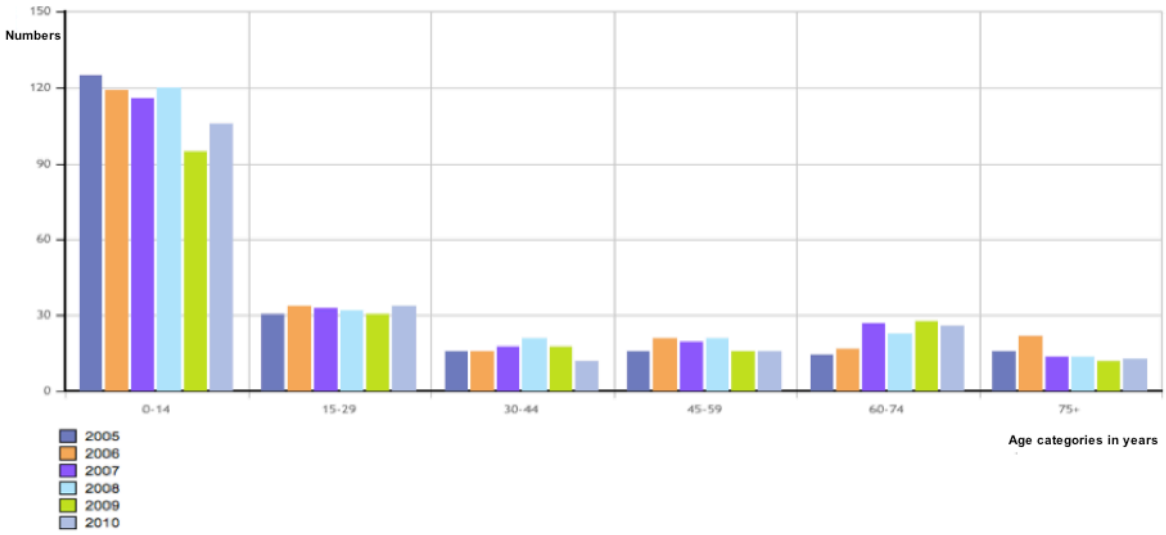
many abnormal white blood cells and not enough normal white cells, red cells, and platelets can affect several processes in the body. Fatigue, fever, weight loss, frequent infections, bruising or bleeding easily, blood in urine or stools, bone pain, breathlessness, and swollen lymph glands may be possible symptoms of ALL (CancerrResearchUK 2012). The precise pathogenetic events causing ALL are unknown. Less than 5% of the cases are associated with inherited, predisposing genetic syndromes, such as Down's syndrome, or with radiation or exposure to specific chemotherapeutic drugs (Pui et al. 2008).

Leukemic lymphoblasts lack specific morphologic or cytochemical features, so diagnosis of ALL depends on immunophenotyping (Pui & Evans 1998). The diagnosis and classification of leukaemia are based upon specialised tests. These tests are performed on cells collected from a bone marrow aspirate or tissue biopsy specimens. When clinical circumstances prevent bone marrow examination, the diagnosis can be made from cells collected from peripheral leukopheresis or pleural effusions. On the basis of immunophenotypic analyses, a diagnosis can be made in 99% of the cases. The diagnosis can be refined to B-lineage or T-lineage, according to the recognised steps of normal B- and T-cell maturation. Specific genetic abnormalities such as chromosomal gains or losses, chromosomal translocations and deletion or functional inactivation of tumour-suppressor genes, are found in the blast cells of 60-75% of patients with ALL. The recognition of these abnormalities contributes greatly to the understanding of the pathogenesis and prognosis of the disease (Pui 1995; Look 1997).

Epidemiology of acute lymphoblastic leukaemia

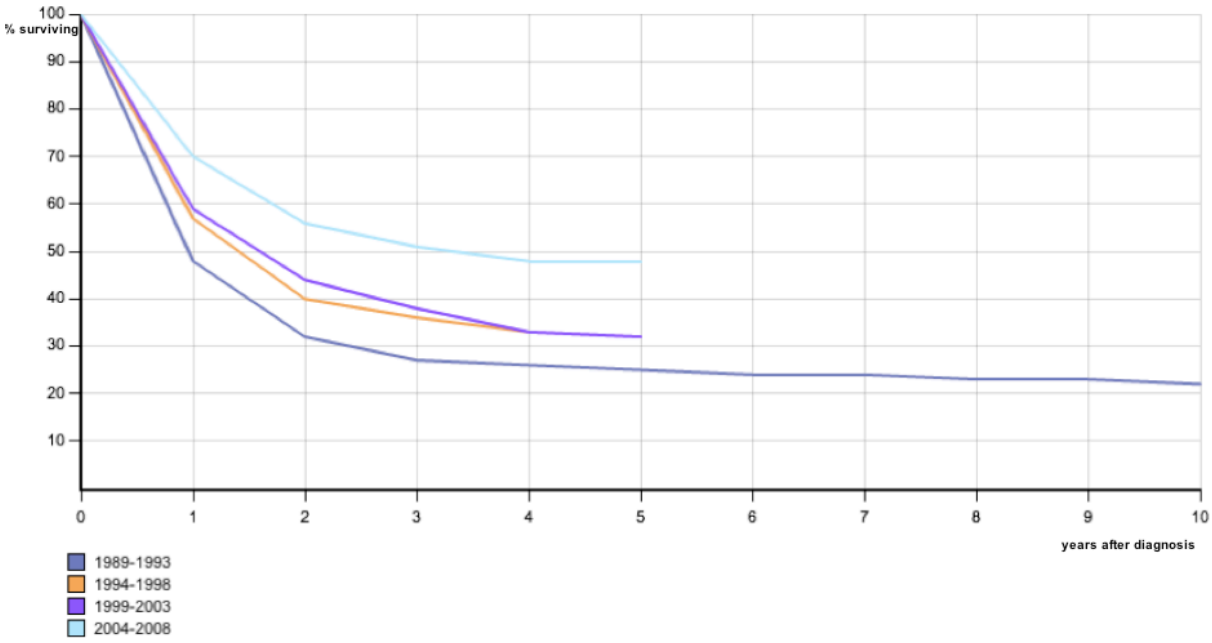
Leukaemia is the most common type of cancer in children in the Netherlands. In males aged 15-29 years leukaemia takes the fourth place of common types of cancer (Visser et al. 2003). However, ALL is rare in elderly patients. In 2010 the number of adult patients diagnosed with ALL in the Netherlands was 207. Each year the incidence of ALL patients is around 200-220. In Figure 2 the number of patients diagnosed per age-category is shown. This figure shows that most persons diagnosed with ALL are younger than fifteen years.

Figure 2 Patients diagnosed with ALL divided per year and age-category (IKNL 2012).



As noted before, the five-year overall survival-rate has increased over the last years. Adult patients diagnosed with ALL in the period 2004-2008 had a five-year overall survival-rate of almost 50%. In the early 90s this rate was around 25% (Figure 3). Due to an optimal use of chemotherapeutic agents that were developed from the 1950s thourgh the 1980s, together with a stringent application of prognostic factors for risk-directed therapy in clinical trails, the survival rate in children even increased to approximately 80% (Pui et al. 2004; Gatta et al. 2003; 2005; Gustafsson et al. 2000). The experience with adults has been far less rewarding. The poor outcome in adult ALL has been attributed to an increased frequency of high-risk leukaemia with greater drug resistence, poorer tolerance of and compliance with treatment, reluctance to accept certain temporary toxic effects, and less effective treatment regimens (Pui & Evans 2006).

Figure 3 The overall survival-rate per period of diagnosis in adult patients in the Netherlands (IKNL 2012).



Treatments

ALL can deteriorate quickly, therefore treatment of ALL starts immediately after diagnosis. The most applied treatments for ALL are chemotherapy and stem cell transplantation (SCT). The acknowledgement that ALL is a heterogeneous disease has led to treatment directed according to the genotype, phenotype, and risk of ALL per patient. For all patients, specific treatment approaches differ but consistently emphasise remission-induction therapy followed by consolidation therapy and maintenance therapy to eliminate the leukaemia cells that are still in the body of the patient. The specific treatment approach depends on the risk of relapse of the patient, the intensity of systemic treatment, and whether or not cranial irradiation is used. The treatment of the central nervous system (CNS) starts early in the clinical treatment and is given for varying lengths of time, if the disease has spread to the CNS (Pui & Evans 2006). Before starting remission-induction chemotherapy, patients receive rasburicase in the pre-phase to prevent metabolic complications. After the pre-phase the induction-consolidation-maintenance chemotherapy starts. This treatment regimen will be stratified

according to age (>40 years versus ≤ 40 years). The most important difference between the two protocols is the less intensive schedule of chemotherapy for older patients (HOVON/EORTC 2012).

After pre-phase, patients will receive remission-induction therapy. Remission-induction therapy has to eliminate more than 99% of the leukaemia cells in order to restore the normal haematopoiesis (formation of blood cellular components) and a normal performance status (complete remission) (Boissel et al. 2003; Kamps et al. 2000). This phase nearly always includes the use of a glucocorticoid (prednisone, prednisolone, or dexamethasone), vincristine, and at least one other agent. During remission-induction therapy patients with high-risk or very-high-risk ALL receive four or more drugs. Remission rates increased to approximately 98% for children and to nearly 85% for adults due to improvement in chemotherapy and supportive care (Pui & Evans 2006). After a month the response to remission-induction therapy will be evaluated. Patients in haematological complete remission continue with consolidation treatment. Patients without complete remission receive intensive reinduction and consolidations, followed by allogeneic SCT (HOVON/EORTC 2012).

Consolidation therapy starts soon after attainment of complete remission. Despite histologic evidence of complete remission after remission-induction therapy, on-going treatment is required because small numbers of leukemic lymphoblasts remain in the bone marrow. If therapy would not be continued, the chance of relapse is higher. The purpose of consolidation chemotherapy is to prevent leukemic regrowth, reduce residual tumour burden, and prevent the emergence of drug-resistance in the remaining leukemic cells. Consolidation therapy lasts usually from four to six months. Normally it involves the use of drugs with other mechanisms of action that differ from those used during the remission-induction chemotherapy (Harris et al. 1998; Lauer et al. 2001).

In today's clinical trials, patients are treated two years or more during maintenance therapy. A combination of methotrexate administered weekly and mercaptopurine given daily represents the basis of most maintenance regimens. The dose in maintenance therapy is the same for younger and older patients (HOVON/EORTC 2012).

The final form of treatment consolidation is allogeneic transplantation for patients younger than 55 years. Patients with a suitable stem cell donor who should consider an allogeneic SCT as consolidation immediately after induction include patients with normal cytogenetics or adverse cytogenetic abnormalities, and patients who require more than one induction cycle to achieve a remission. High-risk patients in complete remission after consolidation with a suitable alternative stem cell donor should also process to allogeneic SCT (HOVON/EORTC 2012).

As noted before, if the leukaemia has spread to the CNS another type of chemotherapy is needed. Unfortunately, most chemotherapy drugs are unable to reach into the area of the CNS from the bloodstream. Craniospinal radiotherapy or intrathecal chemotherapy are options to treat patients when the ALL has spread to the CNS (Yarbro et al. 2000).

Prognostic factors

Several parameters correlate with response rate and response duration in adult ALL. Factors correlating with poor prognosis are: unfavourable karyotype, increasing age, pro-B cell ALL, and a high white blood cell count when diagnosed. Early clearance of lymphoblasts from the bone marrow and the presence of minimal residual disease (MRD) at day 15 at the end of induction therapy are the

best prognostic indicators. A rapid response to remission-induction therapy is positive for the patients. When patients have a detectable MRD they have a higher risk of relapse after conventional therapy. Those who respond slowly or who fail remission-induction therapy have a more guarded prognosis (Hann et al. 2001; Kantarjian et al. 2004; Visser et al. 2001). Intensification of therapeutic regimens of consolidation therapy has been adjusted based upon the risk of poor outcome of the patient (Möricke et al 2008).

Adverse effects of treatment

Patients can experience significant adverse effects during different phases of treatment. During remission-induction chemotherapy toxicity can result from the chemotherapeutic agents or from the rapid elimination of a large tumour burden. The adverse effects of induction can be life threatening. Examples are lysis syndrome, thrombosis, bleeding, and infection (Truong et al. 2007; Priest et al. 1980; Schiffer et al. 2001). Craniospinal radiotherapy or cranial radiotherapy is effective in preventing CNS leukaemia but is associated with significant toxicity, such as cognitive impairment and altered white matter development (Von der Weid & SPOG 2001). Patients treated with craniospinal radiation can develop CNS changes, secondary brain tumours, and experience decreased performance on neuropsychological testing (Hertzberg et al. 1997; Kingma et al. 1993). As a result, craniospinal radiotherapy has been replaced by intrathecal chemotherapy in several CNS preventive therapy protocols. Furthermore, outcome data from these protocols have demonstrated that replacement of craniospinal radiotherapy with intrathecal therapy does not compromise event-free or overall survival. Most patients still have significant myelo- and immunosuppression during the consolidation phase of chemotherapy. During treatment patients are at risk for bacterial, viral, and fungal infections. While on remission-induction and consolidation therapy patients are preventively treated for these infections (Pui et al. 2009; Clarke et al. 2003).

Late effects

As long-term survival in ALL improves, more patients experience late adverse effects. These late adverse effects can be CNS impairment, cardiotoxicity, infertility, and an increased incidence of secondary cancers (Robison & Bhatia 2003). Neurocognitive dysfunction, depression, fatigue, and anxiety can cause an overall decreased health status (Hudson et al. 2003; Meeske et al. 2005). The patient's age and the type and intensity of therapy influence the occurrence of specific complications (Moore et al. 2000; Ise et al. 1986). Some of the late side effects of treatment are described in more detail below.

The effects of leukaemia treatment on CNS developments differ. Some patients experience subsequent CNS impairment (Von der Weid & SPOG 2001). Particularly, patients who received cranial radiation or intrathecal chemotherapy can have a decline in cognitive function (Moore et al. 2000). Survivors can experience other neurologic abnormalities as auditory-vestibular-visual sensory deficits, coordination and motor problems, seizures, and headaches (Goldsby et al. 2010). Leukaemia survivors are also at higher risk for late-occurring stroke (Bowers et al. 2006).

Obesity and other cardiovascular risk factors can be a long-term adverse effect (Oeffinger et al. 2001; 2003). Obese survivors have a lower five-year event-free survival rate and a higher risk of

relapse compared to non-obese survivors (Butturini et al. 2007). Cardiovascular complications, including irreversible and fatal cardiomyopathy, might be caused by treatment with anthracyclines (Singal & Iliskovic 1998).

Patients treated for ALL can develop a second malignancy. The risk is highest among patients who received cranial radiotherapy or intensive therapy for relapse. Hematologic malignancies, such as acute myeloid leukaemia and brain tumours are the most common secondary malignancies (Kimball et al. 1998; Löning et al. 2000; Borgmann et al. 2008).

Therapy influences the sexual functioning and the reproductive capacity of ALL survivors. The effect on sexual functioning and the reproductive capacity depends on the age at time of therapy. Post-pubescent males with ALL can have treatment-related declines in reproduction function, especially if treated with high-dose alkylating agents (Ise et al. 1986). Both sexes are more likely to have decreased fertility when treated with high-dose cranial radiotherapy. Women are more likely to have a lower fertility when they receive cranial radiotherapy during the menarche (Byrne et al. 2004).

1.2 Health-related quality of life

Definition

There are several definitions of HRQoL. However, all definitions refer to the health status or well-being of an individual on different domains. HRQoL can be defined as an impact of a person's health on his or her ability to lead a fulfilling life (Bullinger et al. 1993) or as well-being of a person in a social, emotional, and physical way (Greer 1984). In this thesis the definition of the World Health Organization (WHO) will be used, saying the following: "Quality of life is defined as individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (WHOQOL Group 1994). Furthermore, according to the WHO, the domains of physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment are part of the HRQoL. Table 1 shows the facets of each domain.

Table 1 HRQoL domains and their facets (WHOQOL GROUP 1994).

Domains	Facets
Physical health	• Energy and fatigue • Pain and discomfort • Sleep and rest
Psychological health	• Bodily image and appearance • Negative feelings • Positive feelings • Self-esteem • Thinking-learning, memory and concentration
Level of independence	• Mobility • Activities of daily living • Dependence on medicinal substances and medical aids • Work capacity
Social relations	• Personal relationships • Social supports • Sexual activity
Environment	• Financial resources • Freedom, physical safety and security • Health and social care: accessibility and quality • Home environment • Opportunities for acquitting new information and skills\participation in and opportunities for recreation/leisure • Physical environment (pollution/noise/traffic/climate) • Transport
Spirituality/Religion/Personal beliefs	• Spirituality/Religion/Personal beliefs

To define HRQoL of a person, a special measurement is needed. Different measurements have been developed to define the HRQoL of an individual. HRQoL-measures are useful for a number of purposes, including the evaluation of the nation's progress in achieving population health goals, assessment of health disparities across different segments of the population, and measurement of the effectiveness of interventions in health care for age-related diseases. The tools used for measuring HRQoL depend on what needs to be measured and the future purposes of the outcome (The Health Measurement Research Group 2011).

Questionnaires for measuring health-related quality of life

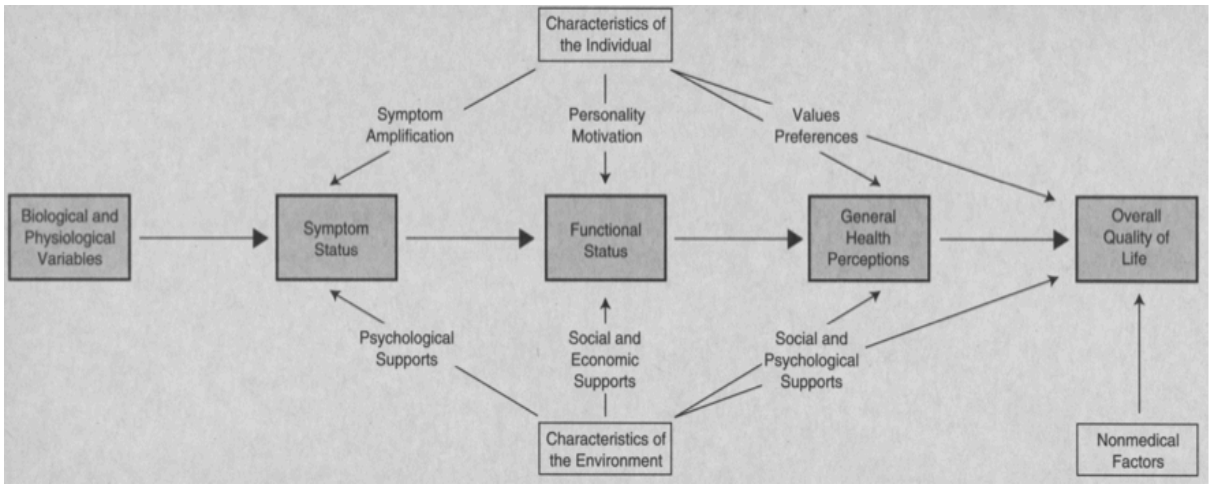
Most HRQoL questionnaires incorporate at least the three main dimensions of the WHO definition: physical, psychological, and social health (WHRQOL Group 1994). The indicators in the questionnaires are often divided in different dimensions, such as self-perceived health, mobility, energy, sexual functioning, and spiritual well-being (Hays et al. 1993; Ware & Sherbourne 1992).

A distinction in HRQoL-measurements can be made into generic measures and disease specific measures. The comparison between different diseases asks for a generic measure. Those instruments are particularly useful for economic evaluations. Measurements that are disease specific are used for measuring special states and concerns of a group of patients. Criteria for disease specific measures are more sensitive to change and more responsive than generic measurements (Patrick & Deyo 1989).

Variables associated with health-related quality of life

As described before ALL and the treatment of ALL can cause many adverse effects. It is interesting if these adverse effects are associated with changes in HRQoL and how these changes take place. Wilson & Cleary (1995) designed a model (Figure 4) to explain the different relations with HRQoL, as therapeutic efforts focus more on improving patient function and well-being, and the need to understand the relationships between variables and HRQoL increases. Their model integrates two different paradigms: the clinical paradigm and the social science paradigm.

Figure 4 Relationships among measures of patient outcome in a HRQoL conceptual model (Wilson & Cleary 1995).



Measures of health can be thought of as existing on a continuum of increasing biological, social, and psychological complexity. Biological measures differ from the complex and integrated measures such as physical functioning and general health perceptions. These different measures are brought together in the conceptual model. Arrows in the model show the dominant causal associations (Figure 4).

The model starts with biological and physiological factors. Here the focus lies on specific cells. The biological and physiological factors are commonly conceptualised, measured, and applied in routine clinical practice. The focus changes with the next factor, symptoms, from specific cells and organs to the organism as a whole. Symptoms can be divided in different classes: physical symptoms, psychophysical symptoms, symptoms not clearly physical or psychological in origin, and emotional and psychological symptoms. To include all of these different phenomena in the model, a symptom is defined as a patient's perception of an abnormal physical, emotional, or cognitive state. The relationship between biological or psychological variables and symptoms is complex. Certain biological and psychological variables can be profoundly abnormal without the patient experiencing any symptoms. This can also be the other way around. Exploring other likely determinants of patient-reported symptoms such as psychological factors, patient expectations, social factors, and aspects of the physician-patient relationship may help clinicians to better address both the clinical and non-clinical factors related to the reported symptoms (Barsky et al. 1992).

The functional status is an important point of integration. One major determinant of functioning is symptom status. However, other patient specific factors such as personality and motivation, and many aspects of an individual's social environment will also be important (Greenfield & Nelson 1992). Physical function, social function, role function, and psychological function are the four major domains of functioning that are commonly measured.

General health perceptions integrate all health concepts previously discussed, as well as other concepts such as mental health, and is by definition a subjective rating. It has been shown that general health perceptions are the best predictors for the use of general medical and mental health services. Furthermore, these perceptions are strong predictors of mortality, even after controlling for clinical factors (Connelly et al. 1989; Wells et al. 1986; Kaplan et al. 1988).

Respondents' subjective health perceptions are frequently assessed by researchers with general measures of how happy and satisfied they are with their life as a whole. General measures of life satisfaction or happiness are not as strongly related to functioning symptoms as might be anticipated. Lower levels of functional status are not necessarily related to lower levels of satisfaction, and measures of life satisfaction seem to be unstable. A possible explanation is that people change their expectations and aspirations as circumstances change.

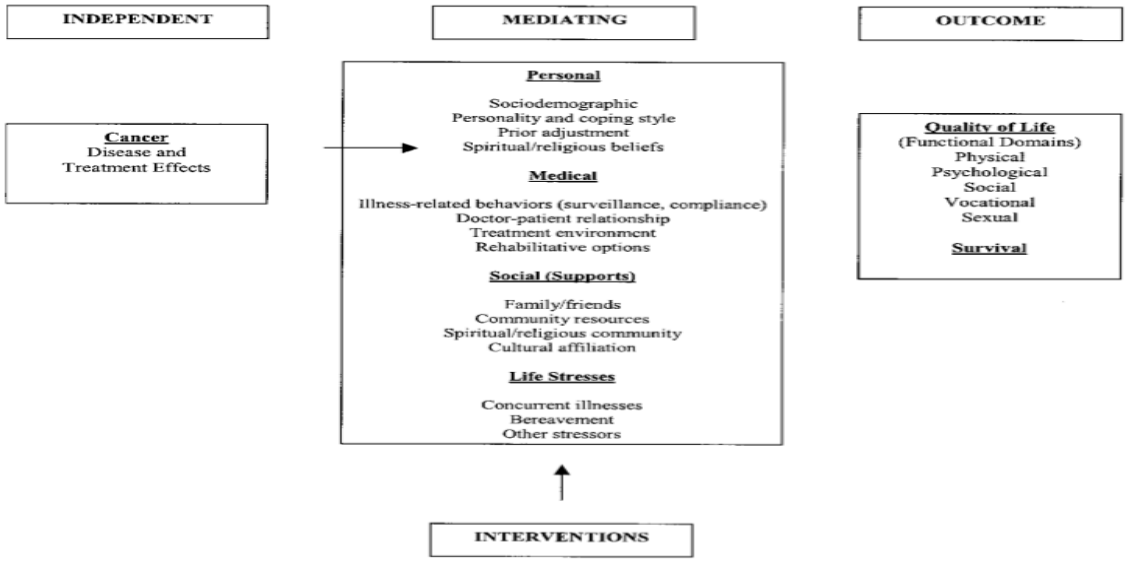
Emotional and psychological factors are related with all variables at every level of the model. Furthermore, most of these relationships can be bidirectional. The effect of emotional factors on general health perceptions and overall quality of life can be profound. However, this can also be the other way around. A certain state of HRQoL can cause depression, anxiety or fear. The issue of bidirectional influences of factors in the model is important, also for the other variables.

Summarising the model the following can be concluded. Overall HRQoL is influenced by different factors of health outcomes. These outcomes can be divided in four other levels: biological

and physiological factors, symptoms, functioning, and general health perceptions. Furthermore, the symptom status, functional status, general health perceptions, and the overall HRQoL are influenced by both characteristics of the individual and characteristics of the environment. In this model there are an increasing number of inputs at each level that cannot be controlled by clinicians or the health care system, as it is traditionally defined. This model can be helpful when treatment strategies are developed, considering all the variables that are associated with the overall HRQoL.

The model of Wilson & Cleary is a general HRQoL model. Holland (2002) made a specific HRQoL model for cancer patients (Figure 5). The model shows different variables associated with the HRQoL of cancer patients. Holland uses the term psycho-oncology and he defines it as the subspecialty of cancer dealing with two psychological dimensions. The first dimension is the psychological reaction of the patients with cancer and their family at all stages of disease and the stresses on staff. Secondly, the psychological, social, and behavioural factors that influence the development of cancer and survival. In the model, cancer and its treatment are the independent variables. This can be compared to the factor of biological and physiological variable in the model of Wilson & Cleary. This independent variable influences the mediating variables, which can be divided in four groups. These groups are personal variables, stage of illness variable, social support variable, and the variable that refers to concurrent stresses related to illnesses that add to psychological burden. These mediating variables can be compared with the characteristics of the individual and the characteristics of the environment in the model of Wilson & Cleary. Both these characteristics are associated with different domains of HRQoL such as pain, anxiety and social functioning, just like the mediating variables in the model of Holland are associated with the outcome of that model, HRQoL.

Figure 5 Model of research in psycho-oncology Holland (2002).

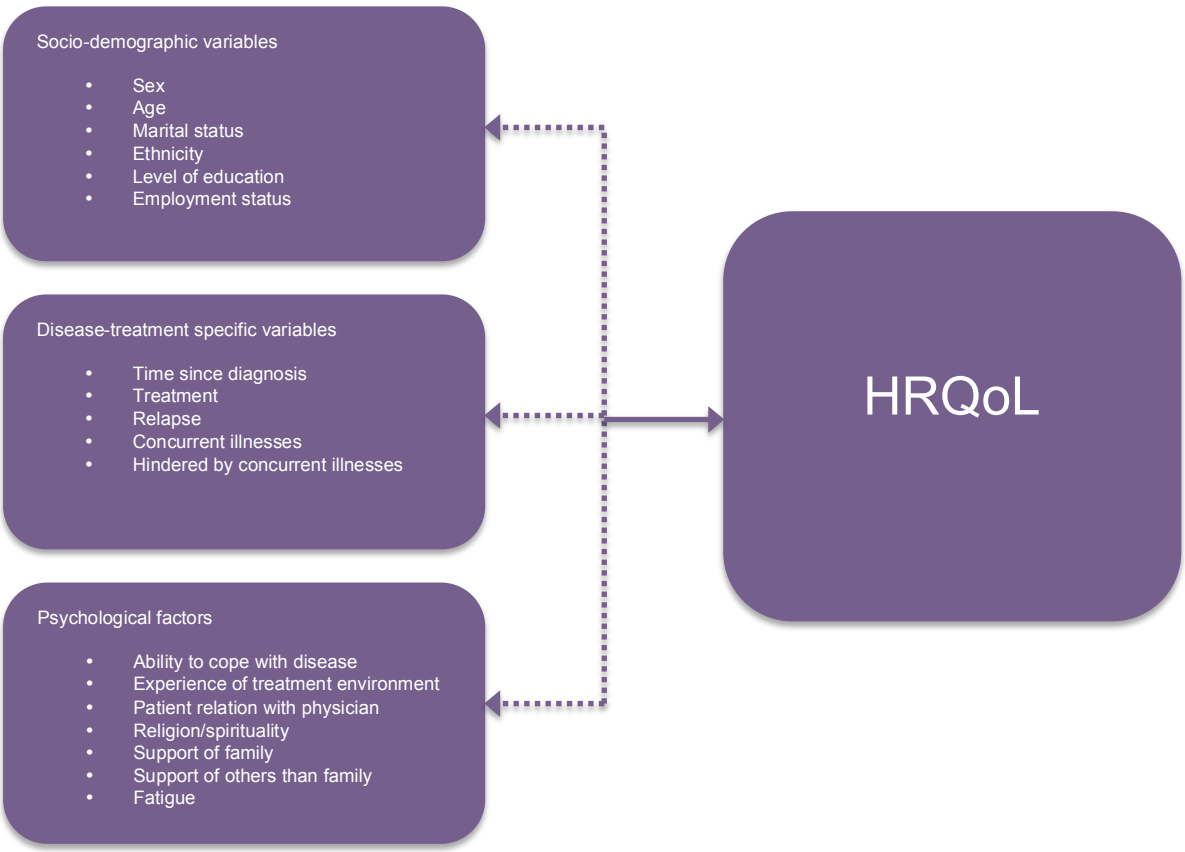


Both models make clear that HRQoL is a complex variable, influenced by different factors such as symptoms and functioning. These relationships can go in different directions and are integrated at different points. Despite the complexity of HRQoL both models make clear how HRQoL is associated with different variables.

Conceptual model

Combining the models of Wilson & Cleary (1995) and Holland (2002) leads to a conceptual model, as a fundament for this research. Both theoretical models describe different variables associated with the HRQoL. The theoretical model of Wilson & Cleary (1995) described the two main characteristics of both the environment of the individual and the characteristics of the individual himself. Examples of these characteristics are gender, age, social support, and concurrent illnesses. The model of Holland (2002) showed four mediating variables, divided in personal, medical, social, and life stresses. To clarify these variables in both theoretical models, the conceptual model contains three types of categories of the individual. Both the individual and environmental characteristics and the personal, medical, social and life stresses variables can be subdivided in these three categories explained in the conceptual model. These categories are socio-demographic variables, disease-treatment specific variables, and psychological factors (Figure 6). This conceptual model contains the information of both theoretical models, were variables associated with a change in HRQoL are described. This model is possibly not only applicable to patients with ALL but to all cancer patients, as this model is partly based on the HRQoL model of cancer of Holland (2002). The dotted arrows show the possible relationships between the independent variables. The purple arrow shows the associations of the independent variables with the HRQoL.

Figure 6 Associations of psychological factors, socio-demographic-, and disease-treatment specific variables with the HRQoL.



2. Methods

This chapter is divided in two parts. In the first paragraph is described how the literature review was performed. The second paragraph describes how the respondents for the explorative study were selected, what types of questionnaires were used, and how the statistical analysis was performed.

2.1 Literature review

A literature review was performed to summarise studies regarding HRQoL and the factors that where associated with the HRQoL in ALL patients. Before starting the literature review different criteria for searching were selected. These inclusion and exclusion criteria focused on the types of studies and types of outcome measures.

The database searched for potentially eligible studies for this review was PubMed. The following search terms were used: quality of life combined with acute lymphoblastic leukaemia (and the other terms and notations of the disease. The word leukaemia was also written as leukemia in the search. This review was restricted to studies published between 1st January 1990 and 30th June 2012. These criteria gave the following query: ((quality of life AND acute lymphoblastic leukemia) OR (quality of life AND acute lymphoblastic leukaemia) OR (quality of life AND acute lymphoid leukemia) OR (quality of life AND acute lymphoid leukaemia) OR (quality of life AND acute lymphocytic leukaemia) OR (quality of life AND acute lymphocytic leukemia) OR (quality of life AND acute lymphatic leukaemia) OR (quality of life AND acute lymphatic leukemia) AND ("1990/01/01"[PDAT] : "2012/06/30"[PDAT])). When cited studies in a publication were useful for this review, these studies were included even if they did not show up in the initial search in PubMed.

Published studies that investigated HRQoL in patients receiving treatment for ALL were considered for inclusion provided that they addressed the objectives of this review. Only quantitative studies were considered. Studies on the development of instrument and measurements were included if empirical data on HRQoL could be extracted. Only English language studies were considered. While many studies have investigated HRQoL of different types of childhood cancers, these were not included if data specific to patients diagnosed for ALL were not provided.

Patients on or off treatment for ALL were selected. This would probably be children, as most studies were performed in younger populations. Only studies in western countries were selected, so results could be translated to the explorative study. The number of patients in the study had to be twenty or higher, approximately the same number as the study population in the explorative study. The outcome measure central to this review was HRQoL in patients during and after treatment for ALL. Data on all widely recognised aspects of HRQoL (physical, psychological, social) or other dimensions were included. Studies containing outcome data on specific side effects (e.g. oral infections) were excluded in this review. Studies that examined HRQoL in the context of specific drug therapies or procedures were included if they measured the overall HRQoL of a group of patients with ALL.

2.2 Explorative study

Study population

Adult patients diagnosed with ALL between 1999 and 2011 in the EMC and still alive were invited to participate in the study. The patients have received their treatment in the academic hospital of

Rotterdam (Erasmus MC). In total 23 patients were asked to fill in the questionnaire made for this study. A participant for this study had to be eighteen years or older at time of diagnosis, so there would be no childhood survivors in this study. The selection of the patients diagnosed with ALL took place with the help of HOVON study.

Data collection

All (former) patients that were invited with the help of HOVON to participate were informed about the study by receiving a letter from the specialists in the hospital (Appendix I). To personalise the letter more, it was printed on hospital paper and signed by the head of the haematology department. In the letter the patient was informed that by returning the completed questionnaire, the patient agreed to participate in this study. It had to be clear for the patients that non-participation would not influence their follow-up care or treatment. After two months, from the spread of the questionnaire for the first time, a reminder letter was sent to the ones who not yet returned the questionnaire (Appendix II). An envelope with the correct address was included to make sure the questionnaires were returned to the correct address.

The questionnaire used for this study consisted of six parts (Appendix III). The first part referred to personal information of the respondent. The second part consisted of five questions about diagnosis and treatment of the patient. The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 is used for the third part of the questionnaire. The fourth part of the questionnaire is the EQ-5D-5L. Fifth part was the Fatigue Assessment Scale (FAS). The questionnaire ended with two questions about support of family and friends. All questions were measured on a nominal or ordinal scale, except the date of birth and the age at diagnosis. There was also some space for the patients to write down comments on the questionnaire or anything else.

The EORTC developed a specific measure to assess the HRQoL of cancer patients. The QLQ-C30 incorporates nine multi-item scales. These nine scales can be divided in five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea & vomiting), and a global health and quality of life scale. In this questionnaire several single-item symptom measures are also included (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties) (Aaronson et al. 1993). To convert the scores of the questionnaire, the EORTC Data Centre scoring manual was needed. The usable score is a score on a scale from 0 to 100. The higher the score on the functional scales and the global health scale the better. The scores on the symptom scales and the single-item symptoms measures were reversed, the lower the score the better (EORTC 1995).

The EQ-5D, a generic specific questionnaire, contains the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depressions. The EQ-5D-5L is used in this study and consisted of five levels on each domain. This standardised instrument is applicable to a wide range of health conditions and treatments. Furthermore it provides a simple descriptive profile and a single index value for health status. The scores on the five questions can be any combination of the numbers 1 and 5. Every combination between 11111 and 55555 is possible. These combinations had to be converted to an utility score. To convert this, the EQ5D-5L Crosswalk value set for the Netherlands was needed (EuroQol 2011). The visual analogue scale (VAS), part of the EQ-5D, is a

type of single-time measure in which respondents indicate their HRQoL on a line or scale. The score can go from 'worst possible HRQoL' (0) to 'best HRQoL' (100). One of the advantages of the VAS is that it is very easy to work with (De Boer et al. 2004).

Fatigue is both a ubiquitous symptom and difficult to define. Several attempts have been made to produce scales that measure both severity and perception of fatigue, without general acceptance (Hueting & Sarphati 1966; Monk 1989). Due to the fast growing number of persons suffering from chronic fatigue syndrome in the nineties, interest in fatigue has grown. This has led to the FAS, a measure of chronic fatigue that consists of ten items. These ten items are statements and can be scored from 1 (never) to 5 (always). These scores have to be converted to a score on a 0 to 50 scale. The higher the score, the more fatigue. A score higher than 21 means a respondent experiences fatigue and a score higher than 34 means a respondent experiences extreme fatigue (Michielsen et al. 2003). The FAS is not a HRQoL-questionnaire, but a measurement to investigate the fatigue of a patient. Outcome of the FAS was only used as an independent variable to find possible associations with a change in HRQoL.

Statistical analysis

The research data was processed with IBM SPSS Statistics 20.0. To analyse the frequency, mean and median of the independent variables, basic descriptive statistics were used. Relationships between the independent variables and the outcomes of EQ-5D utility, and QLQ-C30 domains were analysed using the non-parametric Mann-Whitney and Kruskal Wallis tests due to a small study population. Comparisons between the independent variables and the problems on the different domains of the EQ-5D utility were made doing a Chi-square test, because these domains were measured on an ordinal scale. Beside the comparison of the independent variables and dependent variables, outcomes were compared to a score from the norm population. Norm scores were abstracted from: Van de Poll-Franse et al. (2011) (QLQ-C30) and Essink-Bot et al. (1993) (VAS). No Dutch norm score was available on the EQ-5D-5L.

The lower the significance level, the more conservative the statistical analysis and the more the data must diverge from the null hypothesis to be significant. The level of significance in this study was $p<0.1$ and $p<0.05$. A level of $p<0.1$ was chosen as this explorative study used a very small population. With this higher significance level possible associations between the independent variables and the HRQoL could be detected for future studies. Variables associated with a change in HRQoL and a significance level of $p<0.05$ were not seen as a possible association but as a significant association with changes in HRQoL.

3. Results

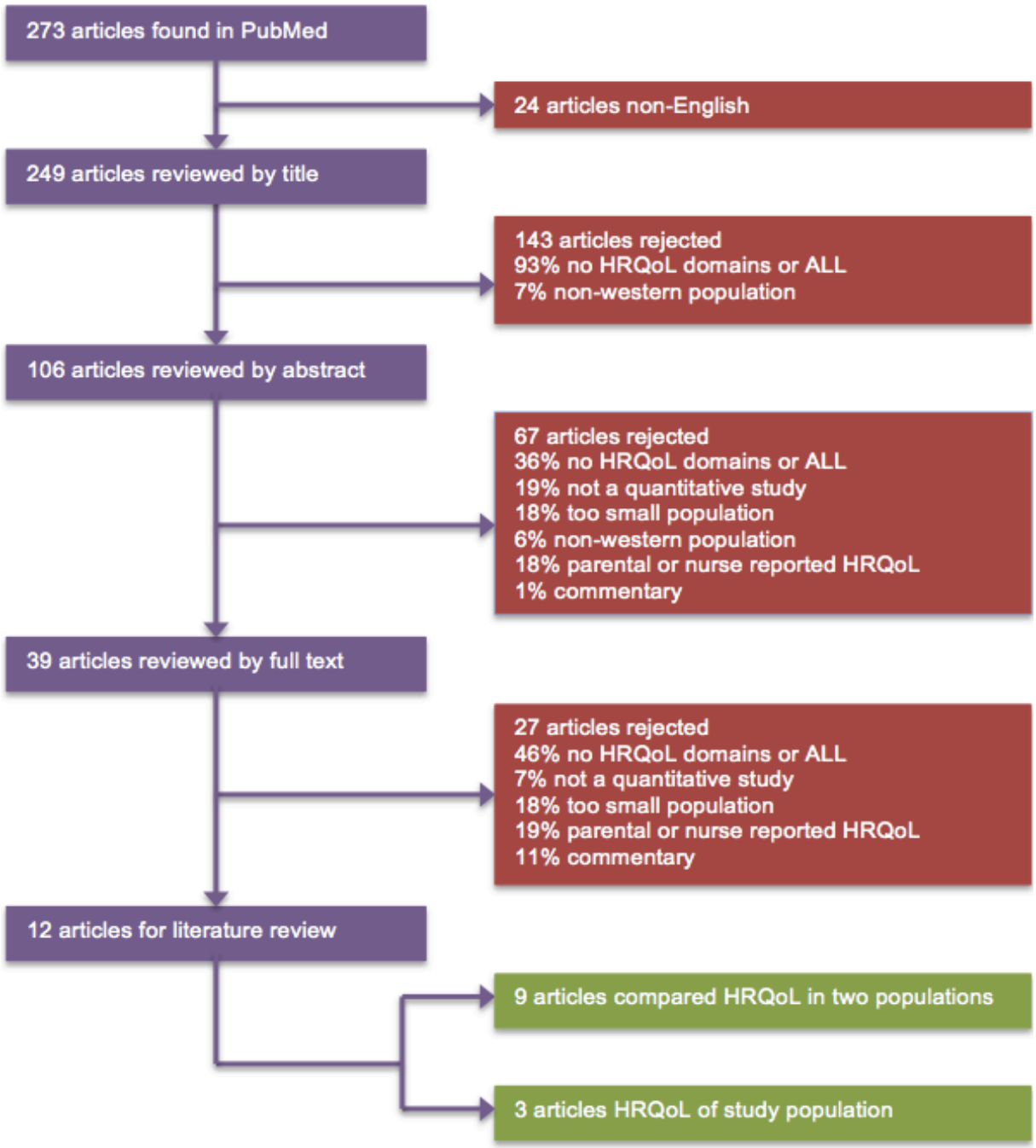
In this chapter the results of the literature review and explorative study are presented. The first paragraph describes the results of the literature review, while in the second paragraph the results of the explorative study are given.

3.1 Results literature review

Method of review

In Figure 7 the selection procedure of the articles for the literature review is shown. Twelve articles met the criteria. All other 261 articles were rejected for different reasons, such as too small populations, not being a quantitative study or not measuring the HRQoL domains used in this thesis.

Figure 7 Overview of the method review.



Study characteristics

In the literature review (Table 2) different questionnaires were used. These questionnaires were structured into generic-, cancer/leukaemia specific- or problem specific questionnaires.

Ten studies used at least one generic questionnaire (Cabanillas et al. 2012; Eiser et al. 2005; Essig et al. 2012; Furlong et al. 2012; Harila et al. 2010; Moe et al. 1997; Pound et al. 2012; Ramchandren et al. 2009; Vance et al. 2001). Domains as pain, fatigue, anxiety, and physical health/self care were scored in the Edmonton Symptom Assessment Scale (ESAS) (Cabanillas et al. 2012), the Paediatric Quality of Life Inventory (PedsQL) (Eiser et al. 2005; Pound et al. 2012; Ramchandren et al. 2009), the Short Form-36 (SF-36) (Essig et al. 2012; Harila et al. 2010), the Health Utility Index (HUI) (Furlong et al. 2012), the General Health Questionnaire (GHQ-28) (Moe et al. 1997), and the Disquol (Vance et al. 2001). Short Form-12 (SF-12) (Moe et al. 1997) is a short version of SF-36. The Disquol (Vance et al. 2001) described situations that commonly occur for children. They are asked how much they are like the child in the description and how much they want to be like the child with the help of a VAS.

Cancer/disease specific questionnaires were used in three studies (Cabanillas et al. 2012; Link et al. 2006; Vance et al. 2001). The Functional Assessment of Cancer Therapy-Anaemia (Fact-an) (Cabanillas et al. 2012) measured fatigue and anaemia-related concerns in people with cancer. AGHDA (Link et al. 2006) was used as a tool for HRQoL in adults with growth hormone deficiency (GHD), where domains were measured such as energy level and emotional reactions. A specific questionnaire for children with cancer is the Paediatric Cancer Quality of Life-32 (PCQL-32) (Vance et al. 2001) and contained domains such as physical functioning and cognitive functioning.

Questionnaires concerning one specific problem were used in four studies (Bauld et al. 1998; Link et al. 2006; Moe et al. 1997; Mulrooney et al. 2008). The State-Trait Anxiety Inventory (STAI) (Bauld et al. 1998) measured two types of anxiety: trait and state anxiety. Trait anxiety is ingrained in a person's personality, meaning that individuals tend to worry more than most people and feel inappropriately threatened by several things in the environment. State anxiety is characterised as a temporary change in a person's emotional state due to an outside factor. The Symptom Checklist-90 (SCL-90) (Link et al. 2006) measured the psychosomatic and emotional distress. Eysenck's short scale of the Eysenck Personality Questionnaire-Revised (EPQ-R) (Moe et al. 1997) measured possible late effects of anxiety and worry on personality. The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) (Mulrooney et al. 2008) measured fatigue.

Nine studies compared the HRQoL between ALL survivors/patients and an ALL-free population (Bauld et al. 1998; Eiser et al. 2005; Essig et al. 2012; Furlong et al. 2012; Harila et al. 2010; Link et al. 2006; Moe et al. 1997; Mulrooney et al. 2008; Ramchandren et al. 2009). The ALL-free population was a control population in four studies (Bauld et al. 1998; Eiser et al. 2005; Furlong et al. 2012; Link et al. 2006), a norm population in two studies (Essig et al. 2012; Ramchandren et al. 2009), and was a sibling/cousin population two studies (Moe et al. 1997; Mulrooney et al. 2008). One study compared the ALL population with both norm and control population (Harila et al. 2010). Taking a control population instead of a norm population means that the control population can be adjusted to a preferred population. A control population makes it possible to match different characteristics with the study population. However, this information is not available and has to be collected specifically for

the study. Information about the norm population is a standard set of data and is already available. This norm population can be seen as a mean of the total population, which is different from a control population that has been specifically selected for a study.

Health-related quality of life in acute lymphoblastic leukaemia survivors

Most studies (Cabanillas et al. 2012; Essig et al. 2012; Link et al. 2006; Mulrooney et al. 2008; Ramchandren et al. 2009) in Table 2 did not investigate or detect factors that were associated with the HRQoL. The other studies found that gender (Bauld et al. 1998; Moe et al. 1997; Pound et al. 2012), treatment phase (Fulrong et al. 2012; Harila et al. 2010), age (Vance et al. 2001), and physical and psychological status (Eiser et al. 2005) were related to the HRQoL. However these factors did not have a great impact or where not supported by other studies. The small populations in most studies might be an explanation for this lack of factors that were related to HRQoL.

A quick look to Table 3 shows that ALL survivors did not experience a significantly worse overall HRQoL (Harila et al. 2010; Link et al. 2006; Moe et al. 1997; Mulrooney et al. 2008; Ramchandren et al. 2009) or even had a better overall HRQoL than the ALL-free population (Essig et al. 2012; Harila et al. 2010). However, a more detailed view on this table showed remarkable and inconsistent findings when different studies were compared.

Firstly, one study showed a significant worse HRQoL on more than one domain compared to the ALL-free population (Furlong et al. 2012). Interesting is that this was the only study that followed the ALL population during treatment and in the post-treatment phase. In all treatment phases the HRQoL of the ALL population was significantly worse than HRQoL of the ALL-free population. However, in the post-treatment phase, there was no significant difference. In all other studies the populations were off treatment and in these studies not more than one domain was significantly worse compared to the ALL-free population. Being on treatment might be associated with a difference in HRQoL.

Secondly, there is a difference in outcomes when an ALL population is compared to the norm population or control population. This was best illustrated in the study that compared the ALL population to both population types (Harila et al. 2010). When compared to the control population (Harila et al. 2010A) there was no significant difference on five HRQoL domains and on three domains the ALL population scored significantly better. When compared to the norm population no significant difference was found in two domains and in six domains the ALL population scored significantly better (Harila et al. 2010B). These differences showed that it mattered to what kind of population the comparison was made. This explanation was supported by findings in other studies. Looking to the domain of self-care & physical functioning the ALL population scored significantly better (Essig et al. 2012; Harila et al. 2010B) or the same (Ramchandren et al. 2009) when compared to the norm population. The ALL population scored the same (Harila et al. 2010A) or significantly worse (Furlong et al. 2012), when compared to the control population. The same findings appeared when looking to the domain of global health and quality of life scale. The ALL population scored significantly better (Essig et al. 2012; Harila et al. 2010B) or the same (Ramchandren et al. 2009), compared to the norm population. The ALL population, when compared to the control population, scored significantly worse (Eiser et al. 2005; Furlong et al. 2012) or the same (Harila et al. 2010A). When the ALL population

was compared to their siblings and/or cousins (Moe et al. 1997; Mulrooney et al. 2008) there was no difference on the different domains. Only in one of these studies a significant worse score was found on the domain fatigue (Moe et al. 1997). Probably there was no difference in HRQoL between ALL survivors and their siblings and/or cousins because their siblings and/or cousins might experience the consequences of ALL and the therapy on themselves as well, both positive and negative. This might explain why no difference was found in these two studies.

Thirdly, age seemed to be related with the scores on HRQoL. Looking to the domain of global health and quality of life scale the studies with a young population (Eiser et al. 2005; Furlong et al. 2012; Ramchandren et al. 2009) had a significant worse or the same score compared to the ALL-free population. The studies with an older population (Essig et al. 2012; Harila et al. 2010; Moe et al. 1997) had a significant better or the same score as the ALL-free population. This same finding was more or less found on other domains as self-care & physical functioning and mental health. These findings might show that age can be related to changes in HRQoL.

Table 2 Literature review

Authors	Study	Country	Questionnaire	Study characteristics	Mean/median age and range at time of study (years)	Time since treatment (TT) or time since diagnosis (TD)	Treatment	Results HRQoL	Factors influencing HRQoL
Bauld et al. 1998	The psychosocial status of adolescent childhood cancer survivors compared with healthy peers.	Australia	STAI	32 adolescent cancer survivors (ALL) compared with 34 healthy adolescents.	Control mean: 14.76 Clinical mean: 14.93 Range for both: 12-17	TT: Different groups of 0-2 years, 2-5 years and >5 years.	Chemotherapy only or with radiation, and chemotherapy with a combination of other modalities.	A significant group-effect for State Anxiety was identified with survivors scoring higher on the STAI than healthy controls, which meant the survivors experienced more anxiety that developed in a response to a fear or danger of a particular situation. No significant difference between cancer survivors and healthy controls was identified for anxiety or a general level of stress that was characteristic for an individual (Trait Anxiety).	A significant effect for gender on State Anxiety. Healthy control females reported a worse State Anxiety than males.
Cabanillas et al. 2012	Determining the effects of Epoetin Alpha on HRQoL.	United States	ESAS (symptoms of pain, fatigue, depression, well-being, and shortness of breath), FACT-Anaemia questionnaires (well-being and fatigue).	74 patients participated in the HRQoL endpoint, of which 40 patients received Epoetin Alpha.	Epoetin Alpha: Mean: 41, median: 39 and range: 18-76 No Epoetin Alpha: mean: 42, median: 42 and range: 15-84	-	Bone marrow transplantation, chemotherapy	No significant differences between the two groups were detected.	-
Elser et al. 2005	A study of the HRQoL of survivors of ALL.	United Kingdom	PedsQL 4.0, separate versions for 8-12 years and 13+ years.	51 survivors of childhood ALL (42 did not receive growth hormone treatment (GHT) and 9 did receive GHT). A comparison was made with population norms.	No GHT mean: 13.38 GHT mean: 15.44 Range for all: 8-18	No GHT mean TD: 9.72 years GHT mean TD: 10.93 years Free from disease ≥ 4 years	Chemotherapy only, radiotherapy only, radio- and chemotherapy.	Survivors of ALL reported significantly poorer total HRQoL compared to UK population norms.	Psychosocial and physical health.
Essig et al. 2012	A comparison of HRQoL of ALL survivors with the general population. Relapsed and non-relapsed ALL survivors were also compared.	Switzerland	SF-36	457 ALL survivors diagnosed between 1976-2003 at age <16 years.	ALL population ≥16	TD: ≥5 years	Chemo-/radiotherapy, bone marrow transplantation.	On physical functioning, role physical, bodily pain, general health, vitality, and mental health ALL patients scored significantly better than norm population. Compared to the norm population ALL patients scored the same on social functioning and significantly lower on role emotional.	-
Furlong et al. 2012	Quantify the HRQoL of children treated for ALL and identify specific disabilities for remediation.	Canada	HUI®, HUI2, HUI3	357 ALL patients in a multi-center clinical trial and general population control groups. Patients were assessed during all four major phases of active treatment and approximately 2 years after treatment.	ALL range: 5-19	Followed during treatment.	Chemotherapy and radiation.	Mean HRQoL increased from induction through the post treatment phase. Differences in mean HRQoL scores between patients and controls were significant during the active treatment phases but not during the post-treatment phase.	Treatment phase.
Harila et al. 2010	HRQoL was studied in a cohort of long term-childhood ALL survivors.	Finland	SF-36	74 survivors of ALL. The control group consisted of 146 healthy young adults selected from local population registry. Results were also compared with the Finnish population norms.	ALL mean: 24 Control mean: 25 Range for both: 17-37	TD: 20 years Range: 10-32 years	Chemotherapy, chemotherapy and cranial irradiation.	ALL survivors achieved significantly better scores than controls on three of the eight subscales: role limitations, mental health, and vitality. ALL survivors achieved significantly better) scores than Finnish population norms on six of the eight subscales: physical functioning, role limitations due to emotional problems, vitality, mental health, general health, and social functioning.	Long follow-up time, more severe late effects and treatment for a relapse were associated with higher HRQoL, especially in the vitality and mental health subscales.
Link et al. 2006	A study of HRQoL of survivors of childhood ALL treated with cranial radiotherapy (CRT).	Sweden	SCL-90 and AGHDA	44 adults who had been treated for childhood onset ALL with CRT. Comparison was made with matched population controls.	ALL median: 24.8 ALL range: 19.8-31.3	TT median; 16.7 years TT range: 6.3-23.9 years	Chemotherapy and radiotherapy.	Compared to controls, the patients did not show a poor HRQoL. The patients did not show any significant difference in social interaction.	-

Table 2 (continued)

Authors	Study	Country	Questionnaire	Study characteristics	Mean/median age and range at time of study (years)	Time since treatment (TT) or time since diagnosis (TD)	Treatment	Results HRQoL	Factors influencing HRQoL
Moe et al. 1997	Long-term survival and HRQoL in patients treated with a national ALL protocol.	Norway	GHQ-28 Eysenck's short scale of the EPQ-R.	94 long-term survivors treated with a national ALL protocol compared to a group of 90 sex-matched siblings/cousins.	ALL mean: 22	TD range: 15-20 years	Chemotherapy	With regard to mental and physical aspects of HRQoL, ALL survivors and controls did not differ significantly. Female ALL survivors experienced a higher level of fatigue.	Gender is a factor that influenced fatigue.
Mulrooney et al. 2008	Prevalence of and risk factors for fatigue and sleep disturbance among adult survivors of childhood cancer.	United States	FACIT-Fatigue	298 childhood ALL survivors diagnosed before age 21, surviving at least 5 years from diagnosis. 500-sibling comparison group.	ALL and control ≥ 18	TD: ≥ 15 years	Chemotherapy and radiotherapy.	No difference was found in fatigue between siblings and the survivors.	-
Pound et al. 2012	The effects of high-dose corticosteroids on behaviour and HRQoL of children with ALL in maintenance therapy.	Canada	PedsQL 3.0.	43 patients returned the questionnaire.	ALL mean: 7 ALL range: 3-18	During ALL maintenance therapy.	Chemotherapy	Children 5 years and above reported more pain and hurt when receiving steroid therapy and teens 13 to 17 years reported more cognitive problems.	Gender is a factor that influenced cognitive problems.
Ramchandren et al. 2009	The HRQoL among children who survived ALL.	United States	PedsQL	37 survivors of childhood ALL aged 8-18	ALL mean: 14.4 ALL range: 8-18	TD mean: 7.4 years	Chemotherapy	The total summary score of PedsQL was in the normal range of population values.	-.
Vance et al. 2001	The relationship between child- and parent-reported HRQoL.	United Kingdom	PCQL-32 and Disquol.	32 children with ALL, 36% was on treatment.	ALL mean: 8.92 ALL range: 6-12	TD mean: 4 years	Any stage of cancer treatment.	On PCQL-32 older children reported better physical functioning than younger children. On Disquol the older children reported better actual self-scores than younger children.	Age influenced physical functioning and actual self-scores.

Table 3 Summary of studies that compared ALL survivors with a healthy or norm population.

Study no.	Population	Mean/median age and range (years)	Time since treatment (TT) or time since diagnosis (TD)	Questionnaire	Comparison group: Control population = CP Norm population = NP Siblings = SB Sibling/cousins = SC	Self care & Physical functioning	Role limitations due to physical problems	Pain	Global health and quality of life scale	Fatigue	Social functioning	Anxiety and depression	Mobility	Emotional functioning	Mental health	Cognitive functioning	Vitality
Bauld et al. 1998	32	Control mean age: 14.76 Clinical mean age: 14.93 Age range for both: 12-17	TT: Different groups of 0-2 years, 2-5 years and >5 years.	STAI	CP vs. survivors of ALL							S T					
Eiser et al. 2005	51	No GHT mean: 13.38 GHT mean: 15.44 Range for all: 8-18	No GHT mean TD: 9.72 years GHT mean TD: 10.93 years Free from disease ≥ 4 years	PedsQL 4.0	CP vs. survivors of ALL												
Essig et al. 2012	457	ALL population ≥16	TD: ≥5 years	SF-36	NP vs. survivors of ALL												
Furlong et al. 2012	357	Range: 5-19	Followed during treatment	HUI®, HUI2, HUI3	CP vs. ALL patients												
Harila et al. 2010 (A)	74	ALL mean: 24 Control mean: 25 Both range: 17-37	TD: 20 years Range: 10-32 years	SF-36	CP vs. survivors ALL												
Harila et al. 2010 (B)	74	ALL mean: 24 Control mean: 25 Both range: 17-37	TD: 20 years Range: 10-32 years	SF-36	NP vs. survivors ALL												
Link et al. 2006	44	ALL median: 24.8 ALL range: 19.8-31.3	TT median; 16.7 years TT range: 6.3-23.9 years	SCL-90, AGHDA	CP vs. survivors ALL												
Moe et al. 1997	94	ALL mean: 22	TD range: 15-20 years	SF-12, GHQ-28, Eysenck's short scale of EPQ-R	SC vs. survivors ALL												
Mulrooney et al. 2008	298	ALL and control ≥ 18	TD: ≥ 15 years	FACIT-fatigue	SB vs. survivors ALL												
Ramchandren et al. 2009	37	ALL mean: 14.4 ALL range: 8-18	TD mean: 7.4 years	PedsQL	NP vs. survivors ALL												

Green indicates a significantly better score, blue indicates a similar score and red indicates a significantly worse score from the study population in the literature review compared to disease-free population.

S= State anxiety

T=Trait anxiety

3.2 Results explorative study

Outcomes on the independent variables

In Table 4 the patient characteristics and outcomes on the independent variables are described. Nineteen respondents returned the questionnaire, which gave a response rate of 82.6%. Mean age of the respondents was 43.21 years, with 7.71 years as mean time since diagnosis. Most respondents were male (57.9%), came from a western country (84.2%), were married (63.2%), had finished vocational education (68.4%), and received allogeneic SCT (52.6%). Concurrent illnesses were reported by 78.9% of the respondents and 84.2% experienced their environment treatment as pleasant or very pleasant. A patient-physician (attending physician) relation was reported by 63.2%. Nearly every respondent experienced support from his or her friends and family (89.5%). A mean score of 21.7 was reported by the respondents on the FAS. This mean score is lower than 22, on average a respondent did not experience fatigue. However, eight respondents (47,1%) had a higher score than 22. So almost halve of the respondents did experience fatigue. The lowest score on the FAS was 13 and the highest score was 34.

Table 4 Patient characteristics and outcomes on the independent variables.

Independent variables	N/Mean	%	SD	Independent variables	N/Mean	%	SD
Sex				**Age in years**	43.21		13.07
Male	11	57.9%		≤42 years	9	47.4%	
Female	8	42.1%		>42 years	10	52.6%	
Marital status				**Level of education**			
Married/living together	12	63.2%		Primary education	1	5.3%	
Divorced/split up	2	10.5%		Secondary education	2	10.5%	
Never been married or lived together	5	26.3%		Vocational	13	68.4%	
				University/higher education	3	15.8%	
Ethnicity				**Religion/spirituality**			
Western	16	84.2%		Yes	9	47.4%	
Non-western	3	15.8%		No	10	52.6%	
Employment status				**Treatment environment**			
Employed	7	36.8%		Very pleasant	6	31.6%	
Retirement/pre-retirement	3	15.8%		Pleasant	10	52.6%	
Disabled	3	15.8%		Not pleasant/not unpleasant	1	5.3%	
Unemployed/housekeeping	3	15.8%		Very unpleasant	1	5.3%	
Unknown	3	15.8%		Unknown	1	5.3%	
Time since diagnosis in years	7.71		2.62	**Treatment**			
≤6.5 years	9	47.4%		Allogeneic SCT	10	52.6%	
>6.5 years	10	52.6%		Autologous SCT	4	21.1%	
				Chemotherapy	5	26.3%	
Relapse				**Ability to cope with the disease**			
Yes	3	15.8%		Yes	14	73.7%	
No	16	84.2%		Not always	5	26.3%	
Concurrent illnesses				**Hindered by concurrent illnesses**			
Yes	15	78.9%		Yes	9	60.0%	
No	4	21.1%		No	6	40.0%	
Patient relation with physician				**Fatigue**			
Personal relation	7	36.8%		Score between 0-21	9	52.9%	
Patient-physician relation	12	63.2%		Score ≥22	8	47.1%	
Support of family				**Support of others than family**			
Yes	17	89.5%		Yes	17	89.5%	
No	1	5.3%		No	1	5.3%	
Unknown	1	5.3%		Unknown	1	5.3%	

Scores on the health-related quality of life questionnaires

Mean score of the utility of the respondents was 0.86. The lowest EQ-5D utility was 0.37 and almost half of the respondents (47.1%) had the highest possible utility of 1. Respondents reported a mean score of 74.71 on the VAS. The worst reported score on the VAS was 35 and the highest reported score was 99 (Table 5).

On the global health scale of the QLQ-C30 the mean score was 75. All mean scores for the five functioning scales were above 65, with the lowest mean score for role functioning (66) and the

highest mean score for emotional functioning (86). The mean scores for the nine different symptom scales differed a lot. The highest scores were reported for fatigue (31), dyspnoea (24.6), financial difficulties (24.1), and insomnia (20). Mean scores for the other symptom scales were all below 15. All scores for the five functioning scales and the global quality of life of the QLQ-C30 were worse than norm scores. For the nine symptom scales only three mean scores of the respondents for pain, constipation, and diarrhoea were better or the same compared to norm scores in absolute numbers. The lowest number of respondents that scored a better score than the norm score is for the domain of fatigue, only 33.3% scored better. There was a better score was for constipation (88.9%) and diarrhoea (94.4%). Significant differences were found on six domains of the QLQ-C30. A significant worse score was found on physical functioning (p=0.043), role functioning (p=0.016), social functioning (p=0.026), fatigue (p=0.016), dyspnoea (p=0.033), and financial difficulties (p=0.024). There was no significant difference when the norm score of the VAS was compared with the mean score of the respondents.

Table 5 Outcomes of the HRQoL questionnaires and comparison with norm scores.

Domains/Scale	Norm score	Mean score	Range	%+	N	SD	P-value	Score compared to norm population
EQ-5D utility	-	0.86	0.37-1	58.8%	17	0.20	0.611	-
VAS	81.36	74.71	35-99	58.8%	17	16.5	0.116	
Global health QLQ-C30	78	75	33.3-100	44.4%	18	19.1	0.580	
Physical Functioning	90	77	6.7-100	47.4%	19	26.3	0.043*	
Role Functioning	89	66	0.0-100	42.1%	19	37.9	0.016*	
Emotional Functioning	89	86	41.7-100	55.6%	18	15.9	0.452	
Cognitive Functioning	92	83	50.0-100	44.4%	18	19.0	0.069	
Social Functioning	94	76	0.0-100	44.4%	18	31.4	0.026*	
Fatigue	17	31	0.0-66.7	33.3%	18	21.4	0.016*	
Nausea and vomiting	2.7	3.7	0.0-16.7	77.8%	18	7.1	0.558	
Pain	15	15	0.0-66.7	61.1%	18	24.8	0.975	
Dyspnoea	7.1	24.6	0.0-100	55.6%	19	33.0	0.033*	
Insomnia	14	20	0.0-66.7	55.6%	18	25.9	0.312	
Appetite loss	3.3	11.1	0.0-66.7	72.2%	18	19.8	0.113	
Constipation	4.8	3.7	0.0-33.3	88.9%	18	10.8	0.672	
Diarrhoea	3.9	1.9	0.0-33.3	94.4%	18	7.9	0.284	
Financial difficulties	3.1	24.1	0.0-100	61.1%	18	35.8	0.024*	

+% of the respondent which scored better than norm score
*P<0.05
Red indicates a significant worse score
Blue indicates no significant difference

Associations with health-related quality of life

The reported problems on the domains of the EQ-5D are described in Table 6. Most problems were reported on mobility; only half of the respondents did not experience any problems with mobility (52.9%). Respondents reported problems on the domain of pain/discomfort as well. More than 40% experienced little pain/discomfort or more. Nearly everyone experienced no problems with self-care. This made it the domain with the best score. Anxiety/depression was hardly experienced. Only 11.8% reported some anxiety/depression, and the other respondents experienced no anxiety/depression. In daily activities 64.7% experienced no problems.

Table 6 Reported problems on the domains of the EQ-5D.

Domain EQ-5D	No problems	Little problems	In between	Heavy problems	Extreme problems
Mobility	9 (52.9%)	4 (23.5%)	2 (11.7%)	2 (11.7)%	0
Self-care	16 (94.1%)	0	0	0	1 (5.9%)
Daily activities	11 (64.7%)	4 (23.5%)	1 (5.9%)	1 (5.9%)	0
Pain/Discomfort	10 (58.8%)	3 (17.6%)	3 (17.6%)	1 (5.9%)	0
Anxiety/Depression	15 (88.2%)	0	2 (11.8%)	0	0

A closer look (Table 7) showed that employment status was associated with problems on mobility (p=0.051) and daily activities (p=0.081). Disabled people more frequently reported problems with mobility and their daily activities. Furthermore, disabled people had a significant lower EQ-5D utility compared to employed (p<0.000), unemployed/housekeeping (p=0.002), and retired respondents (p=0.004). Reported problems on anxiety/depression were significantly associated with the ability to cope with the disease (p=0.039). Not always capable of coping with the disease was associated with more reported problems on anxiety/depression. Having another disease was associated with more frequently reported problems on mobility (p=0.082). Reported problems on mobility (p=0.057) and problems with daily activities (p=0.015) were both associated with experiencing fatigue. Furthermore, the EQ-5D utility was significantly lower when respondents reported concurrent illnesses (p=0.045), and reported fatigue (p=0.045).

Table 7 Associations between independent variables and the EQ-5D domains and utility score.

Independent variables	Mobility	Self-care	Daily activities	Pain/ Discomfort	Anxiety/ Depression	EQ-5D utility
Sex	1.000	1.000	0.332	1.000	1.000	0.669
Age group	1.000	1.000	1.000	0.637	1.000	0.673
Marital status	1.000	1.000	0.502	1.000	0.137	0.901
Ethnicity	0.576	1.000	1.000	0.603	0.405	0.477
Level of education	1.000	1.000	1.000	0.491	0.490	0.756
Employment status	0.051*	0.533	0.081*	0.252	0.267	0.083*
Employed	***1 (3.3)***		***1 (2.8)***			***0.95***
Retirement/pre-retirement	***2 (1.4)***		***1 (1.2)***			***0.86***
Disabled	***3 (1.3)***		***3 (1.2)***			***0.41***
Unemployed/housekeeping	***1 (0.9)***		***1 (0.8)***			***0.94***
Time since diagnosis group	0.637	0.444	0.630	1.000	1.000	0.541
Treatment	0.813	1.000	0.137	1.000	1.000	0.677
Relapse	0.471	1.000	0.497	0.485	1.000	0.235
Concurrent illnesses	0.082*	1.000	0.119	0.103	1.000	0.045**
Yes	***9 (7.0)***					***0.81***
No	***0 (2.0)***					***1.00***
Hindered by concurrent illnesses	1.000	0.357	0.266	0.592	0.505	0.724
Ability to cope with disease	1.000	1.000	1.000	1.000	0.039**	0.703
Yes					***0 (1.6)***	
Not always					***2 (0.4)***	
Treatment environment	0.620	1.000	0.406	0.590	0.559	0.676
Patient relation with physician	0.335	1.000	0.151	0.134	1.000	0.133
Religion/spirituality	1.000	1.000	0.335	0.637	1.000	0.481
Support of family	1.000	1.000	0.389	0.412	0.111	0.353
Support of others than family	1.000	1.000	0.389	0.412	0.111	0.235
Fatigue	0.057*	0.471	0.015*	0.302	0.206	0.071*
Score between 0-21	***2 (4.2)***		***1 (3.7)***			***0.95***
Score >21	***6 (3.8)***		***6 (3.3)***			***0.74***

*P<0.1 **P<0.05 Scores in bold are the respondents with problems within that domain and the bold scores between brackets are the expected respondents with problems within that domain according the χ^2. The numbers in bold beneath the EQ-5D utility are the mean scores.

The analysis of significant relationships between the independent variables and the QLQ-C30 domains showed different significant associations between these factors and the outcomes on these domains (Table 8). Not always being able to cope with the disease and experiencing fatigue seemed both to be important variables, which were significantly associated with most domains of the QLQ-C30. Respondents that were not always able to cope with the disease had a significant worse score on global health (p=0.026), physical functioning (p=0.026), emotional functioning (p=0.014), social functioning (p=0.046), fatigue (p=0.019), dyspnoea (p=0.014), and insomnia (p=0.075). Respondents that experienced fatigue had a significant worse score on global health (p=0.011), physical functioning (p=0.074), role functioning (p=0.011), social functioning (p=0.011), fatigue (p=0.074), appetite loss

(p=0.093), and financial difficulties (p=0.046). Having no religion accounted for significant worse scores on different domains as, global health (p=0.031), physical functioning (p=0.028), role functioning (p=0.035), social functioning (p=0.077), and dyspnoea (p=0.095).

Other variables were not significantly associated with more than three domains. Respondents with concurrent illnesses scored significantly worse on physical functioning (p=0.062), cognitive functioning (p=0.035), and dyspnoea (p=0.080). Unemployed respondents had a significant worse score on role functioning (p=0.005) compared to employed respondents. Disabled respondents experienced significantly more financial difficulties compared to employed respondents (p=0.037) and had a significant lower score on role functioning compared to retired (p=0.057) and employed respondents (p=0.010). Respondents who divorced or split up scored significantly worse on emotional functioning compared to respondents who married or lived together (p=0.031). Global health was significantly better for respondents diagnosed more than 6.5 years ago (p=0.063). Receiving chemotherapy was significantly associated with more nausea and vomiting than having allogeneic SCT (p=0.014) and autologous SCT (p=0.018), which was typical as SCT could cause nausea and vomiting as well. A personal relationship during treatment with the physician was associated with a significant better score on global health (p=0.069) and role functioning (p=0.036).

Remarkable outcomes were the different scores for the variable relapse compared to the domain fatigue. Respondents with no relapse had a significant worse score on the FAS (p=0.088). However, these same respondents scored on the domain fatigue of the QLQ-C30 significantly better than the respondents with a relapse (p=0.076). Possibly those questionnaires measured fatigue in a different way.

Table 8 The P-values of the QLQ-C30 domains compared with the independent variables.

Independent variables	GH	PF	RF	EF	CF	SF	FA	NV	PA	DY	SL	AP	CO	DI	FI
Sex	0.762	0.717	0.657	0.360	0.515	0.762	0.573	0.897	0.897	0.600	0.633	0.829	0.408	0.696	0.829
Age	0.546	0.604	0.549	0.863	0.796	0.436	0.666	0.436	0.161	0.720	0.863	0.796	1.000	0.730	0.136
Marital status	0.404	0.930	0.492	0.011**	0.584	0.143	0.486	1.000	0.905	0.878	0.126	0.961	1.000	1.000	0.172
Married/living together				***92***											
Divorced/split up				***63***											
Never been married or lived together				***82***											
Ethnicity	0.959	0.810	0.736	0.878	0.959	0.878	0.645	0.959	0.798	0.357	0.277	0.878	0.721	0.878	0.645
Level of education	0.964	0.432	0.327	0.960	0.949	0.790	0.394	0.567	0.861	0.344	0.530	1.000	1.000	1.000	0.403
Employment status	0.277	0.293	0.025**	0.275	0.005***	0.144	0.274	1.000	0.459	0.108	0.740	0.420	0.562	1.000	0.055*
Employed			***95***		***98***										***9.5***
Retirement/pre-retirement			***89***		***78***										***11.1***
Disabled			***56***		***83***										***67.7***
Unemployed/housekeeping			***28***		***61***										***11.1***
Time since diagnosis	0.063*	0.211	0.211	0.436	0.436	0.190	0.161	0.113	0.666	0.720	0.605	0.222	0.436	0.730	0.931
≤6.5 years	***67***														
>6.5 years	***84***														
Treatment	0.472	0.618	0.186	0.196	0.672	0.079*	0.706	0.037**	0.805	0.122	0.815	0.384	1.000	0.444	0.222
Allogeneic SCT						***72***		***1.7***							
Autologous SCT						***100***		***0***							
Chemotherapy						***63***		***12.5***							
Relapse	0.164	0.359	0.171	0.654	0.824	0.426	0.076*	0.164	0.654	0.421	1.000	0.912	0.738	0.912	0.738
Yes							***52***								
No							***26***								
Concurrent illnesses	0.158	0.062*	0.262	0.127	0.035**	0.442	0.158	0.959	0.505	0.080*	0.382	0.878	0.721	0.878	0.645
Yes		***72***			***79***					***31.1***					
No		***97***			***100***					***0***					
Hindered by concurrent illnesses	0.298	0.689	0.689	0.797	0.289	0.699	0.518	0.438	0.898	0.456	0.112	0.518	0.797	0.797	0.898
Ability to cope with disease	0.026**	0.026**	0.298	0.014**	0.208	0.046**	0.019**	0.443	0.443	0.014**	0.075**	0.208	0.633	0.849	0.924
Yes	***83***	***85***		***92***		***87***	***24***			***14.3***	***12.8***				
Not always	***57***	***55***		***70***		***47***	***49***			***53.3***	***40.0***				
Treatment environment	0.250	0.216	0.330	0.269	0.241	0.125	0.105	0.282	0.840	0.282	0.515	0.191	1.000	0.412	0.758
Patient relation with physician	0.069*	0.120	0.036**	0.860	0.425	0.724	0.104	0.724	0.246	0.773	0.659	1.000	0.860	0.659	0.930
Personal relation	***85***		***90***												
Patient-physician relation	***69***		***51***												
Religion/Spirituality	0.031**	0.028**	0.035**	0.863	0.796	0.077*	0.113	0.436	0.666	0.095*	0.605	0.222	0.436	0.730	0.605
Yes	***86***	***88***	***85***			***87***				***11.1***					
No	***66***	***67***	***48***			***65***				***36.7***					
Support of family	0.118	0.444	0.778	0.118	0.824	0.353	0.588	0.824	0.588	0.556	0.235	0.353	0.941	0.941	0.706
Support of others than family	0.235	0.222	0.667	0.235	0.824	0.118	0.118	0.824	0.235	0.222	0.706	0.353	0.941	0.941	0.353
Fatigue	0.011**	0.074*	0.011**	0.277	0.277	0.011**	0.074*	0.743	0.236	0481	0321	0.093*	0.963	0.743	0.046**
Score between 0-21	***87***	***91***	***91***			***94***	***20***					***0.00***			***3.7***
Score >21	***68***	***74***	***54***			***65***	***38***					***20***			***45.8***

*P<0.1
**P<0.05
***P<0.01
Numbers in bold are the mean scores on the domains
GH= Global quality of life **(High score represents high HRQoL)**
Functioning scales: PF=Physical functioning, RF= Role functioning, EF= Emotional functioning, CF= Cognitive functioning and SF= Social functioning **(High score indicates good functioning)**
Symptom scales: FA= Fatigue, NV= Nausea/vomiting and PA= Pain **(High score indicates high level of symptomatology)**
Single items: DY= Dyspnoea, SL= Insomnia, AP= Appetite loss, CO= Constipation, DI= Diarrhoea and FI= Financial difficulties **(High score indicates high level of symptomatology)**

Discussion

The purpose of this study was to collect information about the HRQoL of ALL patients and the factors associated with the HRQoL. This was done by a systematic review of studies focusing on HRQoL and ALL patients, and by performing an explorative study in Dutch adult ALL patients. The literature review and the explorative study gave information about the HRQoL status and the relationships between different variables and the HRQoL outcomes. Information on outcomes of the explorative study differed as this population was diagnosed with ALL when they were adults, while the available studies in the literature review contained children populations when diagnosed with ALL.

According to the literature, patients could experience significant adverse effects during different phases of treatment (Truong et al. 2007; Priest et al. 1980; Schiffer et al. 2001; Von der Weid & Spog 2001; Hertzberg et al. 1997; Kingma et al. 1993). However, the studies in the literature review showed a HRQoL comparable or even better than the ALL-free population. Only when the population was followed during treatment, the HRQoL of this population was lower than in the ALL-free population. Another finding in the literature review was a difference in outcomes depending on the population the ALL population was compared to. A significant better score for the ALL population was shown when compared to a norm population, while there were few significant differences when compared to a control population. The norm population had possibly a lower HRQoL than the control population, as the control population normally consisted of a disease-free population. In the explorative study no HRQoL domains of the ALL population were significantly better than the norm population, but a significant worse score was found for physical functioning, role functioning, social functioning, fatigue, dyspnoea, and financial difficulties. Different variables were associated with a lower HRQoL. Employment status, concurrent illnesses, treatment, relapse, ability to cope with the disease, patient relation with physician, religion, and fatigue were all associated with a significant lower score on more than one HRQoL domain.

The outcomes of the literature review and the explorative study differed from each other. While in the literature review the HRQoL of the ALL population was not worse compared to the general population, the HRQoL of the ALL population in the explorative study was worse compared to the general population on some domains. The outcomes of the literature review and the explorative study could be compared to the HRQoL model based on the models of Wilson & Cleary (1995) and Holland (2002). In this model associations were drawn between psychological factors, socio-demographic variables, and disease-treatment specific variables and HRQoL. Based on the literature review the associations given in the conceptual model would not be applicable to ALL patients. However, the explorative study showed different associations between the HRQoL and the independent variables such as employment status, civil class, treatment, fatigue, and concurrent illnesses. These variables were part of the categories in the conceptual model. The explorative study partly confirmed that socio-demographic variables, disease-treatment specific variables, and psychological factors were associated with changes in HRQoL. In future studies this conceptual model should be studied in-depth as the explorative study showed some possible associations between the independent variables and the changes in HRQoL.

A possible explanation for these differences between the literature review and the explorative study is the study population. The literature review consisted of children diagnosed with ALL, while

adult ALL patients were included in the explorative study. Maybe a person's HRQoL is more influenced when experiencing a disease at an older age. Another difference between these study populations was the time since diagnosis. In the literature review the populations were diagnosed with ALL a longer time ago. It is possible that HRQoL increases overtime. Better scores on HRQoL in the literature review can be caused by the survivors' subjective perceptions of HRQoL. These subjective perceptions may be affected by a desire to be as normal as possible, causing a response shift. Caught in the paradox of satisfaction, ALL survivors also tend to deny difficulties on HRQoL measures and to report high HRQoL even under difficult life conditions (Essig et al. 2012). However, in the literature review some studies showed a lower outcome on some domains. Possible explanations for the inconsistent findings might be the characteristics of the ALL population, the characteristics of the healthy population or the type of questionnaire used. Inconsistent findings between the literature review and the explorative study might be explained by the study characteristics of the normative data used. The normative data of the QLQ-C30 (Van de Poll-Franse et al. 2011) was derived from a population that was older, with fewer males, with more people living together, where more people finished university, and where more people were employed than the study population in the explorative study. The normative data of the VAS (Essink-Bot et al. 1993) was derived from a population where there were fewer males, and most respondents were much younger or much older than the study population in the explorative study. It can be expected that a population with more employed, married or living together, and highly educated respondents has a higher HRQoL. For a better comparison between norm scores and a study population, the study population should be adjusted to this norm population or a special control population should be taken.

Strength of this study is the uniqueness of measuring HRQoL of ALL patients diagnosed at adult age. Previous studies included only children diagnosed with ALL. As this explorative study showed a different outcome compared to the literature review, it is important to perform more HRQoL studies with patients diagnosed with ALL at adult age. Another strength of this study is the focus on different HRQoL domains and not only the overall HRQoL. This makes clear which aspects of HRQoL are affected in people with ALL. The explorative study has also some limitations. It has to be kept in mind that due to a small study population a lack of significant effects on HRQoL can be caused. Maybe some factors are indeed significant associated to the HRQoL outcome, even if this was not shown in the explorative study. Another limitation is the origin of the study population. All respondents are or have been under treatment in the Erasmus MC. It is possible that the treatment atmosphere, patient relation with physician, and other factors might differ compared to other hospitals, and so influence the HRQoL.

Based on the results of the literature review and the explorative study the overall HRQoL of the ALL population is not that worse compared to the general population, while this was expected according to the literature and the HRQoL model. Possible explanations for these differences are given. However, further research on this subject is still recommended. Insight in the HRQoL of adult ALL patients is still useful as the survival rate has been increased and stays stable over the past years. This further research should focus more on the variables such as disability, having concurrent illnesses, psychological factors as the ability to cope with the disease, fatigue, and treatment that were all associated with HRQoL in the explorative study. Focus on these variables would probably make it

possible to give patients the best treatment and support based on their characteristics to not let these factors influence their HRQoL negatively.

It would be more interesting to follow a group of ALL patients over time. This will give insight in the development of their HRQoL right after diagnosis. Research can be done in different time periods such as two years since diagnosis, five years since diagnosis, ten years since diagnosis and even longer. Conclusions can be drawn on the long and very long-term effects and which domains of HRQoL are still being influenced on the long term.

Summarising, the small effects found in this study requires in-depth investigation in larger groups of patients. It should be attempted to better describe and quantify late effects by promoting regular long-term follow-up visits, where survivors can be examined and interviewed. Further preventing and minimising late effects of the disease will improve HRQoL in survivors of ALL, particularly those who were declared disabled, experienced concurrent illnesses, and experienced fatigue.

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Appendix I: Cover letter

Doorkiesnummer 010-4089763
E-mail leunis@bmg.eur.nl
Datum 22 maart 2012

Geachte heer/mevrouw,

U krijgt deze brief omdat in het verleden bij u de ziekte acute leukemie is vastgesteld. U bent voor deze ziekte behandeld in het Erasmus MC. Acute leukemie is een vrij zeldzame ziekte en daardoor is nog weinig bekend over de invloed van de ziekte en de behandeling op de kwaliteit van leven van patiënten. Om hier toch meer over te weten te komen, willen wij u vragen om bijgevoegde vragenlijst in te vullen.

Met de resultaten van dit vragenlijst onderzoek hopen wij meer informatie te hebben over de invloed van de ziekte en de behandeling op de kwaliteit van leven. Deze informatie kan in de toekomst mogelijk helpen bij het kiezen van de beste behandeling voor de patiënt.

Deelname aan het onderzoek
Deelname aan dit onderzoek is heel eenvoudig, u hoeft alleen de vragenlijst in te vullen en met de bijgevoegde antwoordenvelop terug te sturen. Het invullen van de vragenlijst duurt ongeveer 15 minuten. Met het terugsturen van de vragenlijst geeft u gelijk toestemming voor deelname aan dit onderzoek. Als u besluit niet deel te nemen aan dit onderzoek heeft dit geen invloed op de zorg die u ontvangt.

Vertrouwelijkheid
Tot uw persoon herleidbare onderzoeksgegevens kunnen slechts met uw toestemming door daartoe bevoegde personen worden ingezien. Deze personen zijn medewerkers van het onderzoeksteam, medewerkers van de Inspectie voor de Gezondheidszorg of bevoegde inspecteurs van een buitenlandse overheid, en leden van de Medisch Ethische Toetsings Commissie. Inzage kan nodig zijn om de betrouwbaarheid en kwaliteit van het onderzoek na te gaan. Onderzoeksgegevens zullen worden gehanteerd met inachtneming van de Wet Bescherming Persoonsgegevens en het privacyreglement van uw ziekenhuis.

Persoonsgegevens die tijdens deze studie worden verzameld, zullen worden vervangen door een codenummer. Alleen dat nummer zal gebruikt worden voor studiedocumentatie, in rapporten of publicaties over dit onderzoek. Slechts degene, die de sleutel van de code heeft (de onderzoeker) weet wie de persoon achter het codenummer is.

Heeft u nog vragen?
Mocht u na het lezen van deze brief nog meer informatie willen ontvangen of komen er nog vragen bij u op, dan kunt u contact opnemen met de coördinerende onderzoeker van deze studie: Annemieke Leunis. Telefoon: 010-4089763 of via leunis@bmg.eur.nl.

Als u niet tevreden bent over het onderzoek of de behandeling kunt u terecht bij de onafhankelijke klachtencommissie van het Erasmus MC. De klachtencommissie is te bereiken op telefoonnummer 010-7033198.

Met vriendelijke groet,

Annemieke Leunis, MSc Onderzoeker	Prof.Dr. B Löwenberg Principal Investigator Hematologie Erasmus MC	Prof.Dr. P. Sonneveld Afdelingshoofd Hematologie Erasmus MC

Appendix II: Cover letter reminder

Doorkiesnummer 010-4089763
E-mail leunis@bmg.eur.nl
Datum 4 mei 2012

Geachte heer/mevrouw,

U krijgt deze brief omdat in het verleden bij u de ziekte acute leukemie is vastgesteld. U bent voor deze ziekte behandeld in het Erasmus MC. Acute leukemie is een vrij zeldzame ziekte en daardoor is nog weinig bekend over de invloed van de ziekte en de behandeling op de kwaliteit van leven van patiënten. Om hier toch meer over te weten te komen, hebben wij u enkele weken geleden een vragenlijst toegestuurd.

Tot op heden hebben wij van u nog geen vragenlijst retour ontvangen. Om een goed inzicht te krijgen in de kwaliteit van leven bij patiënten die in het verleden zijn behandeld voor acute leukemie willen wij zoveel mogelijk vragenlijsten retour ontvangen. Bijgaand treft u daarom een nieuwe kwaliteit van leven vragenlijst aan. Indien u in de tussentijd toch de vorige vragenlijst heeft geretourneerd, kunt u deze brief als niet verzonden beschouwen.

Met de resultaten van dit vragenlijst onderzoek hopen wij meer informatie te hebben over de invloed van de ziekte en de behandeling op de kwaliteit van leven. Deze informatie kan in de toekomst mogelijk helpen bij het kiezen van de beste behandeling voor de patiënt.

Deelname aan het onderzoek
Deelname aan dit onderzoek is heel eenvoudig, u hoeft alleen de vragenlijst in te vullen en met de bijgevoegde antwoordenvelop terug te sturen. Het invullen van de vragenlijst duurt ongeveer 15 minuten. Met het terugsturen van de vragenlijst geeft u gelijk toestemming voor deelname aan dit onderzoek. Als u besluit niet deel te nemen aan dit onderzoek heeft dit geen invloed op de zorg die u ontvangt.

Vertrouwelijkheid
Tot uw persoon herleidbare onderzoeksgegevens kunnen slechts met uw toestemming door daartoe bevoegde personen worden ingezien. Deze personen zijn medewerkers van het onderzoeksteam, medewerkers van de Inspectie voor de Gezondheidszorg of bevoegde inspecteurs van een buitenlandse overheid, en leden van de Medisch Ethische Toetsings Commissie. Inzage kan nodig zijn om de betrouwbaarheid en kwaliteit van het onderzoek na te gaan. Onderzoeksgegevens zullen worden gehanteerd met inachtneming van de Wet Bescherming Persoonsgegevens en het privacyreglement van uw ziekenhuis.

Persoonsgegevens die tijdens deze studie worden verzameld, zullen worden vervangen door een codenummer. Alleen dat nummer zal gebruikt worden voor studiedocumentatie, in rapporten of publicaties over dit onderzoek. Slechts degene, die de sleutel van de code heeft (de onderzoeker) weet wie de persoon achter het codenummer is.

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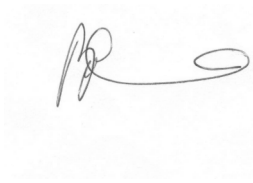
Als u niet tevreden bent over het onderzoek of de behandeling kunt u terecht bij de onafhankelijke klachtencommissie van het Erasmus MC. De klachtencommissie is te bereiken op telefoonnummer 010-7033198.

Met vriendelijke groet,


Annemieke Leunis, MSc Onderzoeker	Prof.Dr. B Löwenberg Principal Investigator Hematologie Erasmus MC	Prof.Dr. P. Sonneveld Afdelingshoofd Hematologie Erasmus MC

Appendix III: Questionnaire

Kwaliteit van leven na de diagnose acute leukemie

Studienummer:

Dit is een vragenlijst voor mensen die zijn gediagnosticeerd met acute leukemie. Vult u de vragenlijst zelf, op uw gemak, in. U kunt steeds antwoord geven door het hokje/cijfer aan te kruisen dat het beste op u van toepassing is. Als u twijfelt, geef dan toch het antwoord dat het dichtst in de buurt komt van uw situatie. Er zijn geen goede of foute antwoorden; het gaat alleen om uw persoonlijke mening. Hoewel sommige vragen op elkaar kunnen lijken, is toch iedere vraag weer anders. Het kan ook zijn dat sommige vragen voor u overbodig of eigenlijk niet op u van toepassing lijken. Wilt u toch proberen alle vragen te beantwoorden?
De antwoorden op deze vragenlijst worden **vertrouwelijk** behandeld en uitsluitend **anoniem** gebruikt voor dit onderzoek.

Persoonlijke vragen:

1. Wat is uw geboortedatum: ___ ___ / ___ ___ / ___ ___ ___ ___

2. Wat is uw geslacht?
   - o Man
   - o Vrouw

3. Wat is op dit moment uw burgerlijke status?
   - o Gehuwd/ samenwonend
   - o Gescheiden/ uit elkaar
   - o Weduwe/ weduwnaar/ partner overleden
   - o Nooit gehuwd/ nooit samengewoond

4. Wat is het hoogste opleidingsniveau dat u heeft afgerond
   - o Lager onderwijs (of minder)
   - o Voortgezet onderwijs, of gelijkwaardig
   - o Middelbaar (beroeps) onderwijs, of gelijkwaardig
   - o Universiteit, Hoger beroepsonderwijs of gelijkwaardig

5. Heeft u op dit moment een betaalde baan?
   - o Ja voor ____ uur per week → ga verder met vraag 7
   - o Nee

6. Indien u geen betaalde baan heeft, wat is er het meest op u van toepassing?
   - o Pensioen/ VUT
   - o Scholier/ student
   - o Werkloos
   - o Arbeidsongeschikt voor _____ procent. Vanwege kanker? o Ja o Nee
   - o Dagtaak aan zorg voor huishouden en eventueel kinderen
   - o Iets anders namelijk:

_____

_____

_____

_____

7. Heeft u het gevoel dat u goed om kan gaan met de ziekte; met de problemen en hevige gedachten of gevoelens die hiermee gepaard gaan?
   - o Ja, ik kan erg goed omgaan met de ziekte
   - o Ik probeer zo goed mogelijk om te gaan met de ziekte maar dit lukt niet altijd
   - o Nee, ik kan absoluut niet goed omgaan met de ziekte

8. Heeft u een bepaalde religie of spiritueel geloof?
    - Ja
    - Nee

9. Wat is uw etniciteit?
    - Nederlands
    - Surinaams
    - Antilliaans
    - Turks
    - Marokkaans

    Anders namelijk: _____

Diagnose en behandeling

10. Wanneer is acute leukemie bij u gediagnosticeerd?

    Maand _____ van jaar _____

11. In welke fase van de behandeling zit u?

    - Na de eerste chemotherapie kuur
    - Na de tweede chemotherapie kuur
    - Na de derde of volgende chemotherapie kuur
    - Na een autologe stamceltransplantatie
    - Na een donor stamceltransplantatie
    - Na recidief behandeling

12. Hoe zou u de relatie met uw behandelend arts omschrijven?

    - Een erg persoonlijke relatie
    - Puur een dokter-patiënt relatie
    - Afstandelijke relatie

13. Hoe ervaart u de omgeving waarin u behandeld werd/wordt?

    - Zeer prettig
    - Prettig
    - Niet prettig maar ook niet onprettig
    - Onprettig
    - Zeer onprettig

14. Hieronder staat een lijst met chronische aandoeningen. Wilt u bij elke ziekte of aandoening aankruisen of u deze nu heeft, of in het afgelopen jaar heeft gehad? Als u bij een aandoening ‘Ja’ antwoordt, wilt u dan per aandoening aangeven of u ervoor behandeld wordt en of u door die aandoening wordt gehinderd bij uw activiteiten.

Aandoening	**Heeft u deze aandoening?**		**Word u ervoor behandeld?**		**Hindert het u bij uw activiteiten?**	
	Nee	**Ja**	**Nee**	**Ja**	**Nee**	**Ja**
Hartaandoening	O	O	O	O	O	O
Beroerte	O	O	O	O	O	O
Hoge bloeddruk	O	O	O	O	O	O
Astma, chronisch bronchitus, COPD	O	O	O	O	O	O
Suikerziekte	O	O	O	O	O	O
Maagzweer	O	O	O	O	O	O
Nierziekte	O	O	O	O	O	O
Leverziekte	O	O	O	O	O	O
Bloedarmoede of andere bloedziekte	O	O	O	O	O	O
Schildklierziekte	O	O	O	O	O	O
Depressie	O	O	O	O	O	O
Gewrichtsslijtage (artrose)	O	O	O	O	O	O
Rugpijn	O	O	O	O	O	O
Gewrichtsontsteking (reuma)	O	O	O	O	O	O
Een ander medisch probleem (hieronder opschrijven):						
_____	O	O	O	O	O	O
_____	O	O	O	O	O	O
_____	O	O	O	O	O	O

Uw Gezondheid
Wilt u onderstaande vragen beantwoorden door het getal te omcirkelen dat het meest op u van toepassing is

	Helemaal Niet	Een beetje	Nogal	Heel erg
1. Heeft u moeite met het doen van inspannende activiteiten zoals het dragen van een zware boodschappentas of een koffer?	1	2	3	4
2. Heeft u moeite met het maken van een lange wandeling?	1	2	3	4
3. Heeft u moeite met het maken van een korte wandeling buitenshuis?	1	2	3	4
4. Moet u overdag in bed of in een stoel blijven?	1	2	3	4
5. Heeft u hulp nodig met eten, aankleden, u zelf wassen of naar het toilet gaan?	1	2	3	4

Gedurende de afgelopen week:	Helemaal Niet	Een beetje	Nogal	Heel erg
6. Was u beperkt bij het doen van uw werk of andere dagelijkse bezigheden?	1	2	3	4
7. Was u beperkt in het uitoefenen van uw hobbies of bij andere bezigheden die u in uw vrije tijd doet?	1	2	3	4
8. Was u kortademig?	1	2	3	4
9. Heeft u pijn gehad?	1	2	3	4
10. Had u behoefte te rusten?	1	2	3	4
11. Heeft u moeite met slapen gehad?	1	2	3	4
12. Heeft u zich slap gevoeld?	1	2	3	4
13. Heeft u gebrek aan eetlust gehad?	1	2	3	4
14. Heeft u zich misselijk gevoeld?	1	2	3	4
15. Heeft u overgegeven?	1	2	3	4
16. Had u last van obstipatie? (Was u verstopt?)	1	2	3	4
17. Had u diarree?	1	2	3	4
18. Was u moe?	1	2	3	4
19. Heeft pijn u gehinderd in uw dagelijkse bezigheden?	1	2	3	4

Gedurende de afgelopen week:	**Helemaal Niet**	**Een beetje**	**Nogal**	**Heel erg**
20. Heeft u moeite gehad met het concentreren op dingen, zoals een krant lezen of televisie kijken?	1	2	3	4
21. Voelde u zich gespannen?	1	2	3	4
22. Maakte u zich zorgen?	1	2	3	4
23. Voelde u zich prikkelbaar?	1	2	3	4
24. Voelde u zich neerslachtig?	1	2	3	4
25. Heeft u moeite gehad met het herinneren van dingen?	1	2	3	4
26. Heeft uw lichamelijke toestand of medische behandeling uw familieleven in de weg gestaan?	1	2	3	4
27. Heeft uw lichamelijke toestand of medische behandeling u belemmerd in uw sociale bezigheden?	1	2	3	4
28. Heeft uw lichamelijke toestand of medische behandeling financiële moeilijkheden met zich meegebracht?	1	2	3	4

Wilt u voor de volgende vragen het getal tussen 1 en 7 omcirkelen dat het meest op u van toepassing is

29. Hoe zou u uw algehele gezondheid gedurende de afgelopen week beoordelen?

1 2 3 4 5 6 7

Erg slecht Uitstekend

30. Hoe zou u uw algehele "kwaliteit van het leven" gedurende de afgelopen week beoordelen?

1 2 3 4 5 6 7

Erg slecht Uitstekend

Zet bij iedere groep in de lijst hieronder een kruisje in het hokje dat het best past bij uw gezondheid VANDAAG.

MOBILITEIT

Ik heb geen problemen met lopen ❑
Ik heb een beetje problemen met lopen ❑
Ik heb matige problemen met lopen ❑
Ik heb ernstige problemen met lopen ❑
Ik ben niet in staat om te lopen ❑

ZELFZORG

Ik heb geen problemen met mijzelf wassen of aankleden ❑
Ik heb een beetje problemen met mijzelf wassen of aankleden ❑
Ik heb matige problemen met mijzelf wassen of aankleden ❑
Ik heb ernstige problemen met mijzelf wassen of aankleden ❑
Ik ben niet in staat mijzelf te wassen of aan te kleden ❑

DAGELIJKSE ACTIVITEITEN ***(bijv. werk, studie, huishouden, gezins- en vrijetijdsactiviteiten)***

Ik heb geen problemen met mijn dagelijkse activiteiten ❑
Ik heb een beetje problemen met mijn dagelijkse activiteiten ❑
Ik heb matige problemen met mijn dagelijkse activiteiten ❑
Ik heb ernstige problemen met mijn dagelijkse activiteiten ❑
Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren ❑

PIJN/ONGEMAK

Ik heb geen pijn of ongemak ❑
Ik heb een beetje pijn of ongemak ❑
Ik heb matige pijn of ongemak ❑
Ik heb ernstige pijn of ongemak ❑
Ik heb extreme pijn of ongemak ❑

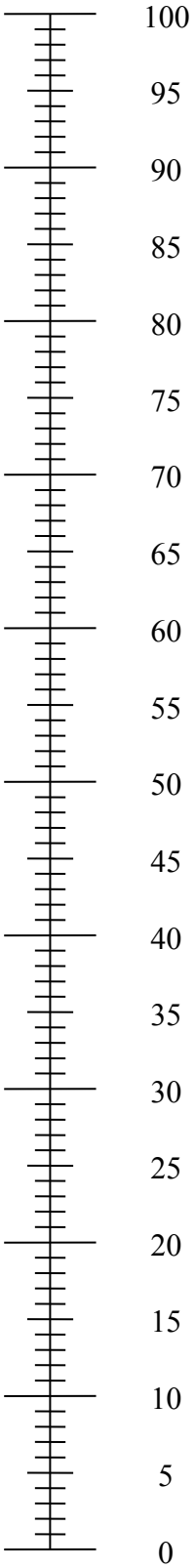
ANGST/SOMBERHEID

Ik ben niet angstig of somber ❑
Ik ben een beetje angstig of somber ❑
Ik ben matig angstig of somber ❑
Ik ben erg angstig of somber ❑
Ik ben extreem angstig of somber ❑

- We willen weten hoe goed of slecht uw gezondheid VANDAAG is.
- Deze meetschaal loopt van 0 tot 100.
- 100 staat voor de beste gezondheid die u zich kunt voorstellen.
  0 staat voor de slechtste gezondheid die u zich kunt voorstellen.
- Markeer een X op de meetschaal om aan te geven hoe uw gezondheid VANDAAG is.
- Noteer het getal waarbij u de X heeft geplaatst in onderstaand vakje.

UW GEZONDHEID VANDAAG = ☐

De beste gezondheid die u zich kunt voorstellen



De slechtste gezondheid die u zich kunt voorstellen

Vermoeidheid

De volgende uitspraken gaan over hoe u zich normaal gesproken voelt.

U kunt per uitspraak kiezen uit 5 antwoordmogelijkheden variërend van ‘nooit’ tot ‘altijd’. Wilt u alstublieft het antwoord dat het best bij uw gevoel past aankruisen?

	Nooit	**Soms**	**Regelmatig**	**Vaak**	**Altijd**
1. Ik heb last van vermoeidheid.	1	2	3	4	5
2. Ik ben gauw moe.	1	2	3	4	5
3. Ik vind dat ik weinig doe op een dag.	1	2	3	4	5
4. Ik heb genoeg energie voor het leven van alledag.	1	2	3	4	5
5. Lichamelijk voel ik me uitgeput.	1	2	3	4	5
6. Ik heb problemen om met dingen te beginnen.	1	2	3	4	5
7. Ik heb problemen om helder na te denken.	1	2	3	4	5
8. Ik heb geen zin om iets te ondernemen.	1	2	3	4	5
9. Geestelijk voel ik me uitgeput.	1	2	3	4	5
10. Als ik ergens mee bezig ben, kan ik mijn gedachten er goed bijhouden.	1	2	3	4	5

Omgeving

1. Heeft u voldoende steun van familie?
   - Ja
   - Nee

2. Heeft u voldoende steun van andere personen dan uw familie (e.g. vrienden) ?
   - Ja
   - Nee

Hieronder kunt u alles vermelden dat u nog kwijt wilt, wat u van de vragenlijst vond en wat eventueel nog over het hoofd is gezien.

Controleer alstublieft of u geen vragen heeft overgeslagen. Wilt u de vragenlijst alstublieft binnen twee weken retourneren in de bijgevoegde antwoordenvelop. **Een postzegel is niet nodig.**

Hartelijk dank voor uw medewerking aan dit onderzoek

Voor informatie over het onderzoek kunt u contact opnemen met Drs. Annemieke Leunis per email leunis@bmg.eur.nl of telefonisch 010-408976.