Chapter 10

Summary & General discussion
Summary

Pediatric cancer is rare. Annually about 120 children are diagnosed with acute lymphoblastic leukemia (ALL) in the Netherlands. Survival of ALL has greatly improved over the past decades and survival is expected to reach 90% in the near future. This success has lead to a stronger emphasis on other outcome measures besides survival, such as (long-term) morbidity, quality of life (QoL) and cost-effectiveness of treatment. Treatment for ALL is long and intensive. Prospects are good but ALL is still a life-threatening illness that is very demanding on patients and their parents. The reports on late effects are not reassuring, with high rates of physical and psychosocial morbidity, especially in patients that received irradiation, in high-risk patients and in patients with relapses. Even though QoL improves in survivors of ALL, it generally remains lower than in healthy children, especially on psychosocial domains. In order to improve QoL during as well as after treatment, it is important to understand the effect of ALL and its treatment on QoL, the development of QoL over time, and the risk factors associated with impaired QoL or insufficient recovery.

Besides clinical endpoints that are relevant to the individual or the whole ALL patient population (survival, morbidity, QoL), other endpoints such as the cost-effectiveness of treatment are more relevant to society. It is likely that further progress in the survival of pediatric ALL will slow down and that future improvement of treatment will involve new and expensive technology and medication. The pressure on limited (financial) resources warrants careful evaluation of healthcare costs in relation to the effects of new interventions on survival, late effects and QoL.

This thesis focuses on these two aspects of care in pediatric ALL: firstly the development of QoL of children during and after ALL treatment and the (change in) determinants of QoL, and secondly the cost-effectiveness of therapy.

Chapter 1 describes the background of this thesis: medical aspects of ALL, the adverse effects of treatment, QoL, sleep and economic evaluations.

In chapter 2 the results of a systematic review of quantitative QoL research in children during and after treatment for ALL are discussed. The studies show that QoL is poor during treatment according to both patients and parents, but improves and nearly reaches healthy norms in survivors for most domains. Parents tend to rate the QoL of their children lower than children do themselves. According to parent-reports, physical QoL is the most frequently (77%) affected domain during treatment, followed by psychosocial QoL (64%) and overall QoL (27%). Self-reports indicate impaired physical QoL in 47%, emotional QoL in 34%, social QoL in 32% and overall QoL in 27% during treatment. Parents of survivors report impaired psychosocial QoL in 24% and overall QoL in 20%. Survivors rate their QoL to be similar to the norm for most scales, and better on
social QoL. The methodological quality of the included studies was often suboptimal, hampering the ability to draw firm conclusions on determinants of QoL.

Chapters 3 and 4 describe the results of a large longitudinal study, which was an add-on study to the national ALL10 treatment protocol from the Dutch Childhood Oncology Group (DCOG). **Chapter 3** focusses on QoL and its determinants during induction treatment. According to parents, QoL of the children was significantly lower than the norm, the effect sizes were large and the differences were clinically relevant. Physical QoL was more often affected than psychosocial QoL and pain was frequently reported. Impaired QoL was most often associated with older children and female gender. Also, father-respondents seemed to have a lower QoL perception compared to mother-respondents. The follow-up of this cohort until shortly after the end of treatment is discussed in **chapter 4**. It describes the change in QoL and its determinants based on parent-proxy assessments. QoL improved during treatment, but generally remained lower than in healthy children. The determinants of QoL changed, from mostly demographic variables during the early phases of treatment to mainly treatment-intensity related factors during follow-up. HR-ALL children were most at risk for having impaired QoL and showed the least recovery of QoL. Higher educated parent-proxy's had a lower perception of child QoL than lower educated parents.

The effect of cyclic treatment with the glucocorticoid dexamethasone on QoL is discussed in **chapter 5**. Because glucocorticosteroids are known to cause physical side-effects as well as emotional and behavioral problems, it was hypothesized that its use would negatively influence QoL. In a multi-center cohort of patients treated according to the DCOG protocol ALL9, the development of QoL during the second year of treatment was evaluated. According to parent-proxy's, QoL was significantly lower in children with ALL compared to healthy children. Overall QoL did not change during the second part of treatment. On certain domains however, such as pain, cognitive functioning, emotion, behavior and physical functioning, QoL decreased over time. Parents as well as patients reported that dexamethasone indeed had an important negative influence on QoL.

In **chapter 6** the relationship between sleep and QoL was investigated in a cohort of ALL10 patients. Disturbed sleep in cancer is a common clinical observation and the quantification of its effect on QoL could provide possibilities for improvement of QoL through treatment of sleep problems. Sleep was assessed with parental questionnaires during maintenance treatment. To allow for the potential effect of treatment with dexamethasone, two assessments were performed: during and after dexamethasone treatment. Children with ALL had more sleep problems than healthy children. Sleep problems were found on the items bedtime resistance, sleep anxiety, night wakening and parasomnias. Younger children had more sleep problems than older children. No statistically significant differences were found in sleep during or after dexamethasone,
but this might be attributed to the sample size as other studies have found such an effect. Impaired sleep was associated with worse QoL. This study shows that impaired sleep is common during ALL treatment and that it may be a contributing determinant to impaired QoL, providing a possibility for intervention.

**Chapter 7** discusses the results of a systematic review of utility scores in pediatric ALL. Utility scores are derived from preference-based health-related quality of life (HRQL) measures and combine health status with community preferences. Utilities can be used for the calculation of quality adjusted life years (QALY). QALY are valuable in economic evaluations because they incorporate the gained life years as well as the quality thereof, and thus allow for more informed decision making. The available evidence for utility scores in pediatric ALL, however, turns out to be sparse and methodologically suboptimal. Information on utility scores in short-term survivors of ALL is lacking. The use of these existing utility scores in (longitudinal) economic evaluations would warrant extensive sensitivity analyses.

In **chapter 8**, QoL and utility scores of short-term ALL survivors are reported. Parent-proxy reports were collected in a cross-sectional single centre cohort study using the *Health Utilities Index Mark 3* (HUI3). Although no impairments were reported for 61% of the survivors, this study suggests a clinically relevant but not statistically significant decreased overall QoL in short-term ALL survivors. The results of this study complete the available information on pediatric ALL utility scores, although rigorous longitudinal studies to assess utility scores during and after treatment of pediatric ALL are still necessary.

Finally, in **chapter 9** the results of the retrospective cost-effectiveness analysis are discussed. A single-center cohort of fifty children treated with chemotherapy only according to the DCOG protocols ALL9 and ALL10 was included. Children treated with stem cell transplantation (SCT) were excluded. The most important differences between both protocols were the use of more expensive medication (pegylated asparaginase) and the implementation of a new diagnostic technique for monitoring responses to treatment (minimal residual disease levels) in ALL10. All direct medical costs made during treatment, including those in satellite hospitals, were determined. Costs per life year saved (LYS), based on national 5-year event free survival, and the cost-effectiveness ratio of ALL10 were calculated. Costs were higher for patients treated according to ALL10 but survival was better. Hospital admissions and medication were important drivers of overall costs, and were higher in ALL10. Costs per LYS were $1,962 (ALL9) and $2,655 (ALL10) and the cost-effectiveness ratio was $8,215. This was well within accepted ranges of cost-effectiveness.
General discussion

Development of QoL

In general there seems to be a trend towards improvement of QoL in pediatric ALL patients as time since diagnosis increases (chapter 2). A similar trend was seen in ALL10 patients that were treated with chemotherapy only, although shortly after the end of treatment QoL remained impaired compared to the norm on the majority of domains (chapters 3 and 4). Remarkably, QoL did not improve and even decreased on some domains during the last year of ALL9 treatment, which consist of chemotherapy only treatment as well (chapter 5). Reasons for these differences could be the reduction of treatment intensity in ALL10-SR patients (about 25% of all ALL10 patients) and the different glucocorticosteroid schedule in ALL10 compared to ALL9. ALL9 maintenance treatment consisted of two weeks of dexamethasone every seven weeks [2], while ALL10 maintenance treatment for MR-patients consisted of five consecutive days of dexamethasone every three weeks. We hypothesize that the shorter ALL10 glucocorticosteroid schedule attenuates the differences in symptoms during periods on and off glucocorticosteroids, thereby improving QoL appraisal, see Box 10.1.

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<th>Box 10.1 Quality of Life differences in ALL9 and ALL10: lessons to be learned</th>
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| One of the differences between the ALL9 and the ALL10 protocol is the corticosteroid regimen, see figures 9.1 and 9.2. ALL9 maintenance treatment consisted of two weeks of 6 mg/m² dexamethasone per day every seven weeks [2]. In ALL10 only MR patients received cyclic corticosteroid therapy during maintenance: 6 mg/m² dexamethasone per day, every three weeks for five consecutive days. The effect of these dexamethasone regimes on QoL has been discussed in chapters 5 and 6. The difference in effect on QoL between these two regimens is of interest to support decisions about counseling and, in the absence of effect on survival and morbidity, future treatment protocols. For this purpose we compared the on-dex and off-dex QoL half-way therapy between children treated according to ALL9 and ALL10. The results presented in chapters 5 and 6 were used for this analysis. The treatment regimens at the time of both studies were similar, insofar that both protocols involved mercaptopurine, methotrexate and vincristine. The differences between ALL9 and ALL10 were analysed using non-parametric tests (Mann-Whitney U). The ALL10 cohort consisted of 18 children and the ALL9 cohort of 15 children. Parent-proxy reported QoL as measured with the generic Child Health Questionnaire was lower during dexamethasone periods in children treated according to ALL9 compared to ALL10 on all scales except physical functioning and family cohesion. This was a non-significant trend for most scales, probably due to the small sample sizes, except for mental health (p=0.045), parental emotional impact (p=0.02) and the psychosocial summary score (p=0.02). During periods without dexamethasone there was a non-significant trend for parents to report a better QoL for ALL9 patients compared to ALL10 patients on all scales except bodily pain. The difference in scores between periods on and off dexamethasone was much smaller in ALL10 compared to ALL9. This was statistically significant for the following scales: behavior (p=0.007), mental health (p=0.008), self-esteem (p=0.02), family activities (p=0.01) and the psychosocial summary score (p=0.03). Parent-proxy reported QoL as measured with the disease specific Pediatric Quality of Life Inventory Cancer version was generally lower in the ALL9 cohort compared to ALL10. This was statistically significant only during periods on dexamethasone and on the following scales: procedural anxiety (p=0.02), treatment anxiety (p=0.02), physical appearance (p=0.02) and overall QoL (p=0.004). The difference in QoL on and off dexamethasone between ALL9 and ALL10 was less outspoken than with the CHQ. Still, the difference was significantly larger in ALL9 for the scales pain (p=0.03) and overall QoL (p=0.02) than in ALL10. Of course, this is an analysis of convience. The ALL9 and ALL10 cohorts are not entirely comparable: the ALL9 cohort was slightly younger (5.7±2.6 years versus 6.7±3.3 years) and the percentage of boys was higher (53% versus 44%), although these differences were not statistically significant (p=0.24 and p=0.73, respectively). No sample size calculation to detect differences between ALL9 and ALL10 was determined beforehand. Also, methodologic flaws in the ALL9 study, i.e. the sending of questionnaires for assessment of the period on and off dexamethasone in one mailing, may have lead to an increase in the reported differences, see chapter 5. Nevertheless, these results suggest that the ALL10 dexamethasone regimen leads to less fluctuation in QoL during maintenance therapy and that QoL was generally lower in ALL9. Assuming that more frequent dexamethasone courses of shorter duration do not negatively affect survival and morbidity, this schedule should be favored over less frequent, longer courses of dexamethasone in future ALL protocols.
Domains especially affected during treatment were physical QoL and pain (chapters 3, 4 and 5), as compared to psychosocial QoL in survivors (chapter 2). A low QoL for pain was frequently reported during the early phases of treatment as well as in short-term survivors (chapters 3, 4, 5 and 8). Research on pain during and after pediatric ALL is scarce, but better pain management could help to improve QoL [122, 123]. It is important to note that even though QoL improved over time in the majority of patients, shortly after treatment QoL generally remained lower than in healthy children (chapters 4 and 8). Previous studies have also reported an impaired QoL in short-term survivors [35, 82, 101, 119], when it is likely that patients still need to recover from the physical and psychosocial effects of treatment. Also, parental adjustment to the completion of their child’s cancer treatment is often accompanied by increased distress and fear of recurrence [23], which can be related to impaired child QoL [74, 91, 120]. QoL seems to further improve in long(er) term survivors, although it is still lower than healthy peers on some domains (chapter 2). It is important to identify patients at increased risk of a lower QoL, or patients with insufficient recovery of QoL. Knowledge on determinants of QoL will lead to better recognition of these patients and will subsequently allow for early counseling and interventions to improve QoL.

**Determinants of QoL**

It is important to realize that not only medical variables can be related to QoL, but that QoL can also be influenced by intermediate variables, such as the child and parents variables explored in this thesis (figure 10.1). Each of these variables can influence QoL, either directly or through interaction with each other. Using the variables identified in this thesis and in the existing literature [188], we propose a theoretical model of QoL in pediatric ALL patients, which is based on the model by Lach et al.[189] on QoL in pediatric epilepsy patients (figure 10.1). This conceptual model can be useful as a scientific basis for further research, a guide for new hypotheses or for testing hypotheses, and to

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**Figure 10.1** Conceptual model of quality of life in pediatric ALL patients. Items in italics have not been the subject of research in this thesis.
explore casual relationships. In clinical settings this model can be used as a guideline for counseling and involvement of specific healthcare services.

**Medical factors**

Treatment intensity is clearly a determinant of QoL during treatment. Children with a higher-risk ALL (and thus intensification of treatment) have more impaired QoL (chapters 3, 4 and 5). An illustration of the positive effect of reduction of treatment intensity in children with a low-risk ALL was demonstrated by the more rapid recovery of QoL in ALL10-SR patients as compared to MR and HR patients, although even in this group on most scales QoL was not yet normalized in short term survivors. Other investigators have reported similar associations [90, 103]. The phase of treatment or time since diagnosis, which can be seen as derivatives of treatment intensity, are equally associated with QoL (chapters 2, 3, 4 and 5). There are no studies dedicated to the assessment of QoL in relapsed ALL patients. Several cohorts of mixed diagnoses including patients with and without relapse were investigated for the effect of relapse on QoL, but these reports are conflicting and it is unsure whether the effects found can not be largely attributed to other diagnosis than ALL and whether the absence of effects is caused by a lack of power [91, 102, 190, 191].

Specific elements of therapy also influence QoL, such as SCT (chapter 4) [73, 102] and glucocorticosteroids (chapter 5) [77, 106]. It is possible that other elements of therapy have an effect as well, such as vincristine through the induction of peripheral neuropathy, although this effect has to date not been objectified [86]. Radiation therapy, although no longer a part of front-line therapy for the far majority of patients, has been associated with worse QoL [102, 171]. It still needs to be considered a relevant determinant of QoL in patients that received a SCT, in long(er) term survivors and in relapsed patients.

Treatment toxicity or days spent in the hospital as a consequence of complications have been negatively associated with QoL in ALL10 (chapters 3 and 4) as well as in other studies [114]. Late effects, which could be regarded as treatment toxicity as well, have been associated with QoL in most studies [119, 188, 190, 191]. Other chronic conditions have been linked to QoL in a mixed diagnosis cohort [102].

**Intermediate variables**

Child demographic factors that have been described to influence QoL of pediatric ALL patients are gender and age. Female patients are at a higher risk of impaired QoL, during treatment (chapter 4) as well as afterwards [82, 103]. This trend is also seen across other types of pediatric cancer [192]. It seems however, that this effect is not specific for childhood cancer. Indeed, it is also found in the healthy population [193]. Since healthy populations are used as benchmarks for normal QoL, one could assume that lower QoL scores in females is normal. The effect of child age on QoL depends
on the QoL domain studied. Younger children experience more problems with anxiety issues and communication, while older children have a lower overall QoL and more problems in areas regarding cognition, worry, pain and physical QoL (chapter 3). Older age at diagnosis has been linked to a lower QoL by other investigators [192]. These differences in affected areas can largely be explained by developmental differences. Child demographic variables were, however, overruled by other determinants such as treatment intensity and parental education in our longitudinal study (chapter 4).

A relatively new area of research in childhood ALL is sleep. We found impaired sleep to be associated with lower QoL (chapter 6). Even though sleep problems have been identified before in ALL patients [41, 123, 143], this was the first study to relate impaired sleep to impaired QoL. It remains to be elucidated whether this is a causal association and to what extend other variables influence this relationship, but the treatment of sleep problems promises to be an interesting tool in the improvement of QoL.

Other child factors that can possibly determine QoL, but have not been included in this thesis, include psychosocial functioning in the broadest sense. In survivors of ALL, smaller discrepancies between what a patient would want to do and is able to do, reflecting the effectiveness of the employed coping strategies, are reported to be associated with a better QoL [75]. In survivors of childhood cancer, coping is associated with QoL [194]. A positive coping style with positive expectations of the future [195] and stronger reliance on the physician [196] have been found to be associated with a better QoL. Up to date, no studies assessing the effect of psychosocial functioning on QoL in children during treatment for ALL have been published. Other child variables that have neither been investigated in ALL, nor in other pediatric diagnosis, but that have been related to QoL in children with epilepsy are for example social skills and self-worth [188, 189].

The available literature on the role of the parental demographic variables age and gender is conflicting. Parental age was associated with a few QoL scales in our study and generally followed the child age trend (chapters 3 and 4). Two other studies investigated the effect of parental age and gender in cohorts of mixed diagnoses. One study reported no effect of both determinants [120], but the other found a positive effect of higher age on physical QoL and a positive effect of male parental gender on emotional QoL [102]. The opposite was found in our study, in which father-respondents reported a significantly lower QoL (chapter 3). The effect of these parental demographics was, however, not the main objective of any of these studies and possible confounders (such as parental psychosocial health) were not accounted for. Therefore, it is difficult to draw any solid conclusions regarding the influence of parental age and gender on QoL of the child.
Conflicting results have been reported regarding derivatives of social economic status (SES), such as highest parental education and household income, and their association with QoL. Higher household income has been associated with a better QoL in children with ALL on treatment [103]. In our ALL10 study (chapters 3 and 4) higher educated parents reported a lower QoL. As higher education has been associated with increased health search behavior [124], we hypothesize that higher educated parents may be better informed about possible late effects and risk of relapse, and are therefore more worried about the future, leading to a perception of lower QoL. This association was, however, not reported by other authors [90].

Some parental determinants that have not been included in this thesis have yielded interesting results in relation to QoL in pediatric oncology. Aspects of parental psychosocial functioning such as depression, worries, psychosocial distress and parental QoL have all been linked to worse child QoL, in proxy-assessments as well as in self-assessments [74, 91, 120]. Parental optimism is associated with better QoL [78]. Children in a mixed diagnostic cohort were reported to have a lower QoL when parents or siblings had a chronic health condition [102]. Parenting strategies have been linked to QoL in ALL [74] and parenting stress has been related to lower QoL [197].

The effect of community variables on QoL, such as school functioning, friends and social support, hospital and medical personnel, have not been studied by us, nor indeed by any investigators in pediatric ALL. Some work in this field has been performed in adult survivors of retinoblastoma, which indicates that school bullying is associated with lower QoL [198].

Finally, an important phenomenon that is not captured by this model of intermediate variables is the (dis)agreement between parental and self evaluation of QoL. As has been discussed in the introduction to this thesis (chapter 1), parents and children do often not agree on QoL, especially regarding the more subjective domains. If parents are unaware of their child’s anxieties, fears and emotional experiences, they can not offer them optimal support and parenting [189]. This discrepancy between child and parental view of QoL is therefore not only an interesting observation, but also a potential instrument for counseling and professional support.

**Economic evaluation of pediatric ALL treatment**

As illustrated in the introduction to this thesis, even though pediatric cancer is rare and costs are relatively low, economic evaluations of cancer treatments are still useful and necessary to make informed decisions. It is likely that the progress of success in pediatric ALL will slow down in future years and that it will increasingly involve (costly) new technologies and medication. Economic evaluations of interventions in pediatric oncology are still in its infancy. Some data on adult ALL is available, but this is not comparable to pediatric ALL both in terms of treatment and in terms of effects [61]. In
chapter 9, a comprehensive cost-effectiveness analysis of the direct medical costs of ALL treatment with chemotherapy only is presented. In this analysis, the hospital perspective was used to assess all costs. However, Dutch guidelines recommend employing the societal perspective in economic analysis [60]. Life years saved (LYS) were used as outcome measure, although it would have been more accurate to adjust these LYS for the quality of the life years, using QALY. However, as illustrated in chapter 6, studies assessing pediatric ALL utility scores are methodologically suboptimal and QALY were therefore not calculated. The aspects of economic evaluations in pediatric ALL that have not been addressed in chapter 9 will be discussed in more detail below.

Effects

In chapter 9, a normal life-expectancy was assumed for patients who were event-free survivors at five years. Children who relapsed were handled as if deceased. Of course, events may still occur after five years, although the rate is much lower than in the earlier time-period. Indeed, after ten years, relapses are so rare that these children have been reported to have a normal survival [7]. Since late effects are far less common in non-relapsed, non-irradiated patients [9, 10], the assumption that this would not tremendously affect life expectancy seems legitimate. Considering relapsed patients, survival rates vary between 12 and 58% depending, among other factors, on whether the relapse is early or (very) late [199]. Treatment of relapses in combination with more late effects after irradiation and a lower QoL makes this group of patients important to include in future economic evaluations.

Finally, the quality of the remaining life-years is of great importance in economic evaluations. Utility scores enable the quantification and comparison of the cost-effectiveness of heterogeneous interventions. Utility scores should therefore be determined with care, and published utilities that were derived from methodologically suboptimal studies should be avoided.

Indirect medical costs

When restricting the indirect medical costs to the costs of diseases related to the primary health condition, relapses and late effects such as secondary neoplasms, cardiotoxicity, bone toxicity and obesity are most relevant in the case of pediatric ALL. With contemporary treatment protocols, about 10-15% of patients relapse after having achieved complete remission [2, 13]. Treatment for early relapse usually includes SCT, while (very) late relapses can be managed with chemotherapy only, depending on early treatment reponse [199]. Considering the costs of relapses, one can assume that the costs of treatment with chemotherapy only will be similar to the costs of front-line treatment as described in chapter 9. Some reports comparing the costs of different pediatric SCT regimens are available [182, 200, 201]. Bone marrow transplantation
seems to be more cost-effective compared to allogeneic peripheral blood SCT and the trajectory following a matched related donor transplantation is less costly than trajectories following unrelated matched donor transplantations or unrelated umbilical cord transplant. In adult leukemia, costs of transplantation are about twice as high as the costs for chemotherapy-based regimens [183], but no such comparisons have been performed yet in pediatric leukemia. The incidence of second malignancies is low and they mostly occur in irradiated patients [7, 13, 14]. Since only a minority of patients receive irradiation nowadays, the costs of secondary neoplasms should not contribute substantially to the indirect costs. Exposure to anthracyclines, especially over 300 mg/m² of doxorubicin or daunorubicin (equivalents), and irradiation to the heart region is associated with cardiotoxicity. In ALL9 and ALL10 SR and MR patients, the maximum recommended dose of anthracyclines is not exceeded, and irradiation to the heart region is only given in relatively small doses as part of total body irradiation in the SCT setting [11]. Therefore, it is likely that the majority of ALL9 and ALL10 survivors will not experience significant clinical cardiac toxicity. Moreover, the trend is to abandon radiotherapy in the SCT trajectory in the near future. Osteonecrosis, associated with glucocorticosteroid exposure [11], can lead to indirect medical costs because of the need for physical therapy, pain management and surgical treatment. Obesity after childhood ALL seems to be mostly associated with radiation therapy, and conflicting results have been reported after treatment with chemotherapy only. Radiotherapy has also been associated with the metabolic syndrome.[11] These conditions can lead to cardiovascular and metabolic diseases such as diabetes mellitus, and could thus be a relevant factor in the indirect medical costs. Finally, for the majority of ALL survivors, the indirect medical costs will mostly pertain the costs of follow-up visits and tests.

Direct non-medical costs

Direct non-medical costs are the costs borne by patients or parents: out-of-pocket expenses (such as over-the-counter drugs, mileage and parking at the hospital) and loss of income. There is limited information available on this cost-category. Two studies performed in Canada, a country with a more or less similar healthcare system as the Netherlands in which most medical costs are fully covered by compulsory health-care plans, reported substantial expenses [202, 203]. In 1986, expenses for the total duration of therapy amounted to 26.070 Canadian dollars (CAD). This represents about 41.610 CAD (2008) or 24.400 euros (2008). A high percentage (64%) of parents had to take time off work and parents of young children with leukemia were most likely to do so. Direct non-medical costs account for about 25% of the families’ total disposable income. Of course, the Dutch situation will not be entirely similar, since distances to hospitals are much smaller and costs for daily living (for example gasoline) are different, but it is likely that the economic burden to families is substantial.
Indirect non-medical costs

This category includes costs made for example for specialized education, and costs associated with the loss of productivity because of disability or death. Neurocognitive deficits are mostly seen in irradiated patients [11] and are subtle in long-term survivors that have been treated with chemotherapy only [12]. Therefore, with contemporary treatment protocols, one could estimate that the additional costs for specialized education are minimally increased in children treated for ALL as compared to healthy children. There are no reports on these indirect medical costs. Education levels are, however, reported to be lower in survivors of ALL compared to healthy peers especially in irradiated patients [9, 17]. Employment rates are similar in non-irradiated, non-relapsed survivors of ALL compared to healthy peers. Irradiation and female gender are however risk factors for unemployment [7, 9, 18]. It is still unclear to what extend employed survivors are absent from work due to illness or disability. Finally, in an extensive economic evaluation, the loss of productivity of the deceased patients should also be included. Since overall survival of ALL is about 85-90% [2, 63, 204], 10-15% of all patients diagnosed with ALL will not survive which is substantial in terms of loss of long-term productivity.

Future directions

Why should QoL monitoring be a regular part of treatment protocols?

As pediatric ALL evolved from a disease with a dismal prognosis to a severe disease with a very good chance of cure, QoL has become increasingly relevant. In our efforts to reach a 100% cure rate, it is likely that future treatments will increasingly be tailor-made to the leukemic characteristics, the response to therapy and the patients’ drug metabolism. Professionals in pediatric oncology have long been aware of the importance of adverse effects of therapy. The systematic follow-up of cohorts has provided us with essential information on late effects, such as anthracycline-induced cardiomyopathy [11] and the detrimental effects of radiotherapy on cognitive functioning [11] and secondary tumors [7, 9, 13, 14]. This crucial information has lead to adjustment of therapy, in order to prevent these late effects while preserving survival rates. Even though QoL has received more and more attention during the past two decades, it does not seem to be systematically included in our treatment protocols yet. One could argue that since the majority of patients fully recover on physical QoL domains and in some studies self-reported QoL on social domains is even better than in healthy peers, QoL is not one of the essential outcome measures of pediatric ALL. However, the inclusion of QoL questionnaires in future protocols is warranted for several reasons. First, intensification of therapy in high(er) risk patients should not lead to a disproportional or unacceptable decrease in QoL, during treatment or in survivors. Since the changes in QoL may be
subtle, or only revealed in long-term survivors, close monitoring of QoL is as essential as the follow-up of cohorts for survival, morbidity and late effects. Second, each new element of treatment may have a different effect on QoL. An example of therapy-specific effects on QoL is the adverse effect of treatment with glucocorticosteroids (chapter 5). Longitudinal follow-up of QoL provides more detailed information on the effects of specific elements and can improve counseling of patients and their families. Historic controls are important to serve as reference to identify these therapy-specific effects. An example of how differences in QoL as a result of therapeutic elements could be used in decisions about future treatment protocols, is illustrated in box 10.1. Finally, during treatment specific patients are at greater risk of experiencing low QoL (chapters 3 and 4), overall QoL is still impaired in short-term survivors (chapter 8) and psychosocial QoL remains impaired in survivors (chapter 2). Even if future treatments do not affect QoL in a negative way, efforts should be undertaken to improve QoL. Also for this purpose, continuous monitoring of QoL will help evaluate the effect of intervention programs for the improvement of QoL and will allow for historic controls.

The science of economic evaluations is relatively undeveloped in pediatric cancer. The lack of attention to this aspect of pediatric oncology care may be because the costs of pediatric diseases are modest compared to the costs of adults, as was referred to in the introduction. Governments and health insurance companies have little to gain economically from pediatric illnesses. Also, sentiments about the treatment of sick children in general and children with cancer specifically may prevent economic evaluations, since people feel that everything should be done to cure these children. It is important to realise that economic evaluations are just one of the tools that can be used to make informed decisions about future policy. It also needs to be stressed that curing children from cancer means curing patients that are at the beginning of their lives. Therefore, survival, late effects and QoL should be leading in the decisions about future interventions. The economic aspects are available for supporting these decisions. As was specified in the previous sections, some aspects need to be further investigated in order for economic evaluations to be fully integrated in the decision process. The most important aspect is to acquire information on utility scores during and after treatment. Since each change in treatment may have an impact on QoL and thus on utility scores, ongoing assessment of utilities parallel to assessment of QoL should be an integrated part of all pediatric oncology treatment protocols.

### Research objectives

Despite the considerable amount of work that has already been done in the field of QoL in pediatric ALL, several important research objectives remain in order to achieve the main goal, namely the improvement of QoL without jeopardizing survival and morbidity (Box 10.2). Firstly, the effect of several potential variables on QoL and the interaction
between the variables in the model discussed before (figure 10.1) have not been elucidated. The available research to date leaves us with some interesting research questions and hypotheses. More detailed norm data should become available in terms of gender and age specific scores. Since healthy females have lower QoL scores it seems indicated to use gender specific norm data in the comparison with patient data. Normal developmental changes in children can be reflected in QoL domains, therefore age-specific references could prove useful. Not much is yet known on cultural differences and their effects on QoL perception. In a multi-cultural society, this could prove to be worthwhile information. We are still not informed on certain aspects of psychosocial functioning in both parents and children, such as social skills, self-worth and social support. The effect of parental gender on the assessment of child QoL renders conflicting results, but since we often rely on parental QoL reports in sick or young children, this effect is highly relevant in order to provide adequate counseling. A potentially important aspect that has not received any attention in the pediatric cancer literature, is the economic burden of having a child with ALL and its effect on child QoL.

The second research objective for the future concerns intervention programs to improve QoL. Interventions aiming at improving QoL in pediatric cancer are still sparse but are emerging. Interventions involving the child could focus on improving coping skills, as is the aim of the intervention program “Op Koers” (On Track) [205]. An interesting randomized trial employing a video-game intervention improved treatment adherence but, unfortunately, not QoL [206]. Still, the use of video-games in interventions seems promising since this is favorite pass time for many children and teenagers. Moreover, video-games have proven to be an effective distraction for pain [207] and therefore constitute a potential intervention for improving QoL in the ALL population. Positive health beliefs [208] or positive expectations of the future in patients [195] as well as optimism in parents [78] have all been related to better QoL and can therefore be part of future intervention programs and counseling. Physical interventions have shown positive effects on QoL [209]. The Quality of Life in Motion (QLIM) study combines a physical exercise program with a psychosocial intervention to enhance physical well-being, socio-emotional functioning and coping [210]. If effective, such a program should be incorporated in standard care in order to improve QoL. Although sleep is a relatively new area of research within pediatric oncology, the first reports on sleep appear to follow the results found in adult cancer patients [140, 141] and show a tendency for sleep to be impaired [41, 118, 123, 143]. More research into the character and

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<td>- Evaluations of the effect of potential determinants of QoL and their interaction</td>
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<td>- Interventions to improve QoL</td>
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evolvement of sleep problems needs to be performed, followed by interventions including behavioral and pharmacological therapy. Of course parents and family are crucial in a child’s well-being and since their psycho-social health is linked to the child’s QoL [74, 91, 114, 120], interventions should target parents and families as well. Cognitive behavioral programs for parents are emerging [205, 211]. It has been proven helpful to involve pediatric oncologists in interventions to improve QoL [212]. This thesis offers some tools for pediatricians to inform and educate parents and patients on the development of QoL during treatment and the effect of specific therapeutic interventions such as glucocorticosteroids and SCT.

A third research line should focus on methodological issues like choice of QoL instrument and respondent. Many valid, reliable and developmentally appropriate instruments are now available for QoL measurement in pediatric oncology [31, 65]. These questionnaires, however, all have different characteristics and it would be interesting to determine which instrument is most appropriate in specific situations. Longer instruments, such as the Child Health Questionnaire can provide us with more detailed information on the child’s QoL, while the more concise Pediatric Quality of Life Inventory can be more useful and patient friendly when multiple repeated measurements are performed. The Health Utilities Index is suitable for determining utilities but may be regarded a too coarse instrument for QoL assessments. Sensitivity to change is also an important aspect. Previous research has shown that the PedsQL is more sensitive to change in repeated measurements than the CHQ and the HUI [213], even though in this thesis the change in QoL was well detected using the CHQ. The choice of respondent is relevant for several reasons: the (dis)agreement between respondents and the psychological processes that influence the respondents’ view on QoL. The issue of the respondent has been addressed in the introduction as well as in the review in chapter 2. The relationship between self and parental assessment of QoL is complex but both perspectives are valuable [172]. The (dis)agreement between parents and children could prove a useful target for interventions, as explained in the previous section on intermediate variables in the QoL model. Psychological processes that can influence QoL appraisal in parent-proxies, such as worries and distress, have been discussed in the previous section. In self reports, it is important to account for the phenomenon called response shift. Response shift is a construct that refers to a change in an individual’s values, internal standards and conceptualization of QoL. Adaption to or denial of difficulties leads to an inflation of self-reported well-being. It is still unclear whether this is an adaptive or a maladaptive phenomenon. [214, 215] In survivors of childhood cancer, it seems that response shift may inflate their reports of socio-emotional functioning [214, 216].

Finally, future research should focus on economic evaluations of pediatric ALL treatment and interventions. It should include all aspects, i.e. utility scores, (in)direct medical and non-medical costs from the societal perspective. This type of research will help
answer relevant questions regarding the efficacy of new interventions and their effect on QoL, and will support decisions about future treatments.

Of course, all these interesting and highly relevant research questions are being hampered by the small patient populations in pediatric oncology. Even though cooperation between national and international institutes is not uncommon in pediatric cancer, it remains essential to unite our forces in order to answer all the remaining questions and optimize QoL and (cost)efficiency of treatment. This will be facilitated by making QoL and utility score studies an intrinsic element of all treatment protocols for children with cancer.