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CHAPTER 7

Cost-effectiveness of a combined physical exercise and psychosocial training program for children with cancer

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ABSTRACT

As resources in pediatric oncology are scarce, policy-makers need information on the relative economic merits of interventions. Therefore, this study aimed to estimate the cost-effectiveness of a combined physical exercise and psychosocial training program for children with cancer compared with usual care.

Sixty-eight children, aged 8-18 years old, during or within the first year post cancer treatment were randomized to the intervention (n=30) and control group (n=38). Health outcomes included physical fitness (i.e. cardiorespiratory fitness, muscle strength) and quality adjusted life years (QALYs); all administered at baseline, 4-, and 12-month follow-up. Costs were assessed from a societal perspective, including health-care, informal-care, parental work absenteeism and unpaid productivity. Costs were gathered by 1-monthly cost questionnaires throughout the trial (12 months), supplemented by medication data obtained from pharmacies.

At 12-months follow-up, no significant differences in costs and effects were observed between the intervention and control group. On average societal costs were € 497 higher in the intervention group than in the control group, but this difference was not statistically significant. Cost-effectiveness acceptability curves indicated that the intervention needs large societal investments to reach reasonable probabilities of cost-effectiveness for quality of life and lower body muscle strength; i.e. at a societal willingness-to-pay of € 100,000/QALY and € 600/Newton (lower-body muscle strength) the intervention reached a maximum probability of cost-effectiveness of 0.67 and 0.79, respectively.

Based on the results of this study, the intervention is not cost-effective in comparison with usual care.

INTRODUCTION

In the Netherlands, each year, approximately 600 out of 3.5 million children (0-18 years) are diagnosed with cancer. Although the incidence of childhood cancer is relatively low, the associated treatment costs are high^{265,266} due to expensive chemotherapy, which is often combined with radiotherapy, surgery or bone marrow transplantation. On top of that, children suffering from cancer also receive care by pediatric oncologists/hematologists, and periods of costly hospitalization in specialized pediatric clinics. Next to these direct healthcare costs, their treatment may also result in severe long-term adverse health outcomes, e.g. cardiovascular problems, lung problems, obesity, diabetes type-2, and psychosocial problems.^{17,267,268} To prevent or diminish these consequences of childhood cancer treatment, additional physical and/or psychosocial care seems beneficial. In adults with cancer and healthy children it is found that physical exercise interventions can reduce fatigue²⁶⁹, decrease overweight or obesity²⁴⁹, increase bone mineral density²⁵⁰, and improve health-related quality of life (HrQoL)⁷³. In adult cancer patients, studies also showed that physical exercise interventions are able to improve physical fitness, both during and after cancer treatment.^{82,270} In spite of their small sample sizes, it is noteworthy that the first controlled physical exercise trials among children with acute lymphoblastic leukemia showed promising results on both physical fitness and body composition.¹⁸⁰ Nonetheless, a pilot study on the feasibility of an exercise intervention program for children with cancer showed a 44% drop-out rate.⁹² As increasing psychosocial wellbeing is hypothesized to enhance participation in physical exercise programs, the pilot intervention was changed into a 12-week physical exercise and psychosocial training program, called QLIM (Quality of Life in Motion).¹⁴⁸ The QLIM intervention was primarily aimed at improving physical fitness (cardiorespiratory fitness [VO_{2peak} : ml·kg⁻¹·min⁻¹] and muscle strength [Newton]) and ultimately to improve HrQoL.

As (healthcare) resources are scarce, it is important to not only evaluate the effectiveness of an intervention, but also to assess whether its additional effects are 'worth' their additional expenses. Such expenses may not only be directly related to a child's cancer treatment (i.e. healthcare costs), but also indirectly, such as those resulting from the provision of informal care and (unpaid) productivity losses by the parents or legal representatives. The sum of all these costs is the societal costs. Therefore, this study aims to explore the cost-effectiveness of the QLIM intervention compared with usual care in children with cancer from a societal perspective.

METHODS

Participants

This economic evaluation was conducted alongside a multicenter randomized controlled trial (RCT) comparing the QLIM intervention with usual care. The trial design, rationale, and methods have been described previously.¹⁴⁸ In brief, patients were eligible when they were 8-18 years old, diagnosed with childhood cancer, during (outpatient care) or within the first year after treatment, including at least chemo- and/or radiotherapy. Exclusion criteria were: stem cell transplantation, growth-hormone use, proven cardiomyopathy, wheelchair bound, inability to ride a bike, inability to read and write in Dutch, or serious learning difficulties.

This trial was approved by the medical ethics committees of the four participating Dutch academic hospitals (VU University Medical Center Amsterdam, Academic Medical Center Amsterdam, Erasmus Medical Center Rotterdam, University Medical Center Utrecht). All parents or legal representatives, and children aged ≥ 12 years, provided written informed consent. Patients were recruited between March 2009 and July 2013. Trial registry number: NTR1531.

After baseline measurements, block randomization and stratification was performed by an independent hospital employ using a randomization list; stratification included age, gender, cancer type (hematological cancer vs. solid tumor), and treatment phase (during vs. after treatment)¹⁴⁸. Measurements were performed by blinded assessors.

Intervention

The 12-week intervention consisted of 24 physical exercise and 6 psychosocial training sessions for the children supplemented by 2 psycho-educational sessions for the parents. The physical exercise intervention included cardiorespiratory and muscle strengthening training (twice a week/ 45 min). Under the supervision of a pediatric physical therapist, the training was performed individually at a local physical therapy center. The content of the training and the exercises were described in an extensive instruction manual.

The psychosocial training was provided by a pediatric psychologist at the treating pediatric oncology center (once every two weeks/ 60 min). Two additional 60-minute parent sessions were provided by the same psychologist. For this training, the exercises were also described in an instruction manual.

Outcome measures

Measurements were performed at baseline (before randomization), at four months, and twelve months after baseline.¹⁴⁸

Primary outcomes:

Cardiorespiratory fitness was expressed as peak oxygen uptake (VO_{2peak} ; $ml \cdot kg^{-1} \cdot min^{-1}$) and assessed using the Cardiopulmonary Exercise Test (Godfrey protocol) on an electronically braked cycle ergometer (Lode, Corival P, ProCare B.V. Groningen, the Netherlands).¹⁰²

Muscle strength was assessed using a hand-held-dynamometer (CITEC; C.I.T. Technics, Groningen, the Netherlands). To calculate the sum-score for upper body muscle strength, the highest out of six (three left and three right) shoulder, elbow, and grip strength scores were added up to one final sum-score. The same was done for lower body strength including the highest hip, knee, and ankle scores.

HrQoL was assessed by the PedsQL™ Generic Core Scales child-report version⁵⁷ and *fatigue* was assessed by the child-report version of the PedsQL™ Multidimensional fatigue scale^{57,271}. The total HrQoL and total fatigue score were included in the analysis. HrQoL was also measured using the EuroQoL–youth version questionnaire (EQ-5D-Y).²⁷² The EQ-5D-Y measures five health dimensions (mobility, self-care, usual activities, pain and discomfort, anxiety/depression), all of which contain three severity levels: no problems, some/moderate problems, and a lot of problems.²⁷³ The children's EQ-5D-Y health states were converted into utilities (ranging from 0 [death] to 1 [full health]) using the Dutch adult tariffs.²⁷⁴ To calculate QALYs, the children's utility values were multiplied by their time spent in a particular health state using linear interpolation between measurement points.

Cost measures

Resource utilization data were obtained using monthly cost-questionnaires throughout the 12-month follow-up period of the study. All 12 questionnaires were provided to the parents at baseline. Parents were asked to retrospectively complete these questionnaires on a monthly basis and return them per 3 months using provided pre-paid return-envelops. Total costs of one-year included: intervention, healthcare, parental work-absenteeism, informal care, and unpaid lost productivity costs. All costs were converted to the index-year 2011 consumer prices indices.²⁷⁵ Intervention costs mainly consisted of personnel costs of pediatric physical therapists and psychologists. These costs were estimated by multiplying the intervention staff's time investments by their

respective labor costs (including overhead and holiday allowances). For this purpose, labor cost information was derived from the collective labor both professions.²⁷⁶

Healthcare use included use of primary-care, secondary-care, and medication. It included all visits to local healthcare services, and hospital visits or stays, and radio diagnostic images. Data on primary- and secondary-care were collected using cost-questionnaires. To collect data on the use of medication, each patient's pharmacy was contacted. Medication was subdivided into per-protocol childhood cancer medication and additional medication (i.e. not provided as standard cancer treatment). Primary- and secondary-care utilization was valued using Dutch standard costs.²⁷⁵ If unavailable, prices according to professional organizations were used. Medication use was valued using prices of the Royal Dutch Society of Pharmacy.^{277,278}

Parental work-absenteeism was reported as the number of hours parents had to take off from work to accompany their child to any healthcare facility. Informal-care included the number of hours parents needed extra help from family and friends. Unpaid productivity costs included the hours parents were unable to perform social and/or sports activities due to the sickness of their child. Parental work-absenteeism was valued using the mean hourly productivity cost of the Dutch population in the year 2011 (i.e. € 39.67),^{275,277} while both informal care and unpaid productivity costs were valued using the recommended Dutch shadow price of € 13.08/hour (2011).^{275,279}

Statistical analyses

Unless otherwise stated, analyses were performed with Stata (V12, Stata Corp, College Station, TX, USA). A 2-sided *P*-value of <0.05 was considered statistically significant. Discounting of costs and effects was not necessary due to the 12-month follow-up period.¹³⁷

Analyses were based on the intention-to-treat principle. Patient characteristics were summarized using descriptive statistics and presented per study group, and for patients with complete and incomplete data, separately.²⁸⁰ Missing data were imputed using multiple imputations. The imputation model included: 1) variables that differed between patients with complete and incomplete data, 2) variables which were a predictor for the "missingness" of data, 3) all predictors for total costs and effects, and 4) all available short- and long-term study data on costs and effects.²⁸⁰ Separate models were created for the intervention and control group. Using Fully Conditional Specification and Predictive Mean Matching, 25 different datasets were created in SPSS (IBM SPSS; Version 20.0. Armonk, NY: IBM Corp., USA) (Loss of Efficiency 0.05%). Datasets were analyzed separately as specified below. Pooled estimates were calculated using Rubin's rules.²⁸¹

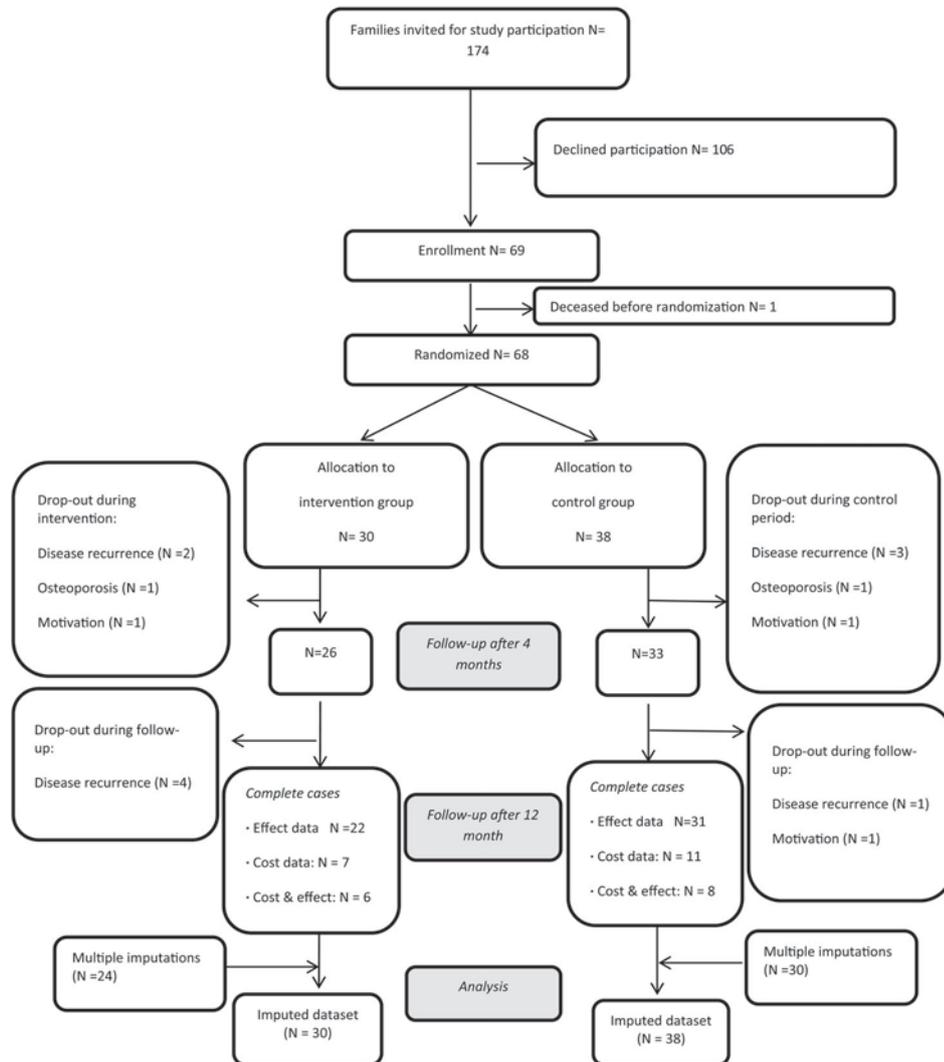


Figure 7.1 CONSORT diagram

Economic evaluation

Effectiveness at 12-month follow-up was analyzed using linear regression. Unadjusted mean cost differences between the intervention and control group were calculated for total and disaggregate costs. The 95% confidence intervals (CIs) around the cost differences were estimated by means of Bias Corrected and Accelerated bootstrapping (5000 replications).²⁸²

Seemingly unrelated regression (SUR) analyses were performed in which cost and effect differences were corrected for baseline values if available.²⁸³ An incremental cost-effectiveness ratio (ICER) provides insight into the additional costs per additional

unit of effect (e.g. cost per QALY gained) and was calculated by dividing the adjusted cost differences by those in effects; the Dutch willingness-to-pay (WTP) threshold for QALYs was set on 20,000 €/QALY. Bootstrapped incremental cost-effect pairs were plotted on cost-effectiveness planes (CE-planes).²⁸⁴ A summary measure of the joint uncertainty of costs and effects was presented using cost-effectiveness acceptability curves (CEACs). The CEAC is a graph that visually represents the level of uncertainty in an economic evaluation (i.e. probability of the intervention being cost-effective in comparison with the control condition) at various WTP thresholds.²⁸⁵

Sensitivity analyses

Three sensitivity analyses were performed to assess the robustness of the results. In a first sensitivity analysis (SA1), an additional 30 min of preparation time per session was added to the actual intervention duration for the calculation of intervention costs. In a second sensitivity analysis (SA2), the Steep Ramp Test (Peak workload) was used instead of the CPET (VO_{2peak}) to measure cardiorespiratory fitness.²⁸⁶ In a third sensitivity analysis (SA3), the healthcare perspective was applied, meaning that solely costs accruing to the healthcare sector were included.

RESULTS

Participants

Of the participants, 30 were randomized to the intervention and 38 to the control group (Figure 7.1). At baseline, no meaningful differences were found between groups. However, age and sex differences were observed between participants with complete and incomplete data (Table 7.1). These were, therefore, included in the imputation model.

Intervention and medication use data were complete for all participants. Except for 15 children who dropped-out during the study; 13 due to recurrence of the disease. Thirty of the 53 remaining participants (57%) did not complete or return all 12 cost-questionnaires. Consequently, complete cost and effect data on all measurement points were obtained of six (20%) intervention group children and eight (21%) control group children.

Use of the intervention

Twenty intervention group children (67%) attended all physical exercise training sessions within the given time span of 12 weeks (protocol), with a maximum extension of

Table 7-1: Baseline characteristics of the study population by study group, and the characteristics of cases with complete and incomplete data sets

Baseline characteristics	Intervention group			Control group		
	Total (n = 30)	Complete (n = 6)	Incomplete (n = 24)	Total (n = 38)	Complete (n = 8)	Incomplete (n = 30)
Age (yrs) (mean [SD])*	13.4 (3.1)	12.6 (2.6)	13.6 (3.2)	13.1 (3.1)	12.8 (2.7)	13.1 (3.3)
Male (n [%])*	16 (53.3)	5 (83.3)	11 (45.8)	21 (55.3)	4 (50.0)	17 (56.7)
Length (cm) (mean [SD])	158.9 (16.5)	152.3 (8.0)	160.6 (17.8)	154.5 (17.2)	154.7 (13.3)	154.4 (18.3)
Weight (kg) (mean [SD])	51.6 (16.0)	46.6 (10.1)	52.9 (17.1)	49.2 (16.9)	47.7 (11.1)	49.6 (18.3)
BMI (Z-score) (mean [SD])	0.5 (1.1)	0.8 (0.6)	0.5 (1.2)	0.6 (1.1)	0.7 (1.0)	0.6 (1.1)
SES (Z-score) (median [IQR])	0.7 (-0.3 - 1.2)	0.9 (0.1 - 1.6)	0.3 (-0.4 - 1.1)	1.2 (0.1 - 1.7)	0.6 (-0.2 - 1.8)	1.2 (0.1 - 1.6)
cardiorespiratory fitness (VO _{2peak} ; ml·kg ⁻¹ ·min ⁻¹) (mean [SD])	30.1 (8.5)	32.2 (11.1)	29.6 (7.9)	31.4 (9.5)	34.6 (8.0)	30.5 (9.8)
Upper body muscle strength (Newton) (mean [SD])	367 (114)	345 (65)	373 (124)	370 (134)	378 (90)	368 (144)
Lower body muscle strength (Newton) (mean [SD])	579 (174)	549 (141)	586 (183)	564 (207)	599 (237)	555 (201)
EQ-5D-Y (mean [SD])	0.8 (0.2)	0.9 (0.1)	0.8 (0.2)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
HrQoL (range: 0-100) (median [IQR])#	72.8 (18.2)	73.4 (55.2 - 89.4)	72.8 (57.9 - 79.3)	76.1 (64.1 - 82.6)	79.3 (67.9 - 89.7)	70.7 (63.1 - 82.6)
Fatigue (range: 0-100) (median [IQR])#	70.1 (19.7)	81.3 (51.1 - 95.1)	68.8 (47.6 - 83.3)	75.0 (61.1 - 88.9)	77.1 (56.9 - 88.2)	75.0 (65.3 - 88.9)
Cancer type						
Hematological malignancy (n [%])	20 (66.7)	4 (66.7)	16 (66.7)	25 (65.8)	5 (62.5)	20 (66.7)
Brain and CNS tumor (n [%])	1 (3.3)	0	1 (4.2)	6 (15.8)	1 (12.5)	5 (16.7)
Other solid cancer (n [%])	9 (30.0)	2 (33.3)	7 (29.2)	7 (18.4)	2 (25.0)	5 (16.7)
During treatment (n [%])	9 (30.0)	2 (33.3)	7 (29.2)	12 (31.6)	3 (37.5)	9 (30.0)
Treatment (n [%])						
CT	19 (63.3)	5 (83.3)	14 (58.3)	23 (60.5)	4 (50.0)	19 (63.3)
CT + RT and/or S	11 (36.7)	1 (16.7)	10 (41.7)	15 (39.5)	4 (50.0)	11 (36.7)

Abbreviations: n: number; SD, standard deviation; IQR: interquartile range; n: number; yrs: years; cm: centimeter; kg: kilogram; BMI: body mass index; SES: socioeconomic status; VO_{2peak}: peak oxygen uptake; ml: milliliters; min: minutes; EQ-5D-Y: EuroQOL five dimensions - youth version questionnaire; HrQoL: health-related quality of life; CT: chemotherapy; RT: radiotherapy; S: surgery; CNS: central nervous system

Note: * meaningful differences between complete and incomplete cases; # data by self-report
Age, sex and disease-related information were obtained from hospital-records. Body mass index (BMI) Z-scores were calculated by correcting BMI for sex and age according to Dutch normative values⁴⁰. Social economic status (SES) was estimated by postal code using the Netherlands Institute for Social Research database⁴¹.

4 weeks (n=24 sessions). The psychosocial part of the training program was completed by 27 children (90%).²⁵⁸

The control group was allowed to receive physical therapy and/or psychosocial support when needed; this was provided in eight children (21%) as part of usual care.

Effectiveness

No statistically significant 'between-group' differences were found for all outcome measures, during follow-up.

Costs

The cost of providing the complete QLIM intervention (i.e. 24 physical exercises and 6 + 2 psychosocial training sessions) was estimated to be € 2148 per participant. When taking into account the number of attended training sessions, the mean intervention costs were slightly lower; i.e. € 1915 (standard error of the mean [SEM]=92) (Table 7.2).

Table 7.2: Average costs per child over 12 months in a group receiving the physical exercise and psychosocial training program (QLIM) or usual care

Cost category	Intervention group n=30; mean (SEM)	Control group n=38; mean (SEM)	Mean cost difference (95%CI)
Intervention costs	1915 (92)	0 (0)	1915 (1621 to 1938)
Medical costs	9777 (1860)	12176 (3609)	-2399 (-20150 to 7203)
Primary care	241 (22)	691 (97)	-449 (-699 to 296)
Secondary care	4515 (389)	5391 (670)	-876 (-2944 to 318)
Medication	5021 (1826)	6094 (3422)	-1073 (-17817 to 8079)
Cancer treatment (protocol)	3758 (2831)	2831 (1097)	928 (-1946 to 5896)
Additional medication*	1263 (765)	3263 (2730)	-2000 (-11397 to 1342)
Informal care costs	417 (386)	396 (276)	21 (-745 to 1066)
Absenteeism costs	3181 (308)	2271 (345)	910 (-123 to 1703)
Unpaid productivity costs	127 (30)	77 (17)	50 (-9 to 131)
Total	15417 (1896)	14920 (3681)	497 (-7383 to 6729)

Abbreviations: n: number; SEM: standard error of the mean; CI: confidence interval; * not provided as standard cancer treatment.

Note: costs are expressed in 2011 Euros

Healthcare costs were non-significantly lower in the intervention group compared to the control group, whereas work-absenteeism, unpaid productivity, and informal care costs were non-significantly higher in the intervention group. Total societal costs in

the intervention group were € 497 higher than in the control group, but this was not significant (95%CI: € -7383;6729). Again not significantly different, non-cancer treatment medication costs were lower in the intervention group compared to the control group (mean difference € 2000, 95%CI: € -11397;1342). This non-cancer treatment medication also included expensive antifungal medication such as VFEND® raising the costs.

Cost-effectiveness

The ICER for QALYs was 14,882, indicating that the intervention costs were € 14,882 higher than usual care per QALY gained (Table 7.3), which is below the Dutch WTP threshold of 20,000 €/QALY. QALY cost-effect pairs were distributed over all four CE-plane quadrants, indicating that the uncertainty surrounding the ICER was substantial (Figure 7.2A). The related CEAC showed that the probability of the intervention being cost-effective was 0.45 when society is not willing to pay anything per QALY gained. This probability gradually increased to approximately 0.67 at a WTP of € 100,000/QALY (Figure 7.2B).

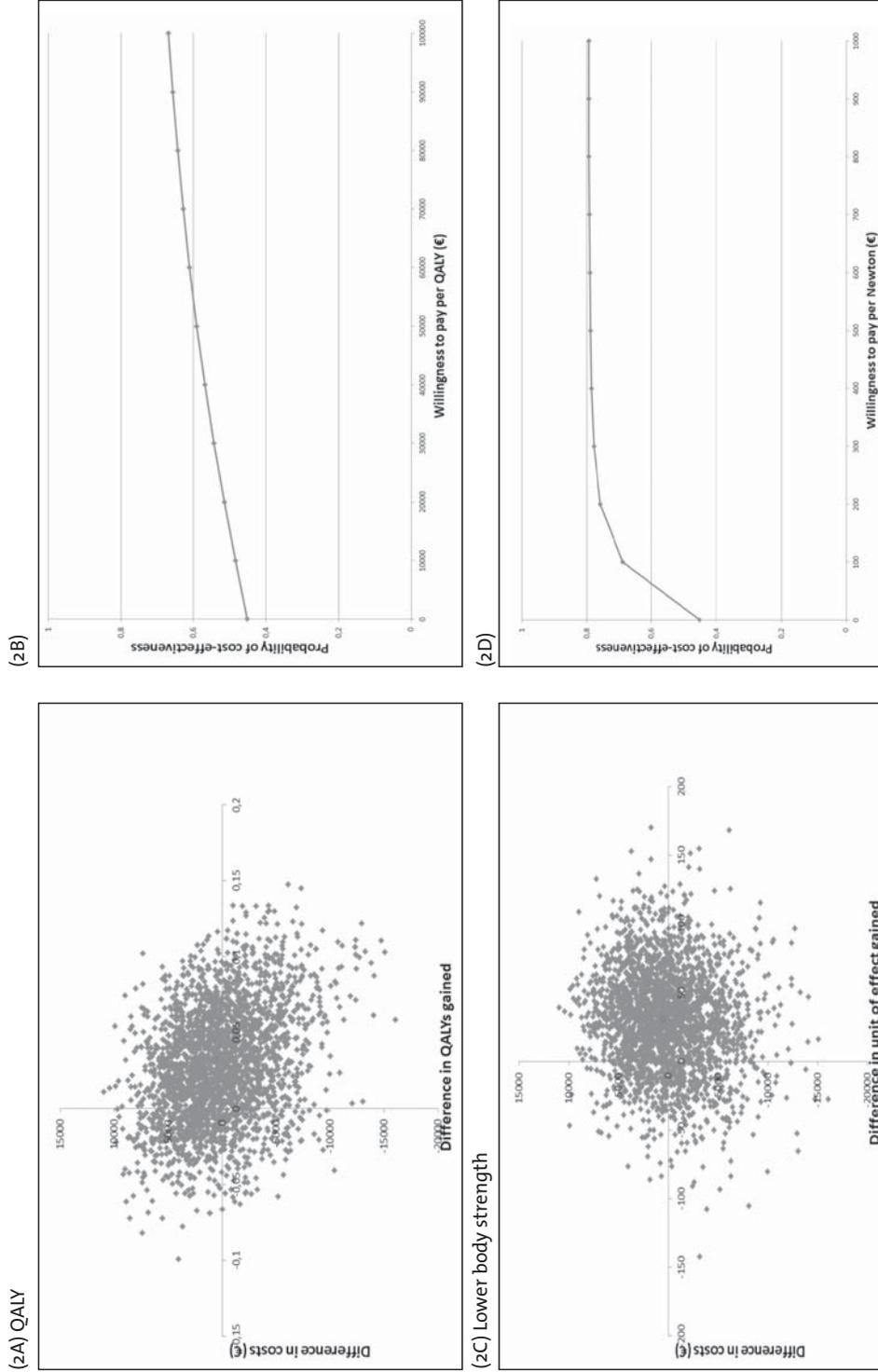
The ICER for lower body muscle strength was 16, indicating that one Newton lower body muscle strength increase was associated with societal costs of € 16. However, the uncertainty around this estimate was large (Figure 7.2C). The CEAC for lower body muscle strength (Figure 2D) showed that the probability of the intervention being cost-effective at a WTP of € 0 was 0.45 and gradually increasing to 0.79 at a WTP of € 600/Newton.

The ICERs for upper body muscle strength and cardiorespiratory fitness were -15 and -1111, respectively. These numbers indicate a societal cost of € 15 and € 1,111 per 1-point decrease in upper body muscle strength (Newton) and cardiorespiratory fitness (VO_{2peak} : $ml \cdot kg^{-1} \cdot min^{-1}$), respectively (Table 7.2; i.e. more costly/less effective). For both outcomes, the maximum probability of cost-effective was 0.45, irrespective of the WTP (Figures not shown).

Sensitivity analyses

The results of SA1 were similar to those of the main analysis, whereas the results of SA2 and SA3 were more favorable. To illustrate, in SA2 a positive rather than a negative difference in cardiorespiratory fitness was found and in SA3 costs were found to be lower rather than higher in the intervention group (Table 7.3). Nonetheless, in accordance with the main analysis, all cost and effect

Figure 7.2: Cost-effectiveness planes indicating the uncertainty around the incremental cost-effectiveness ratio for (A) QALYs and (C) lower body muscle strength; and cost effectiveness acceptability curves indicating the probability of cost-effectiveness for different values (€) of willingness to pay per unit of effect gained for (B) QALYs and (D) lower body muscle strength based on the imputed dataset.



differences were not statistically significant and the associated probabilities of cost-effectiveness were relatively low (i.e. <0.80).

DISCUSSION

Per child, the societal costs in the QLIM intervention group were on average € 497 higher than in the control group. This cost difference, however, was not statistically significant; nor were all other between-group differences in costs and effects. A joint comparison of costs and effects revealed that a substantial amount of money must be paid by the society per unit of effect gained to reach a reasonable probability of cost-effectiveness for QALYs and lower body muscle strength. Although, the ICER for QALYs was well below the informal Dutch threshold of 20,000 €/QALY, the probability of cost-effectiveness at this WTP threshold was low ($p=0.50$) and remained relatively low up to 100,000 €/QALY ($p=0.67$). Currently the Dutch threshold for 1 gained Newton on lower body muscle strength is unknown. However, it can be expected that the maximum WTP will be low, this because the clinical impact of 1 Newton increase is low and the maximum probability of cost-effectiveness for lower body muscle strength remained relatively low ($p=0.79$). Furthermore, the intervention was associated with a low maximum probability of cost-effectiveness for upper body muscle strength and cardiorespiratory fitness (i.e. 0.45).

The present economic evaluation was performed alongside a randomized controlled trial. In the CHEERS guidelines this is acknowledged as the best way to perform an economic evaluation because such a trial provides individual, prospective patient data resulting in reliable estimates of costs and effects.^{287,288} Execution and reporting of a cost evaluation is important as the joint distribution of costs and effects could have resulted in significant cost-effectiveness analyses²⁸⁷; however this was not shown by the results of the current analyses. Also, since full economic evaluations from a societal perspective in children oncology are scarce^{265,266,289}, we think it is valuable to report on the cost-effectiveness of the QLIM intervention in comparison with control. Some study limitations deserve attention. First, both study groups contained a relatively small number of patients, as the RCT was powered to detect an intervention effect on cardiorespiratory fitness. However, it is known that economic evaluations require large sample sizes to detect relevant differences in costs.²⁹⁰ As such, this study was underpowered for costs which are reflected by the large uncertainty in the economic outcomes. Secondly, there was a large amount of missing data (i.e. only 21% of participants had complete data on all measurement points). To deal with this limitation, multiple imputation was used to impute missing values which is generally considered the most appropriate way to deal with missing data.²⁹¹ However, imputed data are not as reliable as a 100% complete dataset. Therefore, for future studies, it

would be advisable to improve the efforts to minimize missing data. For example by the use of an online-cost-questionnaire with an automatic reminder to increase the completeness and quality the of data.²⁸⁷ A third point is that this study could include children with any type of cancer, combined with different treatment morbidities. Likely related to this heterogeneity issue, the confidence intervals around the health-care cost differences were large, which, in turn, may have decreased the probability of the intervention being cost-effective in comparison with usual care. Fourth, we were not able to fully monitor what kind of care the control group received (usual care). Nonetheless, through the cost questionnaires it was found that 21% of the children in the control group received physical therapy and/or psychosocial support as part of usual care. This could have reduced the contrast and with that the effect size of the intervention.

CONCLUSION

In conclusion, the QLIM intervention was not cost-effective compared to usual care for cardiorespiratory fitness, muscle strength and QALYs in children during or within the first year after cancer treatment. Larger studies are needed to decrease the uncertainty in outcomes on costs and effects.