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Economic evaluation of treatments for cancer in childhood

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Abstract

Treatment of cancer in childhood is an expensive undertaking for the health-care system and for the affected families. As there is a substantial burden of treatment-related morbidity, it is important to determine whether the effects of treatment are worth these monetary costs, especially from a societal perspective. Economic evaluation affords a comparison of the costs and consequences (effects) of relevant therapeutic alternatives. Preference-based measures of health-related quality of life are particularly useful for assessing the effects of treatment, for these tools integrate mortality and morbidity. These measures provide utility scores that can be used as weights on survival data to compute quality-adjusted life years (QALYs). Costs are incurred both within and outside of the health-care system. The former should include those in front-line patient care departments (e.g. nursing); the pro-rated share of the expenses of service departments (e.g. materials management) to those in the front line; and the fully allocated costs for capital invested in lands, building and equipment. The latter are costs borne by families that are both out-of-pocket (e.g. for over-the-counter drugs) as well as related to time spent in providing care, which may involve foregone income. Costs and consequences should be subject to discounting; a process for converting those items incurred in the future into contemporary equivalents. Economic evaluation provides estimates of incremental discounted costs per discounted QALY gained. By almost any interpretative standard this appears attractive with respect to cancer in childhood. Examples are provided with the encouragement that economic evaluation be undertaken in more clinical trials in paediatric oncology.

Keywords: Economics; Treatment; Cancer; Child

1. Introduction

The treatment of cancer in childhood is costly. Typically it involves periods of hospitalisation, the use of physician and other professional services, the use of laboratory and other diagnostic tests, the administration of chemotherapy, and the use of other pharmaceuticals. Surgery and radiotherapy may be needed. Treatment also requires frequent outpatient visits. This all imposes a large financial burden on health-care systems and on the families of children who are affected. Of course, the burdens are not only monetary. Treatment often results in a substantial burden of morbidity. Further, not all patients who complete therapy enjoy normal health.

Do the effects of treatment warrant the substantial monetary and non-monetary costs it takes to produce them? This article provides a framework for addressing such questions and summarises some of the scanty evidence on the economics of childhood cancer care, building on a recent review focused on acute lymphoblastic leukaemia[1], the commonest form of cancer in childhood. The current review focuses on a selected set of topics and does not address some other important issues, such as proxy assessment and changes in utilities

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over time. The paper is intended to provoke further interest in economic evaluation and encourage the use of more comprehensive measures in trials of treatments for childhood cancer.

1.1. Framework: economic evaluation of health-care services

The essence of the economic evaluation of health-care services is a comparison of the costs and consequences of relevant alternatives. Partial economic evaluations involve comparisons between alternative courses of action involving one factor at a time [2]. For example, does the addition of another drug enhance survival relative to standard care? What effect does it have on health-related quality of life (HRQL) during treatment? What effect does it have on the quality of survival? What effect does it have on the costs of care? Full economic evaluations involve comparisons between alternatives that involve both costs and consequences (effects). Treatments that cost less and produce better effects are clear winners. Similarly, treatments that cost more and produce less are clear losers. If a new treatment costs more but produces better effects, is the incremental improvement in effect worth the incremental cost? Techniques for the economic evaluation of health-care services are designed to help answer such questions [2–5].

Economic evaluation builds on the results of analyses of clinical effectiveness, such as the results of randomised controlled clinical trials (RCTs) [6]. RCTs provide rigorous evidence on the effects of alternative therapies and their resource requirements. Economic evaluation involves attaching monetary values to the costs of those resources, and for valuing and summarising effects. There are two major components to a full economic evaluation: the consequences (or health effects) and the monetary costs. Each will be discussed in turn.

2. Clinical effectiveness, utility assessment and quality-adjusted life years

Treatment produces a variety of health effects. Measures of these effects include clinical markers (such as normal white cell blood count, absence of tumour), sequelae and survival. Using multiple measures of health effects is appropriate for assessing the complex effects of disease and therapy. However, for the purposes of constructing an economic evaluation, a measure that summarises effects in a single number is required. Because the effects in childhood cancer include death and disease-free survival with varying amounts of sequelae, preference-based measures of HRQL that can integrate mortality and morbidity are especially useful. The utility approach, one of the dominant approaches to assessing HRQL, is based on well-established theories of economics and decision science. Utility scores represent relative preferences for health states. Preferences vary among individuals, and mean community preference scores are most frequently recommended to estimate the HRQL of patients for the purposes of economic evaluation. While it is possible that children might value health states differently than adults, at the group level mean scores from parents and teenagers are similar [7–9]. So empirically it does not appear that there is a great deal of divergence. Again, while society may value life years gained by children more than life years gained by adults, and this is an important issue ethically and philosophically, in practice few if any studies have made any serious adjustments [10].

The conventional scale for preference-based measures of comprehensive health status assigns a utility score of 0.00 to being dead (the absence of health status) and a score of 1.00 to perfect health [11,12]. Negative scores represent health states considered worse than being dead. In this system, children who die get a score of 0.00; children who enjoy disease-free survival without any problems get a score of 1.00. Children with sequelae get scores that represent the value of their overall health state relative to being dead or being in perfect health. For instance, the Health Utilities Index Mark 2 (HUI2) utility score of HRQL for a survivor of high-risk acute lymphoblastic leukaemia (ALL) who learns more slowly than classmates but is otherwise healthy is 0.95.

2.1. Where do you get the utility scores?

There are two major approaches to obtaining utility scores for health states: direct measurement and multi-attribute assessment. In the direct approach a respondent is asked to value a health state using the standard gamble technique. In the standard gamble the respondent is asked to choose an intermediately ranked health state for sure (for instance, disease-free survival with emotional sequelae involving occasional anxiety and worry) for a specified period of time or a lottery. The lottery consists of a highly desirable health state (for instance, perfect health) with probability p and a less desirable health state (for instance, being dead) with probability $1 - p$. The probability p is varied until the respondent is indifferent between the lottery and the sure thing. The more the respondent values the 'sure thing' health state, the higher the probability p he will require to be indifferent; the less he values the sure thing, the lower the indifference probability. The health state being evaluated can be the respondent's current health state or a hypothetical health-state description. Alternatives to the standard gamble direct measurement technique include the time trade-off, in which respondents trade years of life expectancy in a compromised health state for a briefer life expectancy in perfect health [11].

Feeny *et al.* [13] illustrate an application of the direct approach. A set of health-state descriptions covering the phases of therapy (initial induction of remission, bone

marrow transplantation, palliative care, etc.) for high-risk ALL, Wilms' tumour and neuroblastoma were developed. Because relatively few patients (children) would be able to provide preference measurements for these health states (as discussed below), parents of patients were asked to value the states using a visual analogue scale called the 'feeling thermometer' and a chance board to pose standard gamble questions. For instance, the health state describing initial induction of remission that is physically and emotionally well tolerated had a mean utility score of 0.82 (SD = 0.209), while the same phase of therapy that is poorly tolerated physically had a mean score of 0.75 (SD = 0.264). We will return to this example.

The direct approach to utility assessment is well grounded in theory [14] and may be used to measure preferences of patients for their own health status. It is, however, cognitively demanding and imposes a number of other major burdens both on the respondents and on the investigators. Interviewer administration of health-status questionnaires can be accomplished successfully with children as young as 6 years of age but self-completion of such instruments can only be undertaken usually by children who are 12 years of age or older. Evidence to date indicates that a grade 6 reading level (the expected reading level for 12 year olds in Canada) is required before respondents can handle the standard gamble reliably [15,16].

The multi-attribute (or indirect) approach was developed in part as a response to the challenging burdens of the direct assessment of preference scores. Instead of asking the patient (or parent) to value health states, the investigator asks the respondent to complete a health-status assessment questionnaire based on a multi-attribute system (comprising multiple attributes, domains or dimensions of health). The questionnaire responses provide a description of the patient's current health state according to an established multi-attribute health-status classification system. That health state is then scored using a multi-attribute scoring formula, typically based on preference scores obtained from the general population. Parents of patients provide scores similar to those from members of the general population [17].

There are a number of multi-attribute systems. The three major systems are the Quality of Well Being (QWB) Scale [18], the EuroQol EQ-5D [19], and the Health Utilities Index (HUI) [20–23]. The QWB has much less coverage of cognition than HUI and this attribute is absent from EQ-5D. Cognition is compromised in almost all studies of survivors of cancer in childhood in which the HUI has been used.

Because HUI has been applied extensively in paediatric oncology [1], it will be used to illustrate.

2.2. Quality-adjusted life years

Traditional survival analyses assign a score of 1 to those who are alive and a score of 0 to those who are not. This approach assigns the same score to the survivor who enjoys normal health and the survivor with major problems. The utility scores described above provide a way to adjust the quantity of life (years) experienced by the patients for the HRQL that they experience, to compute quality-adjusted life years (QALYs). QALYs are an index computed by multiplying the duration of the health state (life years) by the utility score (quality adjustment) for that health state.

Mean direct utility scores (obtained from parents of patients serving as proxy respondents for children undergoing treatment) for health states associated with high-risk ALL are illustrative [13]. The experience of one child was as follows. During the first month of remission-induction therapy the child experienced a considerable physical burden but handled the experience well emotionally; the mean utility score for this state was 0.75. During the second month of intensive treatment the child tolerated the therapy well both physically and emotionally; the mean score was 0.90. For the next 23 months of less intensive treatment, the child handled the experience well emotionally but not physically; the mean score was 0.78. To estimate the QALYs during the 25-month (2.08 years) period, one multiplies the duration of each state by its utility score and sums over the period, producing an estimate of 1.63 QALYs (78% of the ideal of having enjoyed perfect health during the entire period).

Similarly, multi-attribute systems such as the HUI can be used to assess the HRQL associated with treatment and outcome. Barr *et al.* [24,25] and Furlong *et al.* [22] provide evidence on HRQL during treatment and among survivors using the HUI mark 2 (HUI2) and the mark 3 (HUI3) systems. HUI2 was developed specifically for assessing HRQL of health states experienced by children after treatment for cancer. Seven dimensions (attributes or domains) of health status are included in HUI2: sensation (vision, hearing, speech), mobility, emotion, cognition, self-care, pain, and fertility. There are three to five levels per attribute, ranging from a severe problem to no problem/normal. For instance, there are five levels for mobility ranging from 'unable to control arms and legs' to 'able to walk, bend, lift, jump, and run normally for age' [26]. The comprehensive health state of a patient is described as one level for each of the seven attributes, a seven-element vector. A multiplicative multi-attribute scoring function, based on preference scores obtained from a random sample of parents in the general population, is used to calculate utility scores for HUI2 health states [26]. The HUI2 health-status classification system defines 24,000 unique health states (a factorial of the numbers of levels in each attribute).

HUI3 includes eight attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. There are five or six levels per attribute. The multiplicative, multi-attribute scoring function is based

on preference scores from a random sample of the general population [23]. The HUI3 health-status classification system describes 972,000 unique health states.

HUI2 and HUI3 were used to evaluate HRQL in patients receiving continuing (maintenance) chemotherapy for ALL on an ambulatory basis following successful remission induction using Dana Farber Cancer Institute protocols 87-01 and 91-01 [25]. Children were treated in 3 weeks' cycles. In the first week they received three chemotherapeutic agents and high-dose oral corticosteroids; in the second week they received two chemotherapeutic agents; in the third week the children received no therapy. Problems associated with steroids were expected to be reflected in the week 2 assessment; problems with pain, emotion and mobility/ambulation were anticipated. HUI data were collected by the serial administration of a standard 15-item questionnaire [22]. Results indicate that, for HUI3, 11% had problems with emotion at week 1, 44% at week 2, and 17% at week 3. Mean single-attribute utility scores for HUI3 emotion were 0.99 at week 1, 0.92 at week 2, and 0.94 at week 3. [Single-attribute utility scores are defined on a scale in which severe impairment (lowest level) = 0.00 and no problem/normal = 1.00.] Similarly, single-attribute scores for pain were 0.99 at week 1, 0.94 at week 2, and 0.98 at week 3. Analogous results for ambulation were 0.99, 0.96, and 0.98. Overall HUI3 scores by week were 0.94, 0.74, and 0.85 [22]. Overall HUI2 scores were 0.96, 0.86, and 0.91 [25]. During week 1, children had HRQL similar to that found in the general population; during week 2 HRQL was similar to survivors of brain tumours [27]. Serial assessment of HRQL with a multi-attribute utility measure during therapy provides scores that can be used to calculate QALYs. The burden of obtaining utility scores from a multi-attribute system is very low relative to direct utility assessment. Minimising the burden helps to maximise the quantity of the data (i.e. minimise refusal rates and maximise compliance) and maximise the quality of the data (i.e. make it easy for respondents to provide high-quality measurements).

Barr *et al.* [24] provide an example of the cross-sectional assessment of outcomes in survivors of ALL using a multi-attribute measure (HUI2). Of standard-risk survivors, 60% reported no problems on HUI2; the mean HUI2 score was 0.96. Among survivors of high-risk ALL, 30% reported no problems; the mean score was 0.90. Differences of 0.03 or more in overall HUI2 and HUI3 scores are considered clinically important [28,29]. Using systems such as HUI, investigators can collect utility measurements of HRQL through the treatment process and during long-term follow up. Then, the observed utility scores may be used to calculate QALYs, providing measures of health effects for use in economic evaluations.

3. The economic costs of care

QALYs provide a comprehensive measure of the health effects of treatment, a measure that integrates mortality and morbidity. What did it cost to produce those effects? Costing is designed to estimate the resources consumed, and thus unavailable for other uses, in producing the effects.

3.1. Viewpoint

The societal viewpoint and costs, not charges, are recommended for economic evaluation [2–4]. Using the societal viewpoint, all of the costs of care, regardless of who pays them, are counted. Less comprehensive viewpoints include that of the third-party payer and the family. Relocating care from in- or outpatient settings (where the third-party payer bears the costs) to home care (where family members often bear most of the costs) will reduce costs according to the third-party payer's viewpoint, increase cost according to the family's viewpoint, and may reduce or increase cost from the societal viewpoint. If the cost of the time of family members is much lower than the cost of the time of health-care professionals, on net the total cost of care may be reduced.

3.2. Components of cost

There are a variety of ways to classify the costs of treatment, and it must be recognised that such costs, e.g. of drugs, may change appreciably over time. First, it is useful to distinguish costs within and outside of the health-care system. Costs within the health-care system include hospitalisation, outpatient care, physician services, the services of other health-care professionals (nurses, pharmacists, etc.), and the services of allied personnel (e.g. social workers), laboratory and other diagnostic tests, and pharmaceuticals. Costs outside the health-care system include costs borne by families, both out-of-pocket (e.g. over-the-counter drugs, mileage and parking to attend hospital visits) and the costs of time spent in providing care or being with the child while the child is receiving care (foregone income).

A 1994 report [30] and Barr *et al.* [31] provide data for illustrating a costing analysis from the societal perspective. The Blackhouse report [30] provides estimates for the cost of care from the point of view of the Ontario (Canada) government's health-care system (a third-party payer providing first-dollar coverage of most health-care services). Resource utilisation for treating children for high-risk ALL was abstracted from charts at the Hospital for Sick Children, Toronto, Ont., Canada and the McMaster Children's Hospital in Hamilton, Ont., Canada. The children were diagnosed during the 1975–1985 period and treatment ended during the 1976–1988 period. Chart abstraction provided data on the

duration of hospitalisation, use of diagnostic tests, use of drugs, physician consults (both for in- and outpatient care), use of radiation therapy, and use of bone marrow transplantation (BMT). Utilisation of hospital-based resources was costed according to five categories: drugs, physician fees, radiation treatment, BMT and hospital services (which included inpatient stays in wards and the intensive care unit, visits to clinics and the emergency room, time in the operating room and diagnostic procedures). The results provided a comprehensive estimate of the costs to the Ministry of Health in Ontario for the diagnosis and treatment (in- and outpatient) for the duration of illness. The estimates reflect the direct costs incurred in front-line patient-care departments (nursing, etc.), the pro-rated share of service departments' (materials management, laundry, etc.) expenses to front-line patient-care departments, plus the fully allocated costs for capital invested in land, buildings and equipment.

Several results are notable. The average cost ($Can, 1986) for ALL patients who did not receive BMT was $54,260; the average costs for those who did receive BMT was $102,804. (In 1986 the exchange rate was $1.3894 Canadian per $US.) [32]. Clearly BMT is expensive. The average duration of therapy for patients who survived was 34 months with a total mean cost of $55,731; the average duration for those who did not survive was 19 months with a total mean cost of $65,547. It would appear that the costs of treatment were higher for patients who did not survive.

From the societal point of view these estimates are incomplete. They do not include the costs borne by families. Barr *et al*. [31] provide the complementary information (also in $Can 1986). Families of children on therapy were asked to keep diaries for a week on the family borne costs, including foregone wage income. Diaries were distributed using a sampling plan designed to provide estimates of family borne costs for each phase of therapy. The mean weekly total family cost during remission-induction and consolidation phases of treatment was $370 and during the maintenance phase was $232. Questionnaires were distributed also, to capture one-time expenses such as home renovations to accommodate a wheelchair. The mean of total one-time expenses was $329. Over the 107-week course of treatment for high-risk ALL the average family borne costs were $26,070, 26.8% of average total family income and almost one-third of after-tax income. Clearly the financial burden on families is substantial and these data do not include lost productivity of the survivors and their families.

Combining the two sets of estimates provides an estimate of total cost for treatment from the societal point of view (Table 1). In a cohort of 25 high-risk ALL patients, 24 received radiation therapy and four underwent BMT. General hospital services account for almost half, and family borne costs account for more than a quarter, of total societal costs. The estimates omit future treatment costs associated with managing sequelae among survivors. Nonetheless, results in Table 1 provide an example of how the total societal costs of treatment can be estimated. It is expected that these costs, and their components, will vary widely around the world (as with life expectancy). The absolute amounts quoted here pertain to the local context only.

3.3. Discounting

When costs occur in multiple time periods, it is important to convert costs and effects incurred in the future into their contemporary equivalent. A discount factor (like an interest rate) is used to convert future costs (and effects) into their present value. (Technically the costs in Table 1 incurred during the second year of therapy should be discounted to their present value in year 1.) There are competing theories about the correct measure for determining appropriate discount rates for public projects and, in practice, analysts use discount rates mandated by government or rates consistent with the published literature[2]. The idea of discounting because of a positive rate of time preference is sound; the choice of particular rate is somewhat arbitrary. Thus the discount rate recommended for economic evaluations in Canada is 5% [33] and the rate recommended in the United States is 3% [3]. Using the 3% discount rate, $100 of treatment cost in year 2 is equivalent to $97.09 in year 1 (present value). Similarly, the present value of $100 in year 3 is $94.26. Discounting provides a mechanism for

Table 1
Mean cost of diagnosis and treatment for high-risk acute lymphoblastic leukaemia

Average duration (months)	Drugs	Hospital services	Physician fees	Radiation treatment	Bone marrow transplantation	Family borne costs	Total
25	8029[a]	39,281[a]	8078[a]	1245[a]	4988[a]	26,070[a]	87,691[a] (133,817)[b]
As a % of total cost							
–	9.2	44.8	9.2	1.4	5.7	29.7	100.0

Source: Data from [26,27].
[a] Original 1986 $ Canadian.
[b] Converted from 1986 to 2002 Canadian dollars by a factor of 1.526; the Health and Personal Care Component of the Consumer Price Index from Statistics Canada, 2003 [53].

translating future expenses into their present value equivalents so that valid comparisons of treatment costs can be made. Discounting also implies that long-term effects are not very important.

3.4. Sensitivity analysis

Sensitivity analysis is an important method for assessing the effects of uncertainty about estimates of costs and effects in economic evaluations. It involves identifying the uncertain factors in the data used to fit the economic evaluation model, specifying a plausible range of uncertainty for levels of each factor, and calculating sets of study results based on combinations of factor levels including sets in which several factors are varied simultaneously [2]. The sets of study results should include the combination of best estimates, the combinations of most conservative estimates (e.g. highest cost and lowest effect estimates), and the combinations of most optimistic estimates (e.g. lowest cost and highest effect estimates). Unlike some other methods of dealing with uncertainty, such as statistical inference, sensitivity analysis can be used with deterministic data (i.e. known only as point estimate). The discount rate is generally considered a deterministic factor and sensitivity analyses of rates from 0% to 10% should be used.

Do the health effects warrant the costs? The next step in the process of economic evaluation is to combine the estimates of costs and effects.

4. Integrating effectiveness and costs: economic evaluation

Economic evaluation compares the costs and effects of relevant alternative courses of action. Although there have been economic evaluations of discrete components of care for children with cancer (for instance, antibiotics in febrile neutropenia), there are no published comprehensive evaluations of the costs and effects of overall treatment strategy alternatives [1].

4.1. Cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis

There are three major forms of economic evaluation. All include costs. The forms differ in how effects are measured. In cost-effectiveness analysis (CEA), effects are measured in natural units such as life years gained, as illustrated by the crude example presented above. Because not all life years gained are equal (e.g. disease-free survival in perfect health vs. disease-free survival with cognitive impairment), cost-utility analysis (CUA) uses quality-adjusted effects to estimate the cost per QALY gained (as also illustrated above). Finally, in cost-benefit analysis (CBA), the effects are measured in monetary terms. CEA and CUA are used more frequently than CBA in health-care evaluations, in part because of the difficulties in quantifying the monetary value of health effects.

In each of the three major forms of economic evaluation, the ratios present the incremental cost per incremental effect, comparing one treatment alternative to another. If alternative 'A' costs less and does more than 'B', then this would be strong evidence for the adoption and utilisation of 'A' [2,4,34]. If 'A' costs more and does less, again the implications are clear. More difficult (and perhaps more common) are situations in which 'A' costs more and does more, or costs less and does less. Do the incremental effects warrant the incremental cost? Some guidance is provided in the literature [2–4,34].

To illustrate what an economic evaluation would look like, we use the total societal costs expressed in 2002 Canadian dollars from Table 1. The total cost of treating the convenience sample of 25 high-risk ALL patients was $3345425. This includes the cost of treating relapsed/progressive disease. Ten of the 25 survived. The mean age at diagnosis was 8.2 years. Assuming that disease-free survivors enjoy a close-to-normal life expectancy, treatment results in approximately 70 additional life years per survivor. Thus, the expenditure of $3.3 million adds approximately 700 life years. (Technically, the incremental costs of active therapy are less than the full $3.3 million. The costs of palliative care initiated at diagnosis, an unrealistic policy alternative, should be subtracted from the costs of treatment with the intent to cure to obtain an estimate of the incremental costs of treatment. For purposes of simplifying the exposition, we will ignore those costs.) The undiscounted cost per life year gained would be $4779. However, it is necessary to discount both costs and effects [2,4]. Using a discount rate of 3%, the present value of 70 life years is 30 years. Thus, the cost per life year gained is $11151. Of course, even though most survivors of high-ALL enjoy good health, some survive with important sequelae. Barr *et al.* [24] and Feeny and colleagues [25] provide evidence of the HRQL experienced by high-risk ALL survivors; in both cases the mean HUI2 utility score is 0.90. Using 0.90 and the discounted life years gained of 30 years, the cost per QALY gained is $12390. By virtually any interpretative standard, this looks quite attractive [34]. It should be stressed that this analysis is very crude and presented for illustrative purposes only. It is very crude because the sample of 25 patients is not necessarily a representative sample of an inception cohort of high-risk ALL patients treated between 1975 and 1988, and survival rates have been higher for more recent cohorts of such patients [35]. Furthermore, this analysis does not include long-term costs that may be important in the context of late sequelae.

5. Case studies

5.1. Two illustrative case studies from the literature

There are no rigorous economic evaluations of treatment for childhood cancer in the published literature [1]. Appendix A provides a brief summary of some key factors, from the perspective of economic evaluation, about two published studies. These two case studies illustrate a number of major points. Both studies are very strong with respect to presenting comparisons of clinically relevant treatment alternatives and providing high-quality estimates of clinically important incremental health effects based on data from RCTs. However, neither study includes any information about differences in HRQL between treatment arms, and the cost estimates are for less than comprehensive viewpoints. Furthermore, neither study reports the incremental total cost or the incremental cost-effectiveness ratio for the experimental treatment.

5.2. Stem-cell transplantation

The elements of economic evaluation are no better highlighted than in a consideration of stem-cell transplantation. With respect to costs, important variables are the disease (e.g. leukaemias, lymphomas or solid tumours), the disease status (e.g. remission or relapse), the nature of the donor (i.e. autologous, sibling or matched unrelated), the source of the stem cells (peripheral blood or bone marrow – there appear to be no economic analyses, so far, of umbilical cord stem-cell transplants), and the age and health status of the recipient [36].

Some general deductions can be made. The greater cost of stem-cell harvest from peripheral blood as compared to bone marrow is more than offset by the reduced costs associated with a shorter hospital stay; and transplants early in first remission cost less than those undertaken at later points in disease evolution/treatment experience. Changing the primary locus of care for BMT from inpatient to outpatient may result in notable cost saving for 'low risk' patients but for others the reduction in inpatient days and associated charges may be almost completely offset by increased outpatient costs [37].

The assessments of HRQL in adult survivors of BMT are of limited relevance to children. Somewhat more relevant are accounts of the quality of life in young adults who were transplanted in childhood [38].

In an early application of the HUI to a small paediatric survivor population, the majority of whom had had a solid tumour prior to mega therapy and autologous bone marrow rescue, most children appeared to have a satisfactory HRQL (some assessments being undertaken by parental proxies and some by the children themselves). However, a minority had an important burden of morbidity [39]. A later, more robust study, using the Q-TWiST method, was undertaken in the context of a RCT for acute myeloid leukaemia [40]. Overall, the children who had undergone allogeneic transplants (from matched related donors) enjoyed superior HRQL to those who had undergone autologous transplants or chemotherapy only, even when adjusted for chronic graft-versus-host disease (GVHD).

Application of purpose-designed (specific) measures to paediatric survivors in Italy [41], Austria [42] and the United States [43,44] revealed that the majority enjoyed good HRQL following allogeneic BMT. However, the measurement properties of the European scales are unknown. In one of the studies from the United States [43] the paediatric population was part of a much larger total group and the adult survivors had poorer overall HRQL than the children. In the remaining study, from Boston, children self-reported and parental proxies responded to interviewer-administered generic and specific questionnaires. The parents reported more morbidity, especially in subjective domains of health and particularly in the presence of GVHD.

A study in Toronto, using parental proxy respondents [45], demonstrated an overall improvement in HRQL following both autologous and allogeneic BMT in children, by comparison with the pretransplant status. Investigators in Memphis, meanwhile, in a longitudinal study [46], observed a reduction in HRQL immediately after transplantation, followed by improvement. The determinations were obtained by interviewer-administered self-report in children 5–17 years of age. The morbidity burden was greater in adolescent than in younger subjects and after allogeneic by comparison with autologous transplants.

None of this addresses the burden of morbidity in other members of the family of children who undergo stem-cell transplantation, although this can be considerable [45,47].

Frameworks for undertaking CEA and CUA in stem-cell transplantation have been presented [48]. More than a decade ago, investigators in New Zealand undertook a CUA of BMT without discounting [49] in a population of young patients (mean age 23 years). Although the assessment of HRQL was decidedly imperfect, this represents one of the earliest efforts to perform an economic evaluation of stem-cell transplantation in a group of patients that incorporates the paediatric age range.

Arguably the most informative study to date is that performed by a consortium of institutions in France as part of a RCT in children and adults with solid tumours and lymphomas [50]. The study involved a detailed and comprehensive identification of costs. Effectiveness was measured not by survival but by the time to attainment of several short-term clinical outcomes, of which a platelet count of 50×10^9/l was the main component.

The comparison was between autologous peripheral blood and bone marrow as stem-cell sources. Incremental cost-effectiveness analysis showed that the former was less costly (by almost 30% in children) and more effective (mean time to platelet count target, 17.5 vs. 36.5 days). Although the costs of transplantation are 'front-end loaded', the usefulness of the study would have been enhanced by inclusion of long-term survival and HRQL data. Furthermore, the study did not use a stratified randomisation design. Simple randomisation resulted in more patients with neuroblastoma and other neuroepithelial tumours in the bone marrow group, and more patients with lymphoma in the peripheral blood group, within the paediatric study population.

Haematopoietic stem-cell transplantation in children is an expensive health-care intervention. However, by combining studies of cost with emerging data on long-term survival and HRQL, economic evaluation can determine whether this is a cost-effective procedure by comparison with other health-care interventions. Clearly there is an opportunity to generate reliable data in our patient populations.

6. Conclusions

Although there have been few economic evaluations done in the context of cancer in childhood, the tools of economic evaluation are relevant and have the potential to play an important part in resource allocation decisions in paediatric oncology. The results of economic evaluations complement evidence available from traditional clinical-assessment measures. Economic evaluation provides an estimate of the costs of treatment. Formulations such as CUA also provide crucial information on the quality of the treatment effects. A number of implications will be discussed.

6.1. Including economic evaluation components in selected randomised controlled clinical trials

Paediatric oncology is perhaps unique in that most of the evidence on clinical effectiveness has been derived from multicentre RCTs [51]. The overwhelming majority of children with cancer treated in industrialised countries are treated according to structured formal protocols and most children are enrolled in actual clinical trials. In order to generate rigorous evidence on the costs and consequences among relevant alternative treatments (arms in the trial), it is important to include economic evaluation components in selected trials. In general, prospective data collection enhances the quality of the data. Prospective data collection is essential for capturing family borne costs and the HRQL effects of treatment, although it may be useful to link results from long-term follow-up studies to trial results to extrapolate the future HRQL of survivors. High-quality data on the costs of treatment complement traditional clinical data. Designers of major trials in cancer in childhood who do not include measures of costs and HRQL, and economic-evaluation analyses, should be challenged to justify those decisions.

On the other hand, there may be issues relating to non-generalisability such as RCT protocol-driven costs or the fact that patients in RCTs may not be representative of patients in general. A prospective study, such as an RCT, may be one of the few venues in which patient-borne costs can be captured. Otherwise, for system-based costs, retrospective costing analyses of longitudinal data may be satisfactory.

6.2. Economic evaluation evidence is becoming essential

The policy climate for health care increasingly deman- ds evidence on economic efficiency as well as clinical effectiveness [3]. Clinicians are being asked to 'justify' the often substantial use of resources that the treatments they provide entail. Economic evaluation evidence is a key ele- ment in these policy discussions. Just what are the costs? Just what are the effects? Do the effects justify the costs?

6.3. Evidence on HRQL effects for both treatment and outcome is becoming essential

As survival rates in cancer in childhood have increased, increasing attention is being focused on developing treatments that minimise toxicity and sequelae without jeopardising survival [1,52]. Evidence on HRQL during treatment and among survivors is essential for determining whether new treatments really represent improvements. In the context of treating children, many additional life years are at stake and thus the quality of those life years matters a lot. For the purposes of economic evaluation, collection of data on HRQL must be in the form of utilities.

6.4. Hospitalisation as a major cost driver

Although the evidence is thin, the costs of inpatient care are an important component of the total costs of treatment. As the care of children with cancer has evolved towards outpatient care, inpatient care has become, and is likely to become increasingly, less frequent. A consequence of the shift in the locus of care is the potential to shift costs from the health-care sector to families. It will be important to collect evidence prospectively on the extent of these shifts and the burdens that go with them. As well, we lack rigorous evidence on the HRQL effects of inpatient vs. outpatient care. Without frequent and systematic use of economic evaluation and HRQL tools, we will not know if the

"benefits" of outpatient care (children and families do not enjoy hospitalisation) outweigh the costs.

In summary, well-validated tools of economic evaluation have been developed and are ready for application in paediatric oncology. Similarly, a number of well-validated and relevant tools for assessing HRQL are available. The time is ripe for their routine application in RCTs and other studies. Evidence on costs and effects are crucial for guiding a well-informed evolution of the treatment of cancer in childhood. Estimates need to be adjusted periodically if there is important new evidence on effectiveness and as costs change.

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Appendix A

Studies assessing costs and effects: two examples from the published literature

Major factors	Delorme *et al.* [54]	Charnas *et al.* [55]
Research objectives	To evaluate cost-effectiveness from a hospital perspective of administering granulocyte colony-stimulating factor (G-CSF) during post-induction phase in children with ALL at very high risk of treatment failure	A comparison of a daily vs. an 8-hourly antibiotic regimen for febrile neutropenia in patients with leukaemia, lymphoma or solid tumours
Study design	Multicentre (France), RCT	Multinational (non-USA), prospective, unblinded, standard vs. new therapy, RCT
Sample size	34 patients received G-CSF and 33 did not	265 patients and 364 episodes (181 experimental and 183 standard treatment episodes)
Effects	Chemotherapy dose intensity during the post-induction phase was defined as the primary measure of effectiveness Other measures were 3-year probability of disease-free survival, 3-year probability of relapse, neutropenia, rates of septicaemia, frequency of mucositis	Clinical assessment of microbial response (complete/improved/failed), outcome (survival/death from infection/death from other causes/superinfection), adverse effects (nephrotoxicity/ototoxicity/hepatotoxicity/hypokalaemia)
Costs	Limited to direct medical costs incurred by the treatment and its consequences based on patient-specific utilisation recorded in medical charts for the following types of resources: duration of hospitalisation, blood products, and drugs Units costs for hospitalisation were per diem costs for a paediatric hospital including overhead, drug costs were wholesale prices, and blood products were government official prices	Drug utilisation based on protocol, wholesale prices and published estimates of delivery costs from one USA center Daily hospitalisation costs based on published estimate from one USA centre (*Note*: No USA centres were included in RCT)

Appendix A (*continued*)

Major factors	Delorme *et al.* [54]	Charnas *et al.* [55]
Economic evaluation	A cost comparison study. Does not report incremental estimates of effectiveness or costs. Does not report an incremental cost-effectiveness ratio	Reports incremental estimates for a variety of effect measures. Does not report incremental total cost. Does not report an incremental cost-effectiveness ratio

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