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Quality of life in children with acute lymphoblastic leukaemia - A systematic review

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Abstract

Quality of life (QOL) in children with acute lymphoblastic leukaemia (ALL) is now considered an important outcome measure of treatment for this disease. The aim of this paper is to systematically review studies on QOL in children during treatment for ALL with consideration to methodological details and quality of studies, empirical findings on QOL as reported by children and parents, and whether children and parents differ in their reports on QOL. Searches were conducted in biomedical, psychological and behavioural science databases. Six papers met inclusion criteria for review: 4 cross-sectional studies and 2 qualitative studies. There was little consistency in how QOL was measured or qualitatively assessed across studies. The quality of most studies was limited by small sample sizes and cross sectional designs. Children's reports on QOL were represented in 3 studies and discrepancies were found between children's and parents' accounts of QOL. There is a need for ongoing research on QOL in children with ALL using longitudinal designs, large sample sizes, and child reports on QOL. There is a need for theoretical development of the concept of QOL through concept analysis, grounded theory research and empirical validation of developing theory of QOL. Theoretical development of the concept of QOL will contribute to greater clarification of what is meant by QOL than currently exists which in turn has the potential to advance the methodology of measuring this concept in children.

Introduction

Acute lymphoblastic leukaemia (ALL) accounts for over 75% of childhood leukaemias and is the most common childhood cancer (Coebergh et al., 2006). It is a complex malignant disease that affects haematopoietic cells of the bone marrow and is typified by the malignant proliferation of lymphoblasts that affect the normal process of maturation and differentiation of cells in the bone marrow, resulting in the replacement of normal bone marrow tissue with cancerous cells (Plasschaert et al., 2004).

The highest incidence of ALL occurs in the first five years of life at approximately 5.7 per 100 000 persons per annum (Plasschaert et al., 2004). In the past, a diagnosis of ALL meant a certain fatality. However, over the past five decades, survival rates for childhood leukaemia have increased. European data on patterns of survival between 1988 and 1997 have estimated 5 year survival rates at 80% for children diagnosed between 1-4 years of age, 75% for children diagnosed between 5-9

years of age, 62% for children diagnosed between 10-14 years. Survival rates in infants diagnosed with leukemia was notably lower at 44% (Coebergh et al., 2006).

Aggressive treatment protocols over 2 to 3 years involving combination chemotherapy have greatly influenced improvements in survival of children with ALL. Treatment typically involves a sequence of stages: induction of remission, consolidation, and maintenance therapy. Prophylactic therapy is used to prevent central nervous system disease, involving intrathecal chemotherapy and possibly cranial radiation for children with high risk disease. In the case of disease relapse, children are inducted into remission again and bone marrow transplantation is offered (Cholby-Graham and Chordas, 2003; Schmiegelow and Gustafsson, 2005).

Although the outlook for survival is now positive for children with ALL, facing a life threatening condition can be intensely distressing for children and their parents. Family life as previously understood becomes disrupted and the child, parents and other family members are confronted with a lengthy treatment regime and possible side effects. In the initial and intermediary treatment phase, children can experience unpleasant physical side effects such as nausea and vomiting, mucositis, fatigue, bleeding and infection (Viele, 2003). Behavioural and emotional problems in children may arise (Eiser et al., 2005). The toxic nature of treatment can have long term adverse effects on children including impaired intellectual function, neuroendocrine abnormalities, cardiotoxicity, impaired reproductive capacity and secondary malignancy (Bhatia, 2003).

Recognition of the adverse effects of treatment for ALL has resulted in a growth of interest in quality of life (QOL) assessment of children. In health care, the concept of QOL, often used interchangeably with the term 'health related QOL' is generally understood as a multidimensional construct concerning an individual's perception of the impact of illness and treatment on his/her health, wellbeing or functioning in relation to physical, psychological, and social aspects of life (Eiser and Morse, 2001; Varni et al., 2005). QOL is now considered an important outcome measure for children with cancers not just in the long term but also during courses of treatment. The focus on ALL in this paper is important because, as already noted, ALL accounts for most childhood cancers.

A systematic review by Pickard et al. (2004) provided a comprehensive account of research on health related quality of life (referred to as QOL hereafter) specific to children with ALL spanning over 25 years from 1975 to 2001. A principal

aim of this review was to summarize studies that applied health related QOL measures to ALL. The reviewers noted that researchers have an increasing number of instruments available to them for measuring QOL that are either generic or disease specific. Most of the 29 studies reviewed were found to have used generic measures in children on or off treatment. Generic measures are appropriate for survivors, and may provide useful information for comparing QOL in children on treatment with healthy populations. However, disease specific measures are needed for children on treatment and these should be sensitive to changes in QOL during the course of a particular disease and its treatment. Pickard et al. highlighted a need for ongoing assessment of psychometric properties concerning validity and reliability of existing and newly developed QOL measures in children with ALL as a priority in future research.

A limitation of previous studies, identified by Pickard et al. (2004), was that children's own views on QOL were generally underrepresented. The reviewers cautioned against reliance on proxy accounts of parents when measuring children's QOL because information gleaned from children's reports may not be available in parents' reports. Pickard et al. concluded that children can respond on their own behalf and that they can provide reliable accounts of their QOL by the ages of 7 to 8 years.

Since Pickard et al.'s review, researchers have continued to measure QOL in children with ALL. However, uncertainty remains about how this research has advanced methodologically. To extend knowledge in this area, we conducted a systematic review of recent studies on QOL in children receiving treatment for ALL. In addition to examining methodological aspects of studies similar to Pickard et al., we examined empirical data. A synthesis of empirical data is important to identifying aspects of children's QOL that may be more or less affected during various stages of treatment, which in turn may be useful to practitioners when addressing QOL within the overall care and management of children with ALL.

In this paper, we aim to report on a systematic review of studies on QOL in children with ALL. We specifically focused on QOL of children on treatment for ALL since little is known about children's QOL during treatment stages of their illness trajectories compared to survival stage. The objectives for this review were to: (i) describe the methodological approaches and quality of studies undertaken on quality of life in children on treatment for ALL; (ii) summarise research findings on

children's quality of life as reported by children and/or their parents; (iii) determine whether children and parents differ in their reports on children's quality of life during treatment for ALL.

Criteria for selecting studies

Inclusion and exclusion criteria were specified prior to commencing the search strategy. These criteria related to types of studies, types of participants, and types of outcomes.

Types of studies

Published studies that examined QOL in children receiving treatment for ALL were considered for inclusion provided that they addressed one or more of the objectives of this review. Both quantitative and qualitative studies were considered, including all research designs. A minimum quality threshold for the selection of primary studies was not applied. Studies on instrument development and measurement were included if empirical data on QOL could be extracted. English language studies only were considered. This review was restricted to studies published between 30th April 2001 and 30th June 2007 since a previous review on QOL in children with ALL examined studies up to end of April 2001 (Pickard et al., 2004). Studies that did not address at least one of the objectives of the review were excluded. While many studies have investigated QOL across a range of childhood cancers, these were excluded if data specific to children undergoing treatment for ALL were not provided.

Types of participants

Children on treatment for ALL were selected. Children up to 12 years only were included since most children receiving treatment for ALL can be expected to fall into this age group (Plasschaert et al., 2004). Parents of children on treatment for ALL were also included because of ongoing issues being raised about 'proxy raters' of QOL measures in children (Eiser and Jenney, 2007).

Types of outcome measures

The outcome measure central to this review was QOL in children during treatment for ALL. We were interested in extracting data on all aspects of QOL reported in studies

including widely recognised QOL dimensions (physical, psychological, social) or any other dimension described. Studies with outcome data gleaned from generic or disease specific measures of QOL were considered eligible for inclusion. Studies that examined QOL in the context of specific drug therapies or procedures (e.g. central line insertion) were excluded.

Search strategy for identification of studies

Databases searched for potentially eligible studies for this review included MEDLINE, EMBASE, CINAHL, BIOSIS previews, Faculty of 1000 medicine, Psychology and Behavioral Sciences Collection, PubMed, Social Index and CancerLit. MeSH and subject terms appropriate for each database were applied. The term 'quality of life' was used as a constant search term in all databases and was combined with various terms specific to the disease (acute lymphoblastic leukaemia/acute lymphocytic leukaemia/ leukaemia/neoplasm). These various combinations were further combined with terms specific to the patient group being reviewed (child/children/pediatric/ paediatric). Journals in the fields of paediatric and general oncology were electronically searched, as well as some general paediatric journals noted to publish QOL papers. Oncology journals searched were: *Cancer*; *Journal of Cancer Care*; *European Journal of Oncology Nursing*; *Hematology*; *Oncology*; *Pediatric Blood Cancer*. General paediatric journals searched were: *Acta Paediatrica*; *Journal of Pediatrics*, and *European Journal of Pediatrics*. Journals searched specific to QOL were also electronically searched. These were: *Quality of Life Research*, and *Health and Quality of Life Outcomes*. A search was done by combining the term 'quality of life' with two individual authors (Eiser, C. and Varni, J) on noting from our initial database searches that both authors had multiple publications on QOL in children with cancer. Reference lists of all full papers retrieved from databases, electronic journals and individual author searches yielded additional papers. We limited our search strategy to between May 1st 2001 and June 30th 2007. We did not search for unpublished studies. The restriction of inclusion criteria to papers in the English language and to published studies is a limitation of this review.

Methods of review

A total of 84 records were identified that seemed potentially relevant to this review. The abstract of each record was independently scanned by two reviewers (AOR, ES). Agreement was reached to read 23 papers in full to further examine their relevance based on inclusion and exclusion criteria. Two reviewers (AOR, ES) independently read the papers in full and reached mutual agreement that 4 papers met the inclusion criteria and that 16 papers were to be excluded. There was disagreement on 3 papers. These were then read by MH, and following discussion between all three reviewers, consensus was reached that a further 2 papers be included yielding a total of 6 papers for review.

To address the aims of the review, one reviewer (AOR) extracted data on the methodological details of studies from the 6 papers reviewed (Table 1). A second reviewer (MH) extracted QOL empirical findings of studies (Table 2). Both tables were then checked against the papers by ES. As shown on Table 1, data extracted on methodological details of studies related to: study aims; sampling (e.g. participants, age groups of children, treatment status); study design; data collection procedures; data analysis; QOL measures; reliability and validity; and QOL dimensions measured.

The quality of each quantitative study was rated drawing on criteria previously used by Tsimicalis et al. (2005) which addressed five study parameters. As shown in Table 3, these criteria related to study design, participants and recruitment, comparison group, number of participants, and quality of QOL instruments. Each parameter was scored between 0 and 3 giving a total score range of between 0 and 15 for each study. Criteria for assessing the quality of qualitative studies were based on standards proposed by Popay et al. (1998) which addressed study aims, context sensitivity, sampling strategy, data quality, theoretical or conceptual adequacy, and generalisability (Table 4).

Results

Methodological details of studies

Six studies met the inclusion criteria. Methodological details of these studies are summarised in Table 1. Three studies used the term 'health related QOL' (Meeske et al., 2004; Shankar et al., 2005; Waters et al., 2003) and 3 studies used the term QOL (Earle and Eiser, 2007; Hicks et al., 2003; Vance et al., 2001). For simplicity, the term QOL is used herein.

Four studies used a quantitative approach with a cross sectional design (Meeske et al., 2004; Shankar et al., 2005; Vance et al., 2001; Waters et al., 2003). Two studies were qualitative in approach including a descriptive longitudinal design (Earle and Eiser, 2007) and a phenomenological design (Hicks et al., 2003). Parents only were sampled in 2 studies (Earle and Eiser, 2007; Meeske et al., 2004) and with clinicians in 1 study (Waters et al., 2003). In 2 studies, children were sampled without their parents (Hicks et al., 2003; Shankar et al., 2005). Both children and parents were sampled in 1 study (Vance et al., 2001).

In terms of cancer groups sampled, 4 studies included only children with ALL (Earle and Eiser, 2007; Hicks et al., 2003; Vance et al., 2001; Waters et al., 2003) and 2 of these assessed QOL in children on and off treatment (Hicks et al., 2003; Vance et al., 2001). QOL was addressed in a cross-section of childhood cancers in 1 study which also included an age matched healthy control group (Shankar et al., 2005). One study used age matched healthy population data as a reference for comparison (Waters et al., 2003). One study examined QOL in children with brain tumours in addition to ALL (Meeske et al., 2004). Convenience sampling was used in the 4 quantitative studies and in 1 qualitative study (Hicks et al., 2003). Earle and Eiser (2007) used purposive sampling in their qualitative study. Sample sizes specific to children aged 12 years and younger receiving treatment for ALL ranged from less than 13 to 46 child respondents (Hicks et al., 2003; Shankar et al., 2005) and from 20 to 144 parent respondents (Meeske et al., 2004; Waters et al., 2003).

Interviews were the method of data collection in both qualitative studies. QOL measures differed across the 4 quantitative studies reviewed. A cancer specific measure (Minneapolis-Manchester Quality of Life Youth Form) was used by Shankar et al. (2005). In another study, a generic Child Health Questionnaire was used, complemented with a cancer specific measure (the Pediatric Cancer QL-32 Inventory) (Waters et al., 2003). The Pediatric Cancer QL-32 Inventory was also used by Vance et al. (2001). In addition, Vance et al. used a computer based measure Disqual which by description seemed generic. The PedsQL™4.0 measurement model incorporating generic and cancer specific parent proxy scales was used by Meeske et al. (2004). The PedsQL™4.0 measurement model is the result of over 15 years of programmatic measurement instrument development by researchers (Varni et al. 2002), and incorporates the Pediatric QL-32 inventory used by earlier researchers (Vance et al., 2001; Waters et al. 2003).

Dimensions of QOL assessed across most studies related to physical and psychological functioning or wellbeing. All 4 quantitative studies assessed disease related symptoms. One study assessed emotional functioning in addition to psychological functioning (Meeske et al., 2004) and another study assessed psychosocial health in addition to psychological health (Waters et al., 2003). Social functioning or wellbeing was assessed in 3 studies (Hicks et al., 2003; Meeske et al., 2004; Vance et al., 2001); cognitive functioning was assessed in 2 studies (Vance et al., 2001; Waters et al., 2003), and school functioning was assessed in 1 study (Meeske et al., 2004). Other aspects of QOL assessed were 'outlook in life/family dynamics' (Shankar et al., 2005). One study addressed QOL in the context of children's behaviours over the course of treatment for ALL (Earle and Eiser, 2007).

Quality of studies

A total quality score ranging from 0 to 15 was allocated to each quantitative study based on a number of criteria specific to study design, participants and recruitment, comparison group, number of participants (on treatment for ALL), and QOL instruments (Table 5). Each parameter was allocated a score of between 0 and 3 reflecting lower to higher level of quality. The cross-sectional design yielded a low score of 1 in all 4 studies. Detailed accounts of participants and recruitment processes were provided in all 4 studies and so each study was allocated a maximum score of 3. Only 1 study was allocated a maximum score of 3 for having an age matched healthy control group (Shankar et al., 2005). A score of 2 was allocated to 1 study for including age matched healthy population data as a reference group (Waters et al., 2003). Two studies were allocated a low score of 1 for each having a comparison group: children with brain tumours (Meeske et al., 2004); and children off treatment for ALL (Vance et al., 2001). A low score of 1 was allocated to 3 studies because of small sample sizes of children and/or parents specific to 'on treatment' phase of ALL (Shankar et al., 2005; Vance et al., 2001; Waters et al., 2003). Meeske et al. (2004) was the only study with a sample size (parents) over 100 specific to children 'on treatment' and so was allocated a maximum score of 3.

For psychometric properties, studies by Meeske et al. (2004) and Shankar et al. (2005) were both allocated a high score of 3. Both studies demonstrated strong

psychometric properties in terms of internal consistency, reliability, and construct validity. A lower score of 2 was allocated to studies that reported some weak psychometric properties for the QOL measures used (Vance et al., 2001; Waters et al., 2003). For example, the Child Health Questionnaire used by Waters et al. (2003), although reported as having ‘generally good’ psychometric indices, had internal consistency values of 0.4 or lower for some items in the multi-item scale.

For the qualitative studies, a narrative summary of their quality based on standards proposed by Popay et al. (1998) is presented in Table 4. The longitudinal design in 1 study was a strength in terms of context sensitivity such that changes in children’s QOL could be gleaned over time (Earle and Eiser, 2007). This study also went some way to meeting standards of ‘theoretical and conceptual adequacy’ and ‘potential for assessing typicality’. A strength of Hicks et al.’s (2003) study was that perspectives on QOL were gleaned from children whereas Earle and Eiser (2007) relied on proxy accounts of parents, which they acknowledged as a limitation of the study.

QOL in children on treatment for ALL – children’s and parents’ reports

A summary of empirical findings on QOL in children on treatment for ALL are presented in Table 2. In presenting a narrative account of results, the findings are grouped into dimensions or aspects of children’s QOL addressed across studies.

QOL in relation to physical functioning or health was poorer for children on treatment for ALL compared to age matched healthy controls or population data as reported by children (Shankar et al., 2005) and parents (Waters et al., 2003). Children on treatment were reported by parents as having better QOL than children off treatment for less than 12 months and as having poorer QOL compared to children off treatment for more than 12 months (Meeske et al., 2004). Areas measured for physical functioning were reported in 2 quantitative studies, and these related to energy levels and abilities to engage in physical activities including sports (Shankar et al., 2005; Waters et al., 2003). Qualitative data identified tiredness and depleted energy levels as notable adverse effects of treatment, limiting children’s abilities to be physically active (Hicks et al., 2003). Parents reported their children’s QOL as poorer than what children reported on themselves, and physical functioning was rated by parents as the poorest aspect of children’s QOL compared to other dimensions (Vance et al., 2001).

Although 3 studies reported on psychological functioning subscales (Shankar et al., 2005; Vance et al., 2001; Waters et al., 2003), only 2 reported on psychological functioning in children aged 12 years and less and 'on' treatment for ALL. Children were reported as scoring better psychological functioning than healthy controls (Shankar et al., 2005) and in comparison to parents' reports, they scored poorer functioning (Vance et al., 2001). Shankar et al. (2005) itemised measures of psychological functioning as worrying about health, dying, and 'things in general'. Fears and negative feelings such as sadness, loneliness, and anger were indicative of psychological functioning. When children's views were explored through interviews, fears were found to be associated with medication and treatment effects. Hair loss as a side effect to treatment was reported by some children as distressing (Hicks et al., 2003). Parents' accounts of children's behavioural responses to treatment indicated mood changes with some children described as becoming 'clingy', angry or quieter, and withdrawn. Sleep problems and nightmares in children were also described by parents (Earle and Eiser, 2007).

Findings on psychosocial functioning or health were presented in 2 studies (Meeske et al., 2004; Waters et al., 2003) but data on children aged 12 years and less and on treatment for ALL could be extracted from 1 study only (Meeske et al., 2004). In this study, data on psychosocial functioning were presented as a composite score on emotional, social, and school functioning of children. Children on treatment for ALL were reported by parents as having poorer health than their counterparts off treatment for less than 12 months. In contrast, children on treatment were reported by parents as having better psychosocial health than children off treatment for more than 12 months. Social functioning was a distinct measure in 1 study (Vance et al., 2001) and was reported by children on treatment for ALL as the poorest aspect of QOL when compared with other dimensions measured. Parents differed in their reports by rating children's social functioning as marginally better than what children reported (Vance et al., 2001). Both qualitative studies highlighted problems for children in relation to social interactions with peers, and concerns about appearing different (e.g. hair loss) were particularly notable (Earle and Eiser, 2007; Hicks et al., 2003).

Cognitive functioning was measured by Waters et al. (2003) and Vance et al. (2001), although only 1 of these studies reported on children aged 12 years and less. Vance et al. found that compared to proxy accounts of parents, children scored better on cognitive functioning. Indicative detail on cognitive functioning was not provided.

Outlook in life/family dynamics was measured as a dimension of QOL by Shankar et al. (2005) who found children on treatment for ALL reporting poorer QOL compared to age matched healthy controls. Indicators that measured children's 'outlook in life' related to their sense of happiness with their health and life including expectations for the future. Family dynamics were concerned with whether parents treated children with ALL the same as siblings and also the levels of patience exercised by parents with their children.

When disease and treatment symptoms were assessed, children on treatment for ALL reported poorer QOL compared to children off treatment (Meeske et al., 2004). In another study, children on treatment reported poorer QOL compared to parents' reports (Vance et al., 2001). One study reported marginally better QOL in children on treatment for ALL compared to age matched healthy controls (Shankar et al., 2005). Although 2 studies indicated what symptoms were measured (e.g. pain and nausea), only 1 study provided QOL scores for each symptom and these could not be extracted for children aged 12 years and less (Meeske et al., 2004). Meeske et al. specifically measured fatigue which was reported as problematic for children on treatment for ALL compared to children off treatment. However, compared to children on treatment for brain tumours, children reported better QOL on the Fatigue scale.

Discussion

This review adds to a previous review (Pickard et al., 2004) by providing an update on methodological aspects of studies conducted over a 6 year period (2001-2007). In addition, our review provides empirical findings on children's QOL and draws attention to differences between parent-proxy reports and children's self-reports on QOL. Unlike Pickard et al. who reviewed studies across a broad range of ages and treatment phases including survivors, our review specifically focused on children aged 12 years and less, who were undergoing treatment for ALL. Prior to this review, there has been no systematic examination of empirical data on QOL in children undergoing treatment for ALL.

In the past, the small number of studies conducted on QOL in children on treatment for ALL mostly relied on generic measures which may not be responsive to clinical changes during treatment stages of disease (Pickard et al., 2004). Our review has shown a shift towards using disease specific measures as evident in all 4

quantitative studies summarised in Table 1. A challenge facing researchers is the availability of reliable and valid measures, and shortfalls in meeting these criteria have limited the quality of much QOL studies in the past (Eiser and Jenney, 2007; Eiser and Morse, 2001). Disease specific measures reported as having sound psychometric properties in this review were the PedsQL™4.0 measurement model which included an acute cancer module (Meeske et al., 2004), the Mineapolis-Manchester Quality of Life Youth Form (MMQL-YF) (Shankar et al., 2005), and the Pediatric Cancer Quality of Life-32 Inventory (Vance et al., 2001; Waters et al., 2004). Two of these measures (PedsQL, MMQL-YF) included age appropriate versions which are important to considering developmental changes in QOL across age groups (Eiser and Jenney, 2007).

Of the 6 studies reviewed, only 3 included children as respondents indicating continued reliance on parent proxy accounts by some researchers. Many children on treatment for ALL may be younger than 5 years making self-reports on QOL difficult to obtain from this age group. However, we reinforce the need to directly measure children's QOL from school age years as previously recommended by Pickard et al. (2004). As evident in our review, children as young as 5 and 6 years demonstrated abilities to report on their QOL during treatment for ALL (Hicks et al., 2003; Vance et al., 2001). The need to access children's self-reports and accounts is also highlighted by the finding in our review that parent-proxy reports may not be consistent with children's reports. As demonstrated by Vance et al. (2001), parents may underestimate children's QOL in relation to their physical health. Conversely, they may overestimate children's QOL in relation to their social and psychological health, which were the areas reported by children as the poorest of all QOL dimensions measured. However, in future research, there is a continued need to glean parents' reports in order to better understand the relationships between child and parent reports on QOL therefore adding to the work of Vance et al. (2001).

Although data on various dimensions of children's QOL were gleaned through this review, the findings are somewhat fragmented overall. Studies varied in dimensions of QOL studied and reported on. While most studies assessed physical, psychological and social aspects of QOL, only 1 study explicitly examined cognitive functioning (Vance et al., 2001). Data on social functioning, although examined across most studies, could not be extracted in all cases. For example, these data could not be extracted specific to children aged 12 years and under in the study by Waters et

al. (2003). Furthermore, some quantitative reports were noted to be limited in detail regarding indicators of QOL specific to each dimension, which raises questions about the interpretability and usefulness of QOL data to practitioners working with children with ALL. In contrast to measurement data, the 2 qualitative studies provided insights into the meanings of QOL from children's (Hicks et al., 2003) and parents' perspectives (Earle and Eiser, 2007). The contribution that qualitative data can make to understanding QOL experiences of children with ALL needs consideration in future research to complement measurement data on QOL.

The variations in QOL dimensions measured across studies reflect diversity in how QOL is conceptualised in research (Eiser and Morse, 2001; Wallander, 2001). Although QOL was recognised as a multidimensional construct in all studies reviewed, little discussion was given to the theoretical basis of this construct. Theory development in QOL research is considered paramount for better understanding of its constructs and the relations between constructs (Wallander, 2001). To date, there has been little effort at developing QOL theory in the area of childhood cancers compared to other client groups in health care such as the elderly (e.g. Register and Herman, 2006; Hyde et al., 2003). While it is beyond the scope of this paper to engage in a detailed discussion on QOL theory development, recommendations for developing theory driven models of QOL are offered. A fundamental step towards a better understanding of QOL is to undertake a concept analysis to define the boundaries of QOL by clarifying its critical attributes. A concept analysis also involves examining a concept's current usage, its antecedents (precursors) and its consequences (outcomes). In addition, empirical referents need to be identified to illustrate when a concept is present, which in turn has implications for items included in a measurement scale (Walker and Avant, 1995). Given the subjective nature of QOL that emphasises an individual's perspective (Eiser and Morse, 2001), theory development needs to take account of children's perceptions of QOL. To this end, qualitative research using grounded theory methodology (Glaser and Strauss, 1967) has potential. Empirical validation or testing of developing theory is vital to revising and building a theoretically driven model of QOL (Walker and Avant, 1995).

In moving forward with a theoretically driven model of QOL and its measurement, future research needs to address limitations identified in this review in terms of design and sample sizes. We reinforce previous recommendations made by Pickard et al. (2004) that called for longitudinal research designs and larger sample

sizes in QOL studies in children. European and international collaboration between researchers may be necessary to recruit large samples of children on treatment for ALL. The feasibility of undertaking European and international QOL studies in terms of recruiting large sample sizes across a number of countries despite differences in languages has been demonstrated for populations other than childhood cancer groups (Hardt et al., 2001; White-Koning et al., 2007).

Conclusions

This review reports on QOL research on children with ALL drawing on quantitative and qualitative studies conducted between 2001-2007. Efforts at advancing the study of QOL in children on treatment for ALL were noted, as evident in a longitudinal study design in 1 study, qualitative research in 2 studies, direct access to children's reports on QOL in 3 studies, and a shift towards using disease specific QOL measures. The studies illustrate the potential to continue advancing the methodology of QOL research on children with ALL. The knowledge gleaned from future research, especially empirical data, could provide useful information for practitioners when addressing QOL care with children on treatment for ALL. Although this review is based on a small number of studies, it provides a basis for updating over time as new studies are published.

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Table 1 Methodological details of studies

<i>Authors, year, country</i>	<i>Aim of Study</i>	<i>Sample</i>	<i>Details specific to ALL</i>	<i>Design, data collection and analysis</i>	<i>Details of QOL measures (if applicable) and of reliability and validity</i>	<i>Quality of life dimensions</i>
Earle & Eiser (2007), U.K.	To examine how children of different age groups respond over time to treatment for ALL from the time of diagnosis	32 Mothers of children 0-14 yrs Age groups <12yrs: 0-4yrs (n=14) 5-9yrs (n=11) 10-14 yrs (n=7)	ALL n=32 (100%) All children receiving treatment for ALL over a 2-3 year period	<i>Design:</i> Qualitative, descriptive, longitudinal, prospective design <i>Data collection:</i> Three semi structured interview schedules administered over three time periods Time 1: 3-4 months following diagnosis Time 2: 1 year later at 15 months Time 3: 2 years later at 27 months <i>Data analysis:</i> Thematic content analysis	Qualitative study and so no standardised measure used <i>Reliability and validity:</i> Fifty percent of interviews were coded independently by a second researcher to check for interrater reliability; Interview schedule remained the same at each time point for comparability and reduction of bias; Discrepancies were resolved by discussion	Behavioural responses to diagnosis, treatment symptoms and affects on normal life
Shankar, et al. (2005), USA	To assess the health related quality of life (HRQOL) of children undergoing therapy for cancer and childhood cancer survivors	Convenience sample of children 8-12 yrs with cancer on (n=72) and off (n=90) therapy Cancers: leukaemia, lymphoma, brain tumour & other solid tumours Age matched healthy controls (n=481)	46 (64%) children with ALL on therapy for at least 2 months; 44 (49%) children had completed therapy and were in remission for ≥ 12 months.	<i>Design:</i> Quantitative cross-sectional survey; multicentre <i>Data collection:</i> Standardized self report measure administered by interview at clinics; Minneapolis-Manchester Quality of Life Youth Form (MMQL –YF); Measurement questionnaire was administered to control group by telephone interview <i>Data analysis:</i> Analysis of variance techniques used to compare means between groups; Multi-regression analysis to investigate predictors of poor HRQOL (diagnosis, age, time since diagnosis, gender & ethnicity); Statistical significance set at .05; Multivariate models constructed to calculate relative risk estimates for poor HRQOL	MMQL - YF - Designed for use with survivors of childhood cancer but may be used to assess HRQOL of patients on and off cancer treatment and of healthy controls (4 scale measures with total of 32 items; Scores range from 1-5 (5 = maximum HRQOL); Overall HRQOL score also measured <i>Reliability and validity:</i> Previously published (Bhatia et al 2004) as demonstrating internal consistency reliability ($\alpha = .85$); ability to distinguish between known groups, construct validity with scales correlating highly with CHQ dimensions; Test/retest demonstrated stability in all scales	Physical symptoms, Physical functioning, Psychological functioning, Outlook on life/family dynamics

Meeske et al. (2004), USA	To evaluate and compare HRQOL in children with brain tumours (BT) and ALL	Convenience sample of 256 parents of children aged 2-18 yrs with BT and ALL 60% (n=153) of children were on treatment Age groups <12 years: 2-4yrs (n=53) 5-7yrs (n=72) 8-12yrs (n=83)	170 (66%) children with ALL and of these 144 were on treatment for age groups <12yrs. Age Groups of ALL - 2-4yrs (n=42); 5-7yrs (n=51); 8-12yrs (n=51)	<p><i>Design:</i> Quantitative cross-sectional survey</p> <p><i>Data collection:</i> Standardised parent proxy reports using PedsQL™ 4.0 Measurement Model comprising (i) PedsQL™ 4.0 Generic core scales; (ii) PedsQL™ 3.0 Acute cancer module; (iii) PedsQL™ Multidimensional fatigue scales; (iv) PedQL™ Family Information Form for demographic data</p> <p>All measures administered in clinics</p> <p>Medical chart data extracted from notes</p> <p><i>Data analysis:</i> Descriptive statistics (means, standard deviation, frequencies) for all variables; Inferential statistical analyses (analysis of variance, regression analysis, chi squared tests, t-tests, Pearson correlation) were conducted as appropriate to making group comparisons and correlations between variables including demographic data</p>	<p>PedsQL™ Measurement Model consisting of 4 age appropriate versions designed to evaluate the HRQOL of children</p> <p>(i) PedsQL™ 4.0 Generic core scale – parent proxy report, a 23 item scale consisting of a 5 point likert scale to determine how problematic a particular item has been for the individual child; reference period is past 7days; higher scores indicate greater HRQOL.</p> <p>(ii) PedsQL™ 3.0 Acute cancer module –parent proxy report with dimensions specific to cancer; each dimension is scored and a total scale score is also calculated</p> <p>(iii) PedsQL™ Multidimensional fatigue scales-parent proxy report consisting of 18 items divided into 3 subscales; subscales are scored and a total scale score is also calculated</p> <p><i>Reliability and validity:</i> Previously published (Varni et al, 2002) as demonstrating strong internal consistency reliability for each measure, ability to distinguish between known groups, construct validity for interrelationships between measures; For this study, a Cronbach’s alpha coefficient value of >0.70 was achieved for both the PedsQL™ 3.0 Acute</p>	<p>Physical health, psychological, emotional, social and school functioning</p> <p>Cancer related physical symptoms, psychological concerns, and cognitive problems</p> <p>Fatigue (general, rest/sleep, cognitive fatigue)</p>
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					cancer module and the PedsQL™ Multidimensional fatigue scale which is recommended for group comparisons; A moderate correlation ($r = 0.75-0.79$) between the PedsQL™ 4.0 Generic Core total score and the total scores on the PedsQL™ 3.0 Acute cancer module and the PedsQL™ Multidimensional fatigue scale suggesting that HRQOL and fatigue are highly related although unique.	
Hicks et al, (2003), USA	To allow children with leukaemia describe their QOL experiences	Convenience sample of 13 children aged 5 -9 yrs	All children had ALL and had either completed at least 6 months treatment or were off treatment.	<i>Design:</i> Qualitative phenomenological <i>Data collection:</i> Audiotape interviews by focus groups were held to coincide with treatment schedules; four semi structured questions guided the interviews; the interview room had a two way mirror to allow researchers visual access to data collection process <i>Data analysis:</i> Content analysis to identify significant statements using first 4 steps of Colazzi's phenomenological technique aided by HyperResearch computer package	Qualitative study so no standardised measure used <i>Reliability and validity:</i> Verbatim transcription of interviews; transcripts checked against audiotapes by one researcher to ensure accuracy; significant statements extracted from the data were analysed by three researchers	Conceptual framework of QOL dimensions: physical wellbeing and symptoms; psychological wellbeing; social wellbeing; spiritual wellbeing
Waters et al. (2003), Australia	To compare parents' and clinicians' reports on HRQOL in children with leukaemia Age matched	Convenience sample of 31 parents of children aged 5 -18 years Most parents (n=25) were mothers	All children had ALL and were on maintenance phase of treatment	<i>Design:</i> Quantitative cross- sectional survey <i>Data collection:</i> Standardized parent report questionnaires: child health questionnaire (CHQ) and Pediatric cancer quality of life inventory (PCQL-32); questionnaire to collect	Child Health Questionnaire (CHQ) is a 50 item measure with 13 single and multi item scales of child health and 2 summary scores (physical and psychological health); scores for CHQ range from 0 to 100 i.e. worse to better	Physical health, psychosocial health. Cognitive functioning, Psychological functioning,

	healthy population data (Australian) used for comparison	Age groups <12 yrs were 5-11 yrs (n=20)		sociodemographic information; data collected in out patient clinic <i>Data analysis:</i> Comparison with normative Australian sample previously collected; effect sizes were used to demonstrate the size of difference; independent t-tests were used to determine significance levels; Pearson's correlation test was used to calculate relationships between continuous scale scores of the CHQ and the PCQL; family characteristics were compared across normative and ALL samples	health; CHQ is based on 4 week recall except 'change in health' item which is based on previous 12 months 3 scales from PCQL -32; items that overlapped with CHQ were omitted; items were based on a one month recall; higher scores indicated poorer health status <i>Reliability and validity:</i> CHQ reported to have "good reliability and validity" based on previous population and clinical (incl. oncology) studies, although psychometric indices of items in some scales were weak (0.4 or less); PCQL-32 reported to have previously demonstrated internal consistency reliability (0.92), clinical and construct validity (Varni et al. 1998)	Disease and treatment related symptoms
	<i>Note: Data specific to parents only reported in this table</i>					
Vance et al. (2001), U.K.	To explore the relationship between child self report and parent-proxy report on QOL and the effects of parental mental health, illness stressors, and child vulnerability	Convenience sample of: 36 parents of children aged 6-12 yrs with ALL & 32 children (6-12 yrs)	All children had ALL 36% (n=13) were on "active treatment" Remaining children were follow ups	<i>Design:</i> Quantitative cross sectional survey <i>Data collection</i> Parent completed self administered measures – the Pediatric Cancer Quality of Life-32 (PCQL32) parent form.; Child Vulnerability Scale (CVS); General Health Questionnaire (GHQ-28); Illness stressors scale All 3 measures were completed during a clinic visit. All children completed the Disquot measure	PCQL-32: a 32 item questionnaire with 5 Likert subscales organised around 5 dimensions of QOL; ratings are based on previous month on a 4 point Likert scale ranging from 'never a problem' to 'always a problem' and scored 0-3; includes a child and parent form Disquot: a 12 item computer-measure focusing on picture situations relevant to children 6-12 yrs aimed at measuring 'actual-ideal self-discrepancy'; in a visual	Physical, psychological, social and cognitive functioning; disease and treatment related symptoms.

In addition, children aged 8-12 completed the child form PCQL-32 measure
Researchers worked with children to complete measures in a separate room to parents

Data analysis:

Descriptive statistics (means, standard deviations, ranges) were calculated for all measures; inferential statistics (partial correlations, multivariate analysis, t tests) were used to determine concordance between QOL measures and parent and child reports with PCQL-32; scores were computed with reference to demographic variables; correlation tests were applied to determine relationships between parental mental health, perception of child's vulnerability, perceived illness stressors, and parent and child QOL ratings

analogue scale, children identify how much the picture situation is 'not like me/don't want to be like that' to 'exactly like me/really want to be like that' ranging in score from 0 to 100

Reliability and validity:

Disqol :internal reliability was reported as moderate (>.64) based on previous research and preliminary analyses for this study showed moderate internal consistency for the discrepancy score (.55); evidence of criterion validity and discriminant validity (chronic illness v healthy control) were noted as achieved from previous research
PCQL-32: strong internal consistency reported for child (.86) and parent (.93) measures; reported to have demonstrated clinical and construct validity; external internal consistency previously reported for child (.91) and parent (.92)

Table 2 Summary of Empirical Findings on QOL in Children on treatment for ALL

<i>Authors, year,</i>	<i>Context of Data</i>	<i>QOL Domains & Total QOL scores if stated/applicable</i>
Earle & Eiser., (2007)	Mothers accounts of QOL in children with ALL (aged 0-9 yrs)	<p>Responses to Treatment: Younger children (0-4yrs) described as ‘moody, ‘clingy’ tired and these problems continued over time. Problems reported for older children (5-9yrs) included being: ‘moody’, ‘clingy’ and ‘aggressive’; quieter and passive in behaviour since diagnosis; sleep problems and nightmares. At 15 months following diagnosis, more positive behaviours and better adjustment to illness experience were reported, although treatment procedures were reported as distressing for some children.</p> <p>Focus on Normal Life overall: In the early months following diagnosis, few social problems reported for younger children (0-4yrs) compared to older children (5-9yrs) who had problems mixing socially with peers. At 15 months following diagnosis, some younger school aged children were settling into school whereas others were reported to have problems associated with changes in appearances. Most older children were reported to be self-conscious and reluctant to go to school. Bullying was a concern. At 27 months following diagnosis, socialising at school and bullying was more problematic for younger children. Some older children were now interacting well with peers whereas others were still having problems.</p>
Shankar et al. (2005)	Children’s reports on HRQOL, aged 8-12 yrs, on therapy for ALL compared to children off therapy for ALL, on/off therapy for other cancers & age matched healthy controls group	<p>Physical Functioning: Significantly lower (poorer) HRQOL mean score in children with ALL (3.5) compared to healthy controls (4.0) ($P < .001$), and lower than one other cancer group (solid tumours).</p> <p>Psychological Functioning: Marginally higher HRQOL mean score in children with ALL (3.95) compared to health controls (3.83) ($P = .17$); rated 2nd lowest mean score across all cancer groups.</p> <p>Outlook in Life: Significantly lower mean score in children with ALL (3.9) compared to healthy controls (4.2) ($P < .001$); rated 2nd highest mean score across all cancer groups. Physical Symptoms: Marginally higher HRQOL score in children with ALL (4.21) compared to healthy controls (4.17) ($P = .37$); rated 2nd lowest mean score across all cancer groups. Total QOL Score: Significantly lower (poorer) in children on therapy compared to healthy controls (3.93 v 4.05; $P = .01$) using the MMQL-YF scale with a score of 5 indicating maximum HRQOL. Total HRQOL mean score was higher for ALL compared to children with</p>
Meeske et al. (2004)		

Hicks et al. (2003)	Parent reports on children's HRQOL, extracted for those aged 2-12 yrs on treatment for ALL compared to children off treatment for ALL, and to children with on/off treatment for brain tumour	<p>brain tumours and lymphoma but lower than for children on treatment for solid tumours.</p> <p>Physical Health: Children on treatment for ALL were reported as having a higher (better HRQOL) mean score (71.0) compared to children off treatment for <12 months (65.4) and a lower mean score than children off treatment for > 12months (77.9) (p = 0.03). Children on treatment for ALL were reported as having a higher HRQOL mean score compared to children on treatment for BT. Psychosocial Health (summary score for emotional, social and school functioning): Marginally poorer HRQOL mean score (70.4) reported for children on treatment for ALL compared to children off treatment for <12 months (74.5) and off treatment for > 12 months (72.4) (P = 0.21). Children on treatment for ALL were reported as having higher HRQOL mean scores than children on treatment for BT (70.4 v 64.8). Cancer specific problems: Children on treatment for ALL had a lower (poorer HRQOL) score (73.4) compared to children off treatment for <12 months (79.5) and compared to children off treatment for > 12months (78.5) (P = 0.008). Children on treatment for ALL were reported as having better HRQOL than children on treatment for BT (68.5). Fatigue: Children on treatment for ALL were reported as having a lower (poorer HRQOL) mean score (74.6) compared to children off treatment for <12 months (76.8) and compared to children off treatment for > 12months (80.2) indicating more fatigue symptoms during treatment (P = 0.009). Children on treatment for ALL were reported as having better HRQOL scores compared to children on treatment for BT (74.6 v 64.9). Total HRQOL: Apart from the Acute Cancer Worry Subscale, children with ALL were reported as having better HRQOL than children with BT.</p>
Waters et al. (2003)	Children's accounts of QOL, aged 5-9 yrs, on treatment for ALL	<p>Physical Wellbeing: Limited ability to engage in physical activities (e.g. football, soccer, climbing trees, cycling) due to tiredness. Engaged in passive activities because of limited abilities to be physically active. The theme of tiredness was the most notable theme expressed in the data. Psychological Wellbeing: Fear associated with medication and treatment effects when in hospital. Hair loss was described by 1 participant as distressing although it was mentioned in general by 10 participants. Social Wellbeing: Changes in friendships arising out appearing different due to hair loss. Social interactions with peers limited due to tiredness. Changes in family relationships associated with parental worrying about child.</p>

Vance et al. (2001)	<p>Parent reports on children's HRQOL, extracted for those aged 5-12 yrs, Australian age matched healthy population data used for comparison</p>	<p>Physical Health: Children with ALL were reported as having significantly poorer HRQOL than aged matched population sample. The largest effect sizes (>1 SD below the population mean) were noted on Physical Functioning, Role Physical, and General Health scales. A mean difference score of >5 lower was noted across these scales and was reported as clinically important. (Findings on measurements of HRQOL were presented for all children aged 5 to 18 years and so data specific to those aged 12 years and less could not be extracted).</p>
	<p>Parent and child reports on QOL, aged 6-12 yrs, on /off treatment (Data were controlled for treatment status)</p>	<p>PCQL-32 SCALES Physical Functioning: Children's mean rating was lower (0.60) than that of parents (1.19) indicating poorer QOL perceived by parents ($t = 3.05, p < .01$). Poorest agreement between children and parents was found for this domain ($r = .06$) (and with 'disease and treatment aspects summarised below). Of all domains, parents' mean rating was highest for this domain suggesting that they perceived children's QOL to be poorest in relation to physical functioning. Psychological Functioning: Children's mean rating was lower (0.76) than that of parents (0.81) indicating poorer QOL perceived by parents ($t = 0.57, p < .05$). Although parents and children differed, they were closer in agreement ($r = .15$) for this domain compared to 'physical functioning' ($r = .06$) and 'disease and treatment aspects' ($r = .01$). The mean rating of parents' reports was lowest for this domain (and social domain) suggesting that they perceived children's QOL to be highest in relation to psychological and social functioning. Social Functioning: The mean rating of children's reports was marginally higher (0.89) than that of parents (0.81) indicating slightly better QOL perceived by parents ($t = -0.42, p < .05$). Of all domains, children's mean rating was highest (ie poorest) for this domain suggesting that children perceived their QOL to be poorest in relation to social functioning. Moderate agreement between parent and child reporting for this domain ($r = .40, p < .05$). Cognitive Functioning: Children's mean rating was lower (0.63) than that of parents (0.97) indicating poorer QOL reported by parents ($t = 2.83, p < .01$). Moderate agreement between parent and child reporting for this domain ($r = .44, p < .05$). Disease & Treatment Aspects: Children's mean rating was lower (0.58) than that of parents (0.92) indicating poorer QOL perceived by parents ($t = -2.25, p < .05$). Poorest agreement between children and parents was found for this domain ($r = .01$) (and with 'physical functioning summarised above). Poorer disease and medical functioning was reported by parents of</p>

children on treatment compared to parents of children off treatment ($t(32) = 2.37, p < .05$). **Total QOL:** Mean rating for children's reports was 0.70 compared to 0.94 for parents' reports indicating poorer overall QOL perceived by parents.

Discrepancies between Children and Parents: As noted for the above domains, there was poorer agreement for physical functioning and disease and treatment aspects of QOL compared to psychological functioning, and in addition for total QOL ratings ($r = .21$). Moderate agreement was found between parent and child reports on social functioning and cognitive functioning. Mean differences between parental and child reports on the PCQL-32 scale were not related to age, gender or treatment status.

DISQUOL: Older children reported better 'actual self' scores compared to younger children ($r = .46, p < .01$) and smaller discrepancy scores ($r = -.38, p < .05$). When DISQUOL measures were correlated with PCQL scales, levels of agreement were: good between 'actual self' and social functioning ($r = -.71, p < .01$); and overall QOL score ($r = -.63, p < .05$) QOL (PCQL-32); moderate between 'actual self' and physical functioning ($r = -.48, p < .05$), 'actual self' and psychological functioning ($r = -.37$) and 'actual self' and 'disease and treatment aspects' ($r = -.41$); poor between 'actual self' and cognitive functioning ($r = .11$). For the 'ideal self', level of agreement ranged from poor to good. Poorest agreement was found with cognitive ($r = .18$) and social ($r = -.29$) functioning. The highest level of agreement was with physical functioning ($r = -.58, p < .05$).

Table 3 Criteria for rating methodological quality of quantitative studies

<i>Study parameter</i>	<i>Rating</i>	Criteria
1. Study design	3	Longitudinal prospective design (explicitly stated)
	2	Retrospective or mixed design (explicitly stated)
	1	Cross-sectional (explicitly stated)
	0	Survey or did not report
2. Participants and recruitment	3	Description of the population (1), and eligibility criteria for participants (2), precise details of the recruitment process (3), accounted for the numbers recruited (4), and lost to follow-up (5)
	2	Minimal description of at least four criteria
	1	Two criteria missing
	0	More than two criteria missing
3. Comparison group	3	Healthy, age-appropriate comparison
	2	Reference sample
	1	Other comparison group (i.e. Adult BMT group, parent-report)
	0	No comparison group
4. Number of participants (specific on treatment for ALL)	3	$N > 100$
	2	$N = 50-100$
	1	$N < 50$
	0	Did not report
5. QOL Instruments*	3	Psychometrically sound report of generic and/or disease-specific QOL measures.
	2	Some weak psychometric properties reported for generic

1	and/or disease-specific QOL measures Psychometric properties of instruments reported as inadequate for measuring QOL
0	No psychometric properties reported

Source: Tsimicalis et al. (2005). (Permission given by Elsevier to re-produce Table)

* Amended to give a higher score to use of generic and/or disease specific measure. Reference to child report and/or proxy report removed.

Table 4. Quality criteria for assessment of qualitative research (Popay et al. 1998)

<i>Standards for systematic review of qualitative data</i>	<i>Earle & Eiser, 2007</i>	<i>Hicks et al. 2003</i>
<i>Lay accounts and subjective data as the primary marker</i>	Proxy accounts of parents	Children's perspectives on QOL.
<i>Context sensitivity</i> - flexible and responsive to changes or issues that may arise during the study?	Longitudinal design to capture changes in QOL over time. Semi structured interviews used.	Standardised procedure applied to data collection using semi-structured interviews conducted in clinic settings.
<i>Sampling strategy</i> : - purposively chosen to generate the type of knowledge necessary to understand the structures, contexts and meanings within which individuals are located?	Purposive sample across age groups and at different stages of treatment for ALL.	Convenience sampling
<i>Data quality</i> : - detailed description of the meaning and context of data; comparisons and contrasts of different sources of knowledge about the same issue provided (i.e. constant comparative analysis); transparency of processes by which data have been collected, analysed and presented.	Detailed description of data provided Thematic analysis of data. No specific reference to using constant comparative analysis. A transparent account of research processes was reported.	Detailed quotations presented. Content analysis of data using Colazzi's technique. No specific reference to using constant comparative analysis. A transparent account of research processes was reported.

<i>Theoretical or conceptual adequacy</i> - process of data analysis visible, illustrating the move from description to interpretation of its meaning and significance	Data analysis and presentation moves from description to interpretation of how children adjusted and responded to treatment for ALL over time. Conceptualised as 'coping with treatment' and 'normal life'.	Descriptive presentation of data analysis with little conceptual or theoretical development.
<i>Potential for assessing typicality</i> : - claims about generalizability of findings to either other bodies of knowledge or to other populations or groups?	Applicable to informing professionals about children's likely reactions to treatment, although limited by proxy accounts.	Inability to generalize findings acknowledged.

Table 5 Quality rating of quantitative studies

<i>Study</i>	<i>Study parameters</i>					<i>Total</i>
	Study design	Participants and recruitment	Comparison group	Number of participants	QOL instrument – psychometric property	
Shankar et al (2005)	1	3	3	1	3	11
Meeske et al. (2004)	1	3	1	3	3	11
Waters et al.. (2003)	1	3	2	1	2	9
Vance et al. (2001)	1	3	1	1	3	9