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TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
BACKGROUND 1
OBJECTIVES 3
METHODS 3
ACKNOWLEDGEMENTS 6
REFERENCES 6
ADDITIONAL TABLES 8
APPENDICES 9
CONTRIBUTIONS OF AUTHORS 12
DECLARATIONS OF INTEREST 12
SOURCES OF SUPPORT 12

[Intervention Protocol]

Severe fatigue in childhood cancer survivors

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

The main objective is to estimate the prevalence of severe fatigue, as part of the cancer-related fatigue (CRF) definition, in childhood cancer survivors (CCS).

The second objective is to describe the course of severe fatigue following cancer treatment and examine risk factors for, or factors associated with, severe fatigue (e.g. demographic, life-style, cancer and cancer treatment-related factors and co-morbidity). We will not include studies that assess the genetic basis of severe fatigue.

BACKGROUND

Description of the condition

With current treatment regimens, around 80% of children with cancer are expected to survive at least five years post-diagnosis (American Cancer Society 2014; Gatta 2014). Unfortunately, surviving childhood cancer does not end with the completion of the cancer treatment. The majority of childhood cancer survivors (CCS) will develop late effects during their life (Armstrong 2014; Geenen 2007; Hudson 2013). Late effects are adverse long-term health problems which are related to childhood cancer and its treatment, for example cardiac dysfunction, renal insufficiency and hepatic complications (Knijnenburg 2013; Mulder 2011; Nathan 2016). They can occur years after the completion of treatment and cause substantial excess morbidity and mortality (Armstrong 2014; Diller 2009; Hudson 2013). Research groups in the USA (Oeffinger 2006) and the Netherlands (Geenen 2007) estimated that the cumulative incidence of severe, disabling, and/or life-threatening late effects is about 40% 25 to 30 years after childhood cancer diagnosis. The need for long-term follow-up is, therefore, uniformly recognised (Skinner 2006).

Cancer-related fatigue (CRF) is one of the most common and debilitating symptoms in cancer survivors (Mulrooney 2008; Servaes 2002). CRF is defined by the National Comprehensive Cancer Network (NCCN) of the USA as "a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not pro-

portional to recent activity and interferes with usual functioning" (Mock 2000). It can impair performance so severely that the patient is unable to work or attend school. As such, CRF has a negative effect on quality of life (QoL) (Hjermstad 2006; Kanellopoulos 2013; Meeske 2007; Zeltzer 2009).

The aetiology of CRF is poorly understood and it is likely to be the result of a complex interaction of multiple factors, involving the dysregulation of interrelated physiological, biochemical (e.g. inflammation) and psychological systems (Barsevick 2010; Reyes-Gibby 2008; Ryan 2007). Possible risk factors for CRF can be classified into predisposing (genetic disposition), triggering (disease- and treatment-related factors), maintaining (current health, demographic and life-style factors) and modulating (age at diagnosis and gender) factors. Given the multiplicity of factors contributing to CRF, interventions should be tailored to each of the contributing factors and specific needs of the individual patient.

For the assessment of fatigue many different instruments have been developed. These instruments vary from a single-item question about the presence of fatigue, to fatigue severity scales, and multidimensional assessment tools assessing different dimensions of fatigue (e.g. cognitive, emotional and/or physical fatigue) (Bower 2014b; Jacobsen 2004; Minton 2008). Besides the fatigue questionnaires, there are also questionnaires that assess different symptoms or quality of life, aside from fatigue dimensions (e.g. EORTC QLQ-C30) (Aaronson 1993). To date, there is no consensus on how to accurately assess fatigue. Furthermore, the presence of fatigue on a fatigue assessment tool does not directly mean that a cancer survivor suffers from CRF, as fatigue, according to the definition of CRF, must be persistent, severe, not related to recent activity or co-morbidity, and it must interfere with daily functioning (Bower 2014b).

Previous review studies on severe fatigue in cancer survivors focused mainly on the prevalence of, duration of, and factors associated with severe fatigue in adult cancer survivors (ACS). A review in adult Hodgkin lymphoma survivors, for instance, estimated the prevalence of severe fatigue between 11% to 76% (Daniels 2013). The mean prevalence of severe fatigue in breast cancer survivors is reported to be 27% (range 7% to 52%) in a meta-analysis by Abrahams and colleagues (Abrahams 2016). These studies show that in adult cancer survivors, severe fatigue is a frequently occurring problem. However, the reported prevalence rates vary substantially between studies. Persistence of fatigue in ACS, long after completion of cancer therapy, has been demonstrated in multiple longitudinal studies (Bower 2006; Prue 2006; Reinertsen 2010; Servaes 2007). Factors associated with severe fatigue, reported in ACS, are: higher stage of cancer, intensive cancer treatment, sleep disturbance, lower levels of physical activity, elevated body mass index (BMI) and psychosocial problems (Abrahams 2016; Bower 2014a; Gielissen 2007; Spathis 2015). It is unknown, however, if these findings from ACS studies can be generalised to CCS.

To our knowledge, no systematic review is available describing the prevalence and course of CRF in CCS, or its risk and associated factors. Cross-sectional studies assessing the prevalence of severe fatigue in subgroups of CCS, with different time intervals since diagnosis, different fatigue assessment tools, and using different comparison groups are available (e.g. Johannsdottir 2012; Langeveld 2003; Meeske 2005; Mulrooney 2008). Unfortunately, the results are contradictory, from no excess fatigue to the majority of the CCS group being severely fatigued. Zeller and colleagues conducted a longitudinal study in 102 long-term survivors of childhood lymphoma and acute lymphoblastic leukaemia, at T1 52% had chronic fatigue and after a median interval of 2.7 years, 60% of this chronic fatigued group was still severely fatigued. Important to note is that this study used chronic fatigue (and not CRF) as a definition, so the group included major somatic co-morbidities, which could also explain the chronic fatigue (Zeller 2014). Kenney and colleagues studied the health status of adult CCS with the longest follow-up period so far (age > 50 years, treated for cancer between 1947 and 1968). CCS reported significantly more problems with fatigue compared to their sibling controls, indicating that problems due to fatigue could persist decades after cancer treatment (Kenney 2010). In conclusion, also in CCS subgroups persistent fatigue may be a problem.

Abrahams and colleagues reported a relatively large decrease in the prevalence of severe fatigue in the first half year after completion of breast cancer treatment in ACS (Abrahams 2016). Therefore, interventions during this period would most probably not be cost-effective and put undue strain on cancer survivors since severe fatigue may still resolve spontaneously. No longitudinal studies on the natural course of fatigue directly from completion of cancer treatment in CCS have been published. This makes it difficult to determine at which point in time an intervention for CRF can be best offered to CCS.

Why it is important to do this review

As far as we know, no meta-analysis has been conducted to estimate the prevalence of severe fatigue, assess its course since end of cancer treatment, and identify possible risk factors for the development of severe fatigue following childhood cancer and its treatment. As the number of CCS increases due to better treatment options, more survivors will be at risk for the development of severe fatigue as a late effect of childhood cancer and its treatment. It is unknown if the prevalence rates and risk factors concerning severe fatigue found in ACS can be generalised to the CCS population, as the group of CCS is very heterogeneous with different diagnoses, treatment modalities, late effects, and age at the start of cancer treatment. It is crucial to identify which CCS are more likely to develop severe fatigue following cancer treatment, in order to develop guidelines for follow-up and management of severe fatigue in CCS (Berger 2015). Knowledge about the natural course of severe fatigue in CCS will help to timely initiate

adequate interventions to alleviate severe fatigue and improve the associated quality of life in CCS.

In this review, we will focus on severe fatigue as an aspect of CRF, because severe fatigue has frequently been shown to have a negative effect on a patient's daily life, school performance and/or work ability, and quality of life. The proposed review will, through analysis of the published data on severe fatigue in CCS, increase our knowledge on the prevalence of severe fatigue, its course, and on factors associated with or increasing the risk on developing severe fatigue in CCS.

OBJECTIVES

The main objective is to estimate the prevalence of severe fatigue, as part of the cancer-related fatigue (CRF) definition, in childhood cancer survivors (CCS).

The second objective is to describe the course of severe fatigue following cancer treatment and examine risk factors for, or factors associated with, severe fatigue (e.g. demographic, life-style, cancer and cancer treatment-related factors and co-morbidity). We will not include studies that assess the genetic basis of severe fatigue.

METHODS

Criteria for considering studies for this review

Types of studies

We will include cohort, case-control, cross-sectional and longitudinal studies. We will also include randomised controlled trials (RCTs) and controlled clinical trials (CCTs) in CCS if there was no pre-selection of patients based on the presence or severity of fatigue, and the baseline characteristics included data on fatigue. Finally, we will include RCTs and CCTs in patients with childhood cancer testing the efficacy of cancer treatments, if there is a post-cancer treatment assessment of fatigue. We will exclude case reports and case series (i.e. a description of non-consecutive patients).

Types of participants

Studies that involved cancer survivors of any age, but who were diagnosed and treated for any type of cancer before the age of 18 years, will be eligible for the review. For this review a patient is considered a CCS from end of treatment onwards, with the purpose that we will be able to report the course of severe fatigue after completion of cancer treatment. In addition, the survivor should be in persistent complete remission at the moment of fatigue assessment. Studies that include both CCS and adult cancer survivors (ACS) are only eligible for inclusion if more than 90% of the survivors were under the age of 18 years at cancer diagnosis, or when the study presents results of survivors who were under the age of 18 years at cancer diagnosis separately.

Types of interventions

We will include all studies that report on CCS treated with one or a combination of cancer treatment modalities. Treatments include: chemotherapy, targeted therapy, immunotherapy, stem cell transplantation/bone marrow transplantation, radiotherapy and/or surgery for childhood cancer.

Types of outcome measures

Primary outcomes

The primary outcome is prevalence of severe fatigue in CCS. We anticipate that previous studies have used a variety of tools and outcome measures to evaluate severe fatigue. We will use "severe fatigue" as the main outcome measure, rather than cancer-related fatigue (CRF), which requires that several other criteria are met by patients (Mock 2000). Severe fatigue is defined as scoring above a published cut-off score on a validated or non-validated fatigue questionnaire. We will include all studies that measure severe fatigue with any questionnaire (e.g. fatigue questionnaire, fatigue items as part of a quality of life questionnaire, or criterion on a interview) with the exception of studies that assessed (severe) fatigue with a dichotomous outcome; those studies will be excluded.

Secondary outcomes

- The course of severe fatigue over time. The course of severe fatigue will be assessed in longitudinal studies with more than one fatigue assessment point.

- Risk factors for the occurrence of severe fatigue or factors associated with severe fatigue. Our objective is to study risk factors for the development of severe fatigue. However, we anticipate that most studies will have a cross-sectional design and cannot inform about risk factors for the development of severe fatigue. So, only longitudinal studies with more than one consecutive fatigue assessment points will be included in the study to asses risk factors. Other studies will be included for the analysis of associated factors for the occurrence of severe fatigue. We will use data on demography, life-style (e.g. BMI and physical activity), cancer and treatment-related factors, and current health data (e.g. co-morbidity, late effects of cancer treatment, sleep disturbance and/or psychosocial problems). The

data about the course of severe fatigue and it's associated/risk factors are not criteria for inclusion.

Search methods for identification of studies

Cochrane Childhood Cancer will run the searches in CENTRAL, MEDLINE/PubMed, and Embase/Ovid; all other searches will be done by the review authors.
We will not impose any language restrictions.

Electronic searches

We will search the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library; latest issue), MEDLINE/PubMed (from 1945 to present) and Embase/Ovid (from 1980 to present). All electronic searches have been developed in co-operation with Cochrane Childhood Cancer. The search strategies for the different electronic databases (using a combination of controlled vocabulary and text word terms) are shown in the appendices (Appendix 1; Appendix 2; Appendix 3).

Searching other resources

We will locate information about studies not registered in CENTRAL, MEDLINE/PubMed or Embase/Ovid, either published or unpublished, by searching the reference lists of relevant articles and review articles. In addition, we will also scan electronically the Proceedings abstracts from 2011 to present day of the International Society of Paediatric Oncology (SIOP), The European Symposium on Late Complications after Childhood Cancer (ESLCCC; symposium 2014 and 2016) the American Society of Clinical Oncology (ASCO) and the American Society of Pediatric Hematology/Oncology (ASPHO). The abstracts books of the ESLCCC (symposium 2011) and the International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer will be manually searched for relevant studies. Appendix 4 describes how the search will be performed.

Data collection and analysis

Selection of studies

After performing the search strategy described previously, two review authors will independently determine the eligibility of studies by reading the abstract of each study. These two authors will independently eliminate studies that clearly do not meet the inclusion criteria. One review author will perform the search in the reference lists of relevant articles and review articles, as well as the search within the conference proceedings. Full copies of the selected studies will be read by two authors to select studies meeting the inclusion criteria. We will resolve discrepancies between review authors by consensus. In case of no consensus, a third review author will act as third-party arbitrator for final resolution. We will obtain a full-text version of each study that meets the inclusion criteria based on title and/or abstract for closer inspection. When there are multiple publications of the same study population, we will include a single report in the review, if possible the publication with most patients or most recent data. Reasons for exclusion of studies that were considered for inclusion on the basis of title/or abstract, will be recorded. A flow diagram of the selection of studies will be included in the review.

Data extraction and management

Two review authors will independently perform data extraction using standardised forms. In case of disagreement, they will re-examine the publications and discuss the data extraction items until consensus is reached. If no consensus can be reached a third author will make a final decision. The following data will be extracted.
Study characteristics, including:

- study design;
- number of CCS in the study;
- inclusion/exclusion criteria for participation in the study;
- risk of bias items;
- funding sources;
- declarations of interest.

Outcome measures, including:

- instruments used to asses fatigue;
- cut-off score or criterion for severe fatigue;
- time point(s) at which outcome data were collected;
- number (percentage) of survivors with severe fatigue.

Cancer and treatment-related factors increasing the risk of, or that are associated with, severe fatigue:

- age at cancer diagnosis;
- tumour type and stage;
- type of cancer treatment: number of patients who received chemotherapy, or targeted therapy, or immunotherapy, or stem cell transplantation/bone marrow transplantation, or radiotherapy, or surgery for primary cancer, or combinations of cancer treatment;
- received chemotherapeutic agent;
- duration of follow-up since cancer diagnosis.

Predisposing, demographic, life-style and current health factors that might increase the risk on or are associated with severe fatigue:

- gender;
- ethnicity;
- genetic factors/mutations;
- marital status;
- highest completed education level;
- employment;
- age at fatigue assessment;

- physical activity level;
- body mass index (BMI);
- sleeping problems;
- psychosocial problems;
- co-morbidity, including late effects.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias in the included studies, discrepancies between authors will be resolved by consensus or in case of doubt, a third-party arbitrator. For the assessment of risk of bias in observational studies, we will use a modified checklist based on previously published checklists for observational studies according to evidence-base medicine criteria (Grimes 2002; Von Elm 2007). We will score 'Risk of bias' assessment according to the criteria mentioned in Table 1 (Table 1). For RCTs and CCTs, we will use the 'Risk of bias' items as described in the module of the Childhood Cancer Group (Kremer 2016), which are based on the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and we will slightly adapt the criteria with regard to the selection of case and controls in case-control studies. We will take the risk of bias into account when interpreting the review's results.

Measures of treatment effect

We will not study fatigue interventions, instead we will focus on the estimation of the prevalence of severe fatigue, the course of severe fatigue and risk factor for or factors associated with severe fatigue. We will analyse the prevalence of severe fatigue and the course of severe fatigue with validated and non-validated questionnaires combined, and we will separately analyse data of the subgroup of studies that used validated questionnaires. We will use the following data: prevalence, cumulative incidence, mean difference, absolute and relative risk, odds ratio, attributable risk, and other associated outcomes. All measures will be presented with a 95% confidence interval.

Dealing with missing data

When possible, we will contact authors of individual studies for clarification of unspecified or unclear data, or to obtain missing data regarding study selection, data extraction and 'Risk of bias' assessment.

Assessment of heterogeneity

We expect to find mainly observational studies, in which heterogeneity frequently will play a role due to differences in design, population and in outcome assessment. We will assess heterogeneity both by visual inspection of the forest plots and by a formal statistical test for heterogeneity, i.e. the I^2 statistic. We define significant heterogeneity as $I^2 > 50\%$ (Higgins 2011).

Assessment of reporting biases

In addition to the evaluation of reporting bias as described in the Assessment of risk of bias in included studies section, we will produce a funnel plot to quantify the potential presence of publication bias, provided there are a sufficient number of included studies (i.e. when at least 10 studies are available for meta-analysis). If the inclusion of studies is less than 10, the power of the test is too low to distinguish chance variation from real asymmetry (Higgins 2011).

Data synthesis

We will pool results only if (observational) studies are comparable, including the used outcome definitions and study population (e.g. cancer type and cancer treatment). We mainly expect studies in subgroups of CCS. If pooling of all studies is not possible, we will determine the possibility of pooling of studies with the same subgroup population (e.g. cancer diagnosis of leukaemia, lymphoma or central nervous system (CNS) tumour; history of stem cell transplantation). The pooled prevalence rates of longitudinal studies will be plotted in a graph to provide an overview of the course of severe fatigue over time. If pooling of studies is not possible, we will summarise studies descriptively. We will use a random-effects model. We will conduct all analyses according to the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and with the statistical components of Review Manager 5 (Review Manager 2014). If Review Manger 5.3 is not sufficient to calculate the prevalence's and 95% confidence intervals, we will use the Wilson method.

Subgroup analysis and investigation of heterogeneity

We will, if possible, perform subgroup analysis based on cancer diagnosis (haematological cancer, bone cancer, brain cancer or solid tumours), cancer treatment (chemotherapy, stem cell transplantation/bone marrow transplantation, surgery for primary cancer, radiotherapy and radiotherapy on CNS localisation versus non-CNS localisation), gender (male/female), age at cancer diagnosis (0-4 years / 4-12 years / >12 years) and follow-up time since cancer diagnosis (< 5 years / 5-15 years/ > 15 years). These subgroups were defined as we anticipate that there might be a difference in the prevalence of severe fatigue between these subgroups. If significant heterogeneity ($I^2 > 50\%$) (Higgins 2011) is identified, we will explore possible reasons based on clinical differences and decide if we can pool the data using a random-effects model.

Sensitivity analysis

We will exclude studies with a high risk of bias and studies for which the risk of bias is unclear in the sensitivity analyses. We will perform a sensitivity analyses for all outcomes for which pooling is possible if at least two studies are left in the analysis after excluding

high and unclear risk studies, and compare the results of studies with a low risk of bias with the results of all available studies.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Risk of bias assessment for observational studies

	Internal validity	External validity
Study group	**Selection bias (representative: yes/no)** - if the described study group consisted of more than 90% of the original cohort of cancer survivors - or if the study population was a random sample with respect to the cancer treatment of the original cohort of cancer survivors	**Reporting bias (well-defined: yes/no)** - if the type of cancer and cancer treatment was mentioned - if the inclusion and exclusion criteria are described
Follow-up	**Attrition bias (adequate: yes/no)** - if the outcome was assessed for more than 95% of the study group of interest (++) - or if the outcome was assessed for 65% to 95% of the study group of interest (+)	**Reporting bias (well-defined: yes/no)** - if the length of follow-up was mentioned
Outcome	**Detection bias (blind: yes/no)** - if the outcome assessors were blinded to the investigated determinant	**Reporting bias (well-defined: yes/no)** - if the authors reported what instruments they used to assess fatigue and what they considered to be severe fatigue
Risk estimation	**Confounding (adjustment for other factors: yes/no)** - if important prognostic factors (i.e. age, sex, co-treat-	**Analyses (well-defined: yes/no)** - if one of the following items were calculated: preva-

Table 1. Risk of bias assessment for observational studies (*Continued*)

	ment, co-morbidity) or follow-up were taken adequately into account	lence, cumulative incidence mean difference, relative risk, risk ratio, or odds ratio

APPENDICES

Appendix 1. Search strategy for Cochrane Central Register of Controlled Trials (CENTRAL)

1. For **fatigue** the following text words will be used:
fatigue or fatigu* or tired or tiredness or tired* or asthenia or astheni* or exhaustion or exhausted or exhaust* or loss of energy or energy loss or loss of vitality or (vital* and loss) or weary or weariness or weakness or apathy or apath* or lassitude or lethargy or letharg* or sleep or sleep deprivation or sleepiness or drowsy or drowsiness
2. For **children** the following text words will be used:
infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child OR school child* OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR school OR school* OR prematur* OR preterm*
3. For **childhood cancer** the following text words will be used:
leukemia OR leukemi* OR leukaemi* OR childhood ALL OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR primitive neuroectodermal tumors OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom* OR pediatric oncology OR paediatric oncology OR childhood cancer OR childhood tumor OR childhood tumors OR brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm*
4. For **cancer** the following text words will be used:
cancer OR cancers OR cancer* OR oncology OR oncolog* OR neoplasm OR neoplasms OR neoplasm* OR carcinoma OR carcinom* OR tumor OR tumour OR tumor* OR tumour* OR tumors OR tumours OR malignan* OR malignant OR hematooncological OR hemato oncological OR hemato-oncological OR hematologic neoplasms OR hematolo*
5. For**survivors** the following text words will be used:
Survivor OR survivors OR Long-Term Survivors OR Long Term Survivors OR Long-Term Survivor OR survivo* OR surviving
Final search
1 AND 2 AND (3 OR 4) AND 5
The search will be performed in title, abstract or keywords.
[*= zero or more characters]

Appendix 2. Search strategy for MEDLINE/PubMed

1. For **fatigue** the following MeSH headings and text words will be used:
fatigue[mh] OR fatigue OR fatigu* OR tired[tiab] OR tiredness[tiab] OR tired* OR asthenia[mh] OR asthenia OR astheni* OR exhaustion OR exhausted OR exhaust* OR loss of energy[tiab] OR energy loss[tiab] OR loss of vitality OR (vital* AND loss) OR weary[tiab] OR weariness[tiab] OR weakness OR apathy[mh] OR apath* OR lassitude[tiab] OR lethargy[mh] OR letharg* OR sleep OR sleep deprivation OR sleepiness[tiab] OR drowsy[tiab]OR drowsiness[tiab]
2. For **children** the following MeSH headings and text words will be used:
infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school[tiab] OR school*[tiab] OR prematur* OR preterm*
3. For **childhood cancer** the following MeSH headings and text words will be used:
leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom* OR pediatric oncology OR paediatric oncology OR childhood cancer OR childhood tumor OR childhood tumors OR brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm* OR leukemia lymphocytic acute
4. For **cancer** the following MesH headings and text words will be used:
cancer OR cancers OR cancer* OR oncology OR oncolog* OR neoplasm OR neoplasms OR neoplasm* OR carcinoma OR carcinom* OR tumor OR tumour OR tumor* OR tumour* OR tumors OR tumours OR malignan* OR malignant OR hematooncological OR hemato oncological OR hemato-oncological OR hematologic neoplasms OR hematolo*
5. For**survivors** the following MeSH headings and text words will be used:
Survivor OR survivors OR Long-Term Survivors OR Long Term Survivors OR Long-Term Survivor OR Survivor, Long-Term OR Survivors, Long-Term OR survivo* OR surviving
Final search
1 AND 2 AND (3 OR 4) AND 5
[tiab = title, abstract; mh = MeSH term; *=zero or more characters]

Appendix 3. Search strategy for Embase/Ovid

1. For **fatigue** the following Emtree terms and text words will be used:
1. fatigue/ or cancer fatigue/ or muscle fatigue/
2. (fatigue or fatigu$ or tired or tiredness or tired$).mp.
3. exp asthenia/ or (asthenia or astheni$).mp.
4. exp exhaustion/ or (exhaustion or exhausted or exhaust$).mp.
5. (loss of energy or energy loss).mp.
6. ((loss adj2 vital$) or (loss adj2 energy)).mp.
7. exp weakness/ or (weakness or weary or weariness).mp.
8. exp apathy/ or (apathy or apath$).mp.
9. lassitude.mp. or exp lassitude/
10. exp lethargy/ or (lethargy or letharg$).mp.
11. exp sleep/ or exp sleep deprivation/ or (sleep or sleep deprivation or sleepiness).mp.
12. exp drowsiness/ or (drowsy or drowsiness).mp.
13. or/1-12
2. For **children** the following Emtree terms and text words will be used:
1. infan$.mp.
2. (newborn$ or new-born$).mp.

3. (perinat$ or neonat$).mp.
4. baby/
5. (baby or baby$ or babies).mp.
6. toddler$.mp.
7. (minors or minors$).mp.
8. (boy or boys or boyfriend or boyhood).mp.
9. girl$.mp.
10. (kid or kids).mp.
11. child/
12. (child or child$ or children$).mp.
13. school child/
14. (schoolchild$ or schoolchild).mp.
15. (school child or school child$).ti,ab.
16. (adolescen$ or youth$ or teen$).mp.
17. (juvenil$ or underage).mp.
18. pubescen$.mp.
19. exp pediatrics/
20. (pediatric$ or paediatric$ or peadiatric$).mp.
21. (school or school$).mp.
22. (prematur$ or preterm$).mp.
23. or/1-22

3. For **childhood cancer** the following Emtree terms and text words will be used:

1. (leukemia or leukemi$ or leukaemi$ or (childhood adj ALL) or acute lymphocytic leukemia).mp.
2. (AML or lymphoma or lymphom$ or hodgkin or hodgkin$ or T-cell or B-cell or non-hodgkin).mp.
3. (sarcoma or sarcom$ or Ewing$ or osteosarcoma or osteosarcom$ or wilms tumor or wilms$).mp.
4. (nephroblastom$ or neuroblastoma or neuroblastom$ or rhabdomyosarcoma or rhabdomyosarcom$ or teratoma or teratom$ or hepatoma or hepatom$ or hepatoblastoma or hepatoblastom$).mp.
5. (PNET or medulloblastoma or medulloblastom$ or PNET$ or neuroectodermal tumors or primitive neuroectodermal tumor$ or retinoblastoma or retinoblastom$ or meningioma or meningiom$ or glioma or gliom$).mp.
6. (pediatric oncology or paediatric oncology).mp.
7. ((childhood adj cancer) or (childhood adj tumor) or (childhood adj tumors) or childhood malignancy or (childhood adj malignancies) or childhood neoplasm$).mp.
8. ((pediatric adj malignancy) or (pediatric adj malignancies) or (paediatric adj malignancy) or (paediatric adj malignancies)).mp.
9. ((brain adj tumor$) or (brain adj tumour$) or (brain adj neoplasms) or (brain adj cancer$) or brain neoplasm$).mp.
10. (central nervous system tumor$ or central nervous system neoplasm or central nervous system neoplasms or central nervous system tumour$).mp.
11. intracranial neoplasm$.mp.
12. LEUKEMIA/ or LYMPHOMA/ or brain tumor/ or central nervous system tumor/ or teratoma/ or sarcoma/ or osteosarcoma/
13. nephroblastoma/ or neuroblastoma/ or rhabdomyosarcoma/ or hepatoblastoma/ or medulloblastoma/ or neuroectodermal tumor/ or retinoblastoma/ or meningioma/ or glioma/ or childhood cancer/
14. or/1-13

4. For **cancer** the following Emtree terms and text words will be used:

1. (cancer or cancers or cancer$).mp.
2. (oncology or oncolog$).mp. or exp oncology/
3. (neoplasm or neoplasms or neoplasm$).mp. or exp neoplasm/
4. (carcinoma or carcinom$).mp. or exp carcinoma/
5. (tumor or tumour or tumor$ or tumour$ or tumors or tumours).mp. or exp tumor/
6. (malignan$ or malignant).mp.
7. (hematooncological or hemato oncological or hemato-oncological or hematologic neoplasms or hematolo$).mp. or exp hematologic malignancy/
8. or/1-7

5. For**survivors** the following Emtree terms and text words will be used:

1. (survivor or survivors or (long adj term survivor) or (long adj term survivors) or survivo$).mp.

2. survivor/ or cancer survivor/
3. surviving.mp.
4. 1 or 2 or 3
Final search
1 AND 2 AND (3 OR 4) AND 5
[mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name; ti,ab = title, abstract; / = Emtree term; $=zero or more characters; adj=adjacent]

Appendix 4. Search strategies for conference proceedings

The pdf files of SIOP, ESLCCC (symposium 2014 and 2016) and ASPHO abstracts will be searched for "fatigue", "fatique", "tired", "tiredness", "exhaustion", "exhausted", "weakness", "asthenia" and "survivor". The ASCO abstracts will be searched for "fatigue survivor" in the abstracts (http://meetinglibrary.asco.org/abstracts). The abstracts of the ESLCCC (symposium 2011) and The International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer will be on scanned for "fatigue" and "survivor" on paper.

CONTRIBUTIONS OF AUTHORS

All review authors: contributed to the development of the idea and of the protocol.

AB, EDU, JL, HK: developed and wrote the protocol, developed the search strategies (together with the Information Specialist of Cochrane Childhood Cancer), and the data extraction form.

MR, NB: discussed the protocol and contributed to its development along with the other members of the review team.

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