CANADIAN PARTNERSHIP AGAINST CANCER | PARTENARIAT CANADIEN CONTRE LE CANCER

A Pan Canadian Practice Guideline for Screening, Assessment, and Management of *Cancer-Related Fatigue* in Adults

Version 2 - 2015

Howell D., Keshavarz H., Broadfield L., Hack T., Hamel M., Harth T., Jones J., McLeod D., Olson K., Phan S., Sawka A., Swinton N., & Ali M.

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This Guideline is comprised of the following sections:

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Canadian Association of Psychosocial Oncology
Association Canadienne d'Oncologie Psychosociale

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Table of Content

List of Tables

List of Figures

Executive Summary

Background

Cancer-related fatigue (CRF) is a prevalent problem in cancer and has a side effect of treatment that often worsens during cancer treatment and can persist as a long-term problem for many patients including those in palliative care and cancer survivor populations[1, 2]. Reported prevalence rates for fatigue range from 59% to 100%[3-5]. CRF is reported as the most distressing side effect of cancer and treatment and causes greater interference with daily life than any other symptom[6, 7]. CRF also impacts on personal, social, work roles and it can have a profound negative impact on overall quality of life (QoL)[8-12]. Because its etiology is not well understood, it is frequently unrecognized and is difficult to manage in clinical practice[13].

Scope and Purpose of this Review

The scope of this 2015-Version 2 of CRF guideline is focused on the provision of clinical practice recommendations for members of oncology interdisciplinary team (e.g. primary care physicians, oncologists, nurses, physiotherapist, occupational therapists, rehabilitation specialists), who screen, assess, and manage CRF in their daily clinical practice. Additionally, the recommendations may also help patients and families learn about the most effective strategies for managing CRF. The recommendations apply to those with CRF across the cancer trajectory, from cancer treatment to post-treatment survivorship and palliative or end-of-life care. The guidelines focused on the adult cancer population with fatigue due to cancer and/or cancer treatment.

Intended Users

The intended users of this guideline are the primary oncology interdisciplinary team, and community practitioners such as family physicians and palliative care teams. The recommendations are intended to also be relevant to specialists in fatigue including psychology and psychiatry, and other members of the allied health care team (occupational therapists, rehabilitation specialists, physiotherapists) who provide counselling to patients in the management of cancer-related fatigue. Patients and their families may also find this guideline useful for understanding the current recommendations and evidence for management for cancer and/or treatment related fatigue.

Questions

1. What are the current guideline recommendations for routine screening and assessment of CRF in adults?

2. What is the efficacy of interventions (pharmacological, non-pharmacological, and/or combinations) for reducing CRF in adults?

Methods

We developed a three-step approach:

1) We searched for existing evidence-based guidelines on screening, assessment, and management of CRF from 2009 to Nov 2014. We selected any guideline published since version 1 of the 2011 guideline. We compared their recommendations to version 1 of the 2011 guideline. For screening and assessment of CRF, we adopted the new recommendations, if any, not included in version 1 of the 2011 guideline after reviewing the quality of the guidelines. If there were no new recommendations in these guidelines, we adopted previous recommendations from version 1 of the 2011 guideline on screening and assessment of CRF. The adopted recommendations may have been refined to ensure substantive statements of recommendations were clear and concise.
2) We performed a systematic search for systematic reviews to identify new evidence from 2009 to 2014, and adopted or updated or developed new recommendations based on the level of evidence identified and quality of the reviews accordingly. We included all relevant systematic reviews of Randomized Control Trial (RCTs) that evaluated the effects of any pharmacological and/or non-pharmacological intervention on the management of fatigue in adults with all types of cancer from 2009 to November 2014. We then used the search-end date reported in these systematic reviews to search for new RCTs published, basing our search start date on the last search year of the latest systematic review.
3) We performed a systematic search of RCTs identified beyond the *search-end date* reported in the updated systematic reviews (i.e. not included in systematic reviews identified in the previous step). Our search dates for RCTs covered from 2013, the last year searched in previous systematic reviews up to present date of November 2014.

Data Sources

MEDLINE®, Embase®, CINAHL®, PsychINFO®, CINHAL, Cochrane Database of Systematic Reviews, and Cochrane Central® were searched from 2009 to November 23, 2014. An extensive grey literature search was also undertaken, including scan of international guideline developers and key organizations for evidence-based clinical practice guidelines, systematic reviews and ongoing trials was conducted (September, 2014) for documents about CRF.

Review Methods

Systematic review methodology was employed. Eligibility criteria included English studies of cancer related fatigue adults (aged ≥18 years). Clinical Practice Guidelines (CPGs), Systematic Reviews (SRs) and Randomized Clinical Trials study designs were eligible. Publications focusing only on treatment algorithms were not considered to be CPGs.

Types of Participants (P)

Adults (aged 18 and over) with a clinical diagnosis of cancer known to have clinically significant fatigue score >3 (moderate or severe fatigue) on a 0-10 Numeric Rating Scale or comparable scale with established cut-offs at any stage and at any point of the cancer treatment spectrum, including those undergoing curative treatment, those with advanced disease receiving palliative care, and disease-free post-cancer treatment survivors. Studies with populations without a diagnosis of any type of cancer, or did not experience clinically significant fatigue were excluded.

Types of Interventions (I)

Any pharmacological and any non-pharmacological (psychosocial, CBT, psycho-education or patient education, mindfulness meditation, yoga, exercise/activity, complementary medicine) interventions for the management of CRF in adult patients.

Types of Comparator (C)

Comparison condition is usual care, attention control or other comparator. Studies comparing drug treatment versus no drug treatment or versus alternative drug treatment, or both were also included.

Types of Outcomes (O)

Outcomes (either primary or secondary) included:

1) Clinically significant improvement in fatigue or
2) Clinically significant reduction in CRF (measured by severity) or
3) Differences in fatigue severity between intervention group and controls using self-reported outcome measures

Assessment of Methodological Quality Guidelines, Systematic Reviews and Randomized Clinical Trials

We addressed three different quality assessments: 1)We used the AGREE II to assess the variability in the quality of the guideline process[14]. 2)We used AMSTAR (Assessment of Multiple Systematic Reviews) to assess the methodological quality of the systematic review[15]. 3) We selected the Risk of Bias Tool by the Cochrane Collaboration[16] to assess RCTs.

Quantitative Synthesis:

To perform meta-analysis, immediate post-treatment data (mean, standard deviation) was utilized for continuous outcome measures. The DerSimonian and Laird random effects models with inverse variance method were utilized to generate the summary measures of effect in the form of Standardized Mean Difference (SMD) for continuous outcomes[17]. The SMD was used as a summary statistic because the studies in this systematic review often assessed the same outcomes measured in a variety of ways [i.e., various studies measured CRF but they used different outcome measures such as Brief Fatigue Inventory (BFI), Multidimensional Fatigue System Inventory (MSFI), Functional Assessment of Cancer Therapy-Fatigue (FACT-F), Piper Fatigue Scale (PFS) etc.]. In this situation, it was necessary to standardize the results of the studies before they could be compared across studies or combined in a quantitative synthesis. SDMs were calculated using change from baseline data, i.e. mean difference between pre-treatment (baseline) and post-treatment (final/end-point) scores along with its standard deviation for both intervention and control groups. The SMD effect sizes with scores of 0.2–0.5, 0.5–0.8, and >0.8 were considered as small, medium, and large effects, respectively[18]. The studies, where Standard Deviation (SD) was not reported, we calculated the SD from the reported Standard Error (SE) of the mean, or 95% Confidence Intervals (CIs) using the equations provided in Chapter 9 of the Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane's Q (α=0.10) and I2 statistic were employed to quantify the statistical heterogeneity between studies, where $p<0.10$ indicates a high level of statistical heterogeneity between studies. The analyses were performed using Review Manager Version 5.1 software. For studies not included in the meta-analyses, findings are described narratively in the text[17, 19]. Additionally, we grouped study results: 1) according to the type of treatment categories and the corresponding comparator treatment; 2) the specific grouping of the pharmacological treatment and, 3) nonpharmacological treatment. Forest plots and summary tables were generated to display primary study outcomes of fatigue severity.

Rating the Body of Evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to determine the quality of evidence and strength of recommendations for each important outcome.

We used standardized 'effectiveness statements' to rate the evidence obtained from reviews, using a further synthesis step that aims to extend a simple summary of the main results of each review. These statements were based on the rating scheme developed by the Cochrane Consumers and Communication Review Group (CC&CRG) to guide synthesis and rating of evidence across systematic reviews with complex and diverse intervention[20-22].

Results & Conclusion

There were a total of 6[23-28] CPGs sponsored by unique organizations and described in 7 publications[23-29]. Four[24, 26, 27, 28] out of six guidelines reviewed were consistent in making a recommendation that all cancer patients should be screened for presence and severity of fatigue using a valid, quantitative or semi-quantitative (mild, moderate, severe) measure and established cut-points for differentiating between mild, moderate and severe levels of fatigue. Four guidelines made recommendations for assessment of fatigue that included assessment of a wide range of contributing factors, medical history and laboratory evaluation. The components of the assessment were similar across guidelines with some guidelines stating a strong recommendation for fitness testing and review of patient activity levels.

We identified 26[30-55] unique systematic reviews and 28[56-83] randomized clinical trials in this practice guideline. We categorized included systematic reviews by pharmacological and non-pharmacological interventions. We sub-grouped non-pharmacological interventions into the following categories: 1) educational and psychosocial; 2) physical activity/exercise; 3) complementary.

Existing reviews[31, 35, 37, 40-42, 44, 48, 55] and RCTs reviews[57, 58, 62, 65, 71, 74, 77-79] on pharmacological interventions are largely heterogeneous with small samples and do not offer robust data for firm conclusions about the effectiveness of various drug classes for management of CRF. The majority of studies of pharmacological interventions have examined psychostimulants, in particular, methylphenidate. There is insufficient evidence to recommend pharmacological agents for fatigue at any stage of disease. Tentative trend in benefit for methylphenidate in advanced disease but safety was not confirmed to recommend use[37, 40, 48, 58]. Modafinal evaluated in brain, prostate, breast, lung cancer not superior to placebo[40, 42, 48, 79, 83]. Minimal benefit of short-term use of dexamethasone in advanced cancer[74]. Co-enzyme Q10 (CoQ10) supplementation was not superior to placebo[65].

Existing high quality evidence from multiple systematic reviews[31, 34-36, 38, 39, 41, 43-46, 49, 51-53, 55] and RCTs reviews[56, 59, 60, 68, 70, 73, 75, 76, 80, 81] on physical activity/exercise indicating that strategies for increasing physical activity are associated with a reduction in fatigue in cancer patients and survivors. Overall, we found that exercise moderately reduced CRF among all type of cancer patients diagnosed with fatigue regardless of stage of treatment; significant benefit shown (p=0.0005). There is, however, a large degree of heterogeneity of benefit, among pooled trials from various oncology populations, using various physical activity strategies. Thus, physical activity exercises should be used in the management of CRF in all type of cancer.

We identified 7 systematic reviews[31, 33, 35, 38, 41, 45, 51] and 2 RCTs[67, 72] on psychosocial education. The results of systematic reviews suggest that education and psychosocial interventions are likely to be effective in reducing fatigue but the conclusions are not definitive.

Patients with cancer receiving chemotherapy would benefit from multidisciplinary self-care education strategies and in men with prostate cancer cognitive behavioral therapy and disease-specific education may help alleviate CRF. Interactive education programs designed to educate patients about etiology, dimensions and treatment of fatigue as well as comprehensive coping strategies and stress management for cancer survivors can have a positive impact of perceived fatigue and are both feasible and effective in educating patients on self-management of CRF and may lead to a reduction of CRF in patients with breast cancer.

There is limited evidence that general psychosocial interventions that are not targeted specifically to fatigue are effective. Educational interventions of a minimum of 3 sessions that target improvement in patients' understanding and knowledge of fatigue appear to reduce fatigue but the effect sizes are small. It is unclear if similar effects would be found for post-treatment survivors as most studies were conducted in patients on active treatment and primarily in breast cancer. More intensive interventions such as cognitive behavioral therapy also targeted to fatigue are effective in reducing fatigue and the effect is maintained for longer periods of follow-up.

We identified 6 systematic reviews[30, 32, 38, 47, 50, 54] and 5 RCTs[63, 64, 66, 69, 78] on acupuncture. There is insufficient evidence with low quality and quantity of RCTs to draw firm conclusions regarding the effectiveness of acupuncture for cancer related fatigue.

There is insufficient evidence from 6 identified systematic reviews and 5 RCTs for the effectiveness of acupuncture for cancer related fatigue. Some have reported short-term benefits but not beyond the initial 2-week intervention. The RCTs all had methodological flaws such as small sample sizes. A systematic review of complementary interventions including massage, healing touch, relaxation training, and hypnosis, for treatment of cancer related fatigue provides limited evidence for the effectiveness of these interventions. Ginseng, and vitamin supplements are not beneficial in treating cancer related fatigue. Similarly, a systematic review based on 10 RCTs, most of which had methodological flaws, did not offer firm evidence on safety and efficacy of Chinese herbal medicine.

Lay Summary

More than half of patients with cancer experience fatigue that often worsens during treatment. Fatigue due to cancer negatively affects many aspects of the patient's life. However it often goes undiagnosed and is difficult to treat. The guideline is aimed at health care professionals including oncologists and nurses as well as patients with cancer and their families to help them learn about the most effective strategies, for dealing with fatigue due to cancer.

We identified studies that tested the effectiveness of medications or psychosocial interventions including physical activity in reducing fatigue due to cancer. We then evaluated the quality of these studies and an expert panel of health care professionals formulated their recommendations based on the results of these studies.

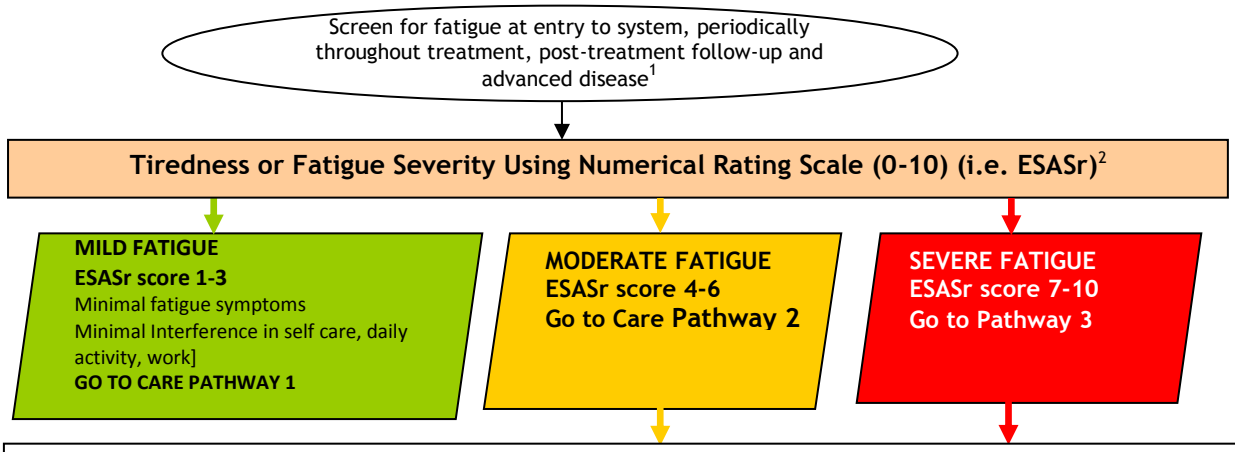
All patients are likely to benefit from counseling and education about fatigue with an emphasis on how to cope and with their fatigue and adjust their activity levels. Cancer services should promote access to educational programs and resources to help patients to understand fatigue and help them to develop coping skills and engage in appropriate levels of activity.

There are no medications that were shown to be effective in reducing fatigue due to cancer. These include herbal medicines, vitamins and supplements such as ginseng. In some instances, use of these medications may lead to more harm than benefit to the patient. Therefore their use is not currently recommended to reduce fatigue due to cancer. Very few studies have been carried out on the effectiveness of acupuncture for fatigue due to cancer. Therefore it is currently not recommended as an effective treatment for fatigue in patients with cancer. However, some studies have shown that mindfulness based interventions may help alleviate fatigue due to cancer.

Physical activity has shown significant benefit in reducing fatigue due to cancer, including breast and colorectal cancers. Patients may be advised by their physician about engaging in moderate intensity physical activity five or more times a week. All types of physical activity including walking and yoga may help decrease fatigue during or after treatment for cancer. Exercise sessions should ideally be supervised and be based on individual tolerance.

Algorithm for Cancer-Related Fatigue

*Screening and Assessment - Cancer-Related Fatigue in Adults with Cancer**



☐ Review Fatigue Severity Scores with Patient (and Family)
☐ Complete a Focused Assessment of Fatigue
- ☐ O-Onset of Fatigue and Duration (When did fatigue begin); ❍ Acute Onset ❍ Chronic (>3 months)
- ☐ P-Perpetuating or Provoking Factors (What makes fatigue better or worse?)
- ☐ Q-Quality of Fatigue (Describe experience of fatigue in own words; how distressing is fatigue)
- ☐ R-Referral or Radiation (Other symptoms with fatigue? i.e. sleep, depressed mood)
- ☐ S-Severity of Fatigue (use of quantitative fatigue severity scale)
- ☐ T-Treatment (What actions are you taking for fatigue, level of physical activity?)
- ☐ U-Understanding (What do you understand about fatigue and its management?)
- ☐ I-Interference (How is fatigue affecting your activities of daily living? [work, social life, concentration, memory, mood, physical activity levels)
- ☐ V-Value (What is your goal/expectations for this symptom?)

Complete a Comprehensive Assessment of Fatigue (Laboratory Tests and Physical Exam)

- ☐ Treatment Complications ❍anemia ❍ infection ❍ fever
- ☐ Nutritional Deficiencies (Caloric intake, weight loss/gain)
- ☐ Fluid and electrolyte imbalances [sodium, calcium potassium, magnesium]
- ☐ Medications -❍ opioids ❍ antihistamines ❍antidepressants ❍alcohol/recreational drug use
- ☐ Comorbid conditions (cardiac, pulmonary, metabolic, endocrine, hepatic or renal insufficiency)
- ☐ Other symptoms/side-effects ❍ Pain (see ESASr score - ≥ 4 see pain guidelines)
  - ❍ Depression (see ESASr score- ≥4 see depression guidelines)
  - ❍ Anxiety (see ESASr score- ≥ 4 see anxiety guidelines)
  - ❍ Sleep disturbances (see ESASr score- ≥ 4 see sleep guidelines)
- ☐ Activity level changes ❍ decreased physical activity ❍ decreased exercise pattern

Conduct Physical exam

- ☐ Gait ☐ Posture ☐ Range of motion
- ☐ Eyes (conjunctival pallor if anemic)
- ☐ Oral Assessment ❍cheliosis ❍angular chelitis ❍angular stomatitis
- ☐ Muscle wasting
- ☐ Tachycardia ☐ Shortness of breath ❍at rest ❍on exertion
- ☐ ***__Typical Symptoms of Fatigue:__ Tiredness, disproportionate to recent activity; Impairment of ADLs/ disturbance in quality of life; Diminished concentration or attention; Significant distress or negative mood to feeling fatigued (e.g., sad, frustrated, irritable); Sleep disturbance (insomnia or hypersomnia); Sleep perceived as non-restorative; Decreased motivation or interest in usual activities.

* - Please see the full guideline for a description of the acronyms used, as well as the copyright and disclaimer prior to use.
1-- Use a Valid Scale to Screen for Presence of Fatigue and Level of Severity (i.e. NRS 0-10 such as ESAS; FACT-F; Fatigue Pictogram; Piper Fatigue Scale)
2 - The health care team for cancer patients may include surgeons, oncologists, family physicians, nurses, social workers, psychologists, patient navigators, fatigue experts, rehabilitation experts and other health care professionals
3. OPQRSTUV-Acronym=O-Onset; P-Provoking/Palliating; Q-Quality; R-Region or Radiating; S-Severity & Duration; T-Treatment; U-Understanding; V-Values (Fraser Health Guidelines, see reference list)

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*Care Map – Cancer-Related Fatigue in Adults with Cancer**

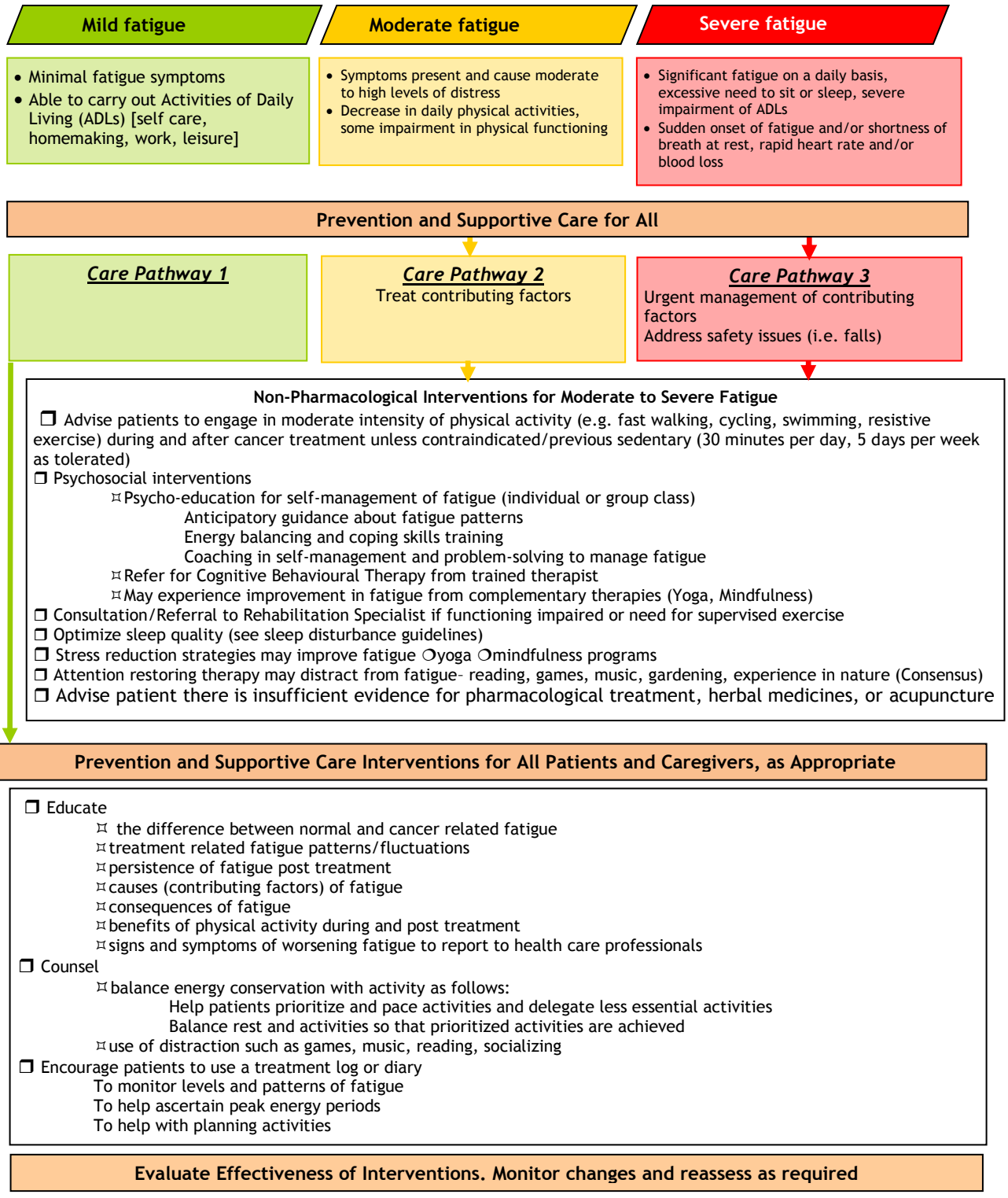

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Figure 1: Quick Reference Algorithm for Screening and Assessment- Cancer-Related Fatigue in Adults with Cancer*

Recommendations

This guideline is a second edition of, and replaces the previous guideline, A Pan-Canadian Practice Guideline: Screening, Assessment and Care of Cancer Related Fatigue in Adults with Cancer version 1-2011.

We formulated standardized 'effectiveness statements' to rate the evidence arising from reviews for the management of CRF, using these statements were based on the rating scheme developed by Ryan[84], to help synthesise and rate the evidence across eligible systematic reviews[84].

We assessed the overall Strength Of the Evidence (SOE) of randomized control trials across the literature using the rating approach as specified by the GRADE[85-87].

GRADE Methodology

Recommendations are graded as either strong or weak according to the Grades of Recommendation Assessment, Development and Evaluation system. GRADE offers two strengths of recommendation: strong and weak. The strength of recommendations is based on the quality of supporting evidence, the degree of uncertainty about the balance between desirable and undesirable effects, the degree of uncertainty or variability in values and preferences, and the degree of uncertainty about whether the intervention represents a wise use of resources.

Category Quality	Definitions	Strong Recommendation	Weak Recommendation
High Quality Evidence	Further research is very unlikely to change our confidence in the estimate of effect.	The work group is confident that the desirable effects of adhering to this recommendation outweigh the undesirable effects. This is a strong recommendation for or against. This applies to most patients.	The work group recognizes that the evidence, though of high quality, shows a balance between estimates of harms and benefits. The best action will depend on local circumstances, patient values or preferences.
Moderate Quality Evidence	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	The work group is confident that the benefits outweigh the risks but recognizes that the evidence has limitations. Further evidence may impact this recommendation. This is recommendation that likely applies to most patients.	The work group recognizes that there is a balance between harms and benefits, based on moderate quality evidence, or that there is uncertainty about the estimates of the harms and benefits of the proposed intervention that may be affected by new evidence. Alternative approaches will likely be better for some patients

			under some circumstances.
Low Quality Evidence	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change. The estimate or any estimate of effect is very uncertain.	The work group feels that the evidence consistently indicates the benefit of this action outweighs the harms. This recommendation might change when higher quality evidence becomes available.	The work group recognizes that there is significant uncertainty about the best estimates of benefits and harms.

Terms and definitions used to formulate standardized effectiveness statements to rate evidence/level of evidence from reviews, adopted from Ryan 2014[84].

Summary statement/level of evidence	Translation
Sufficient evidence	Evidence to make a decision about the effect of the intervention(s) in relation to a specific outcome(s). This includes evidence of an effect in terms of (i) benefit or (ii) harm. Statistically significant results are considered to represent sufficient evidence on which to base decisions, but a judgement of sufficient evidence is also made based on the number of studies/participants included in the analysis for a particular outcome. (See page 43 for details).
Some evidence	Less conclusive evidence to make a decision about the effects of a particular intervention(s) in relation to a specific outcome(s).This may be based on narrative syntheses of review results. (See page 43 for details).
Insufficient evidence	Not enough evidence to support decisions about the effects of the intervention(s) on the basis of the included studies. This should be interpreted as 'no evidence of effect', rather than 'evidence of no effect'. (See page 43 for details).
Insufficient evidence to determine	Not enough evidence to be able to determine whether an intervention is effective or not on the basis of the included studies. (See page 43 for details).

Recommendations for Screening and Assessment of Cancer Fatigue

✔	No change was made to the previous recommendation as a result of the 2015 systematic review of the evidence.
✚	The recommendation and supporting evidence were updated based on the 2015 systematic review evidence.
NEW	A new recommendation was developed based on supporting evidence from the 2015 systematic review.

Note: ✓ *Minor changes were made to the **screening and assessment** recommendations for improved clarity and consistency. The minor change also takes into account an evaluation of recommendations from high quality evidence-based clinical practice guidelines based on our most recent update in 2014.*

Recommendations for screening and assessment for CRF were conducted based on the ADAPTE methodology[24, 26-28], see detail on section B.2.1.

Screening and Assessment		Strength of Recommendation	Status
1.0 **Screening for Fatigue**	1.1 Screen for presence of cancer fatigue[24, 26-28]: • At diagnosis or first intake visit with a health provider; • Start of/throughout treatment at specific interval (e.g. Start, midpoint, and end) or with advanced disease; • Post-treatment follow-up visits; • As clinically indicated-changes in disease status or treatment. **Level of evidence:** 2A	**Expert Panel Consensus Informed by Guideline Evidence**	✔
	1.2 Screen for cancer fatigue severity using a valid quantitative measure[24, 26-28]: • Use a tool with established cut-offs for severity (i.e. Numerical Rating Scale (NRS) 0-10 for severity such as ESASr*)[88]; • Use a semi-quantitative tool (fatigue pictogram). **Level of evidence:** 2A	**Expert Panel Consensus Informed by Guideline Evidence**	✔
2.0 **Assessment of Fatigue**	2.1 Complete a focused assessment if screened positive for fatigue (Score >2 on a 0-10 NRS) to determine[24, 26-28]: • Onset, pattern and duration (acute, chronic); • Extent of interference with work, activity, mood; • Contributing factors (physical activity, other symptoms-pain, insomnia, depression;	**Expert Panel Consensus Informed by Guideline Evidence**	✔

	• Pre-existing co-morbid conditions; • Explore person's beliefs, values, and knowledge about fatigue. **Level of evidence:** 2A		
	2.2 Complete a comprehensive assessment include laboratory tests if screened positive for fatigue (Score >2 on a 0-10 NRS) to determine/treat medical causes[24, 26-28]: • Anemia; • Adrenal insufficiency; • Hypothyroidism; • Fever and/or Infection; • Nutritional deficiencies; • Testosterone levels; • Co-morbid or late effects, particularly in the elderly, (i.e. cardiovascular or pulmonary, metabolic, endocrine, or liver.) **Level of evidence:** 2A	**Expert Panel Consensus Informed by Guideline Evidence**	✔
	2.3 As a shared responsibility, the interdisciplinary team in collaboration with the patient should discuss any need for referral to specialists for further evaluation[24, 26-28]: • Cardiologist; • Endocrinologist; • Rehabilitation/physiotherapy; • Mental health professional. **Level of evidence:** 2A	**Expert Panel Consensus Informed by Guideline Evidence**	✔

*** Definitions for NCCN Categories:**The specific definitions of the NCCN categories for recommendations are *included below:*
Category 1*: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate;*
Category 2A*: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate;*
Category 2B*: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate;*
Category 3*: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.*
For the 'uniform NCCN consensus' defined in Category 1 and Category 2A, a majority Panel vote of at least 85% is required. For the 'NCCN consensus' defined in Category 2B, a Panel vote of at least 50% (but less than 85%) is required. Lastly, for recommendations where there is strong Panel disagreement regardless of the quality of the evidence, NCCN requires a vote from at least three Panel Members (representing at least three different Member Institutions) to include and designate a recommendation as Category 3. The large majority of the recommendations put forth in the Guidelines are Category 2A. Where categories are not specified within the Guidelines, the default designation for the recommendation is Category 2A.

Recommendations for the Management CRF in Adults

✔	No change was made to the previous recommendation as a result of the 2015 systematic review of the evidence.
✚	The recommendation and supporting evidence were updated based on the 2015 systematic review evidence.
NEW	A new recommendation was developed based on supporting evidence from the 2015 systematic review.

*Recommendations were made using evidence from systematic review(s) (see section B.5.2).
**Recommendations were based on at least two RCTs (see section B.5.1.)
*** Recommendations were made based on evidence-base guideline.
**** Recommendation was made based on single RCT and consensus likely to be effective (LTBE).

Pharmacological Management		Strength of Recommendation	Status
3.0 **Pharmacologic Interventions** **(see B.8 for details)**	3.1 Evidence is insufficient to recommend pharmacological agents for fatigue at any stage of disease. • Tentative trend in benefit for methylphenidate in advanced disease but safety was not confirmed to recommend use[37, 40, 48, 58] • Modafinal evaluated in brain, prostate, breast, lung cancer not superior to placebo[40, 42, 48, 79, 83] • Minimal benefit of short-term use of dexamethasone in advanced cancer[74] • CoQ10 supplementation was not superior to placebo[65]. **Level of Evidence:** Insufficient evidence*	**Strong** (Harm may outweigh benefits)	✚
	3.2 Patients should be advised that there is insufficient evidence for Paullinia cupana and certain types of ginseng products for reducing fatigue[63]. **Level of Evidence:** insufficient*	**Strong** (no benefit)	NEW
	3.3 Patients should be advised that there is no evidence for supplementation with CoQ10 for reducing fatigue[65]. **Level of Evidence:** LTBE****	**Weak**	NEW

Recommendations for Non-Pharmacological Management			
Physical Activity[1]		**Strength of Recommendation**	**Status**
4.0 **Physical Activity/Exercise** **(see B.9 for details)**	4.1 Counsel all patients as is safe to engage in moderate-intensity physical activity 55-75% for at least 30 minutes on five or more days of the week, or vigorous-intensity physical activity for at least 20 minutes on three or more days of the week (e.g. fast walking, cycling or swimming). • Progressive resistance training a minimum of three days per week is also beneficial for most patients in combination with other physical activity. • Lack of consensus on optimal exercise dose patients to guage intensity based on appropriate heart rate for age, level of previous activity. • Efficacy and safety mostly established for breast, colorectal, prostate cancer in post-treatment phases. • Likely a role for physical activity in advanced disease but optimal dose not clear and should be supervised and based on tolerance[34-36, 39, 44, 49, 51-53, 55]. **Level of Evidence:** Sufficient*	**Strong** (benefits outweigh harms)	✚
	4.2 All types of physical activity at lower levels of intensity (i.e. walking, yoga) likely will contribute to decreasing fatigue for most patients during active treatment and post-treatment survivorship [59, 68, 70, 73, 76, 80, 81]. **Level of Evidence:** High**	**Strong** (benefits outweigh harms	✚

[1] Physical activity is bodily movement produced by skeletal muscles; such movement results in an expenditure of energy (Center for Disease Prevention and Control 2012).

	4.3 Patients should be advised that there is preliminary evidence that yoga is likely to improve cancer fatigue[76, 81]. **Level of Evidence**: moderate**	**Strong**	
	4.4 A referral to a specialist in rehabilitation should be considered for cancer patients obese individuals, physically inactive patients and, those who require tailored regimes (i.e. peripheral neuropathy and pain, lymphedema)[26]. **Level of Evidence:2A*** **	**Consensus Based (strong)**	
Psychosocial/Education Interventions		**Strength of Recommendation**	**Status**
5.0 **Psychosocial/ Education Interventions** **(see B.10 for details)**	5.1 All patients are likely to benefit from routine patient education about fatigue that emphasizes self-care, coping techniques, energy, and activity management [33, 51]. **Level of Evidence**: Sufficient*	**Moderate**	✔
	5.2 Cancer services should promote access to multi-component, group psycho-education programs targeted to self-management of fatigue for patients and survivors. Components likely to be beneficial include: • Coping with emotions; • Understanding of fatigue; • Healthy sleep; • Positive peer reinforcement; • Overcoming barriers; • Opportunity to share experiences [67, 72, 81]. **Level of Evidence**: High**	**Strong**	New
	5.3 Referral to experts or fatigue clinics that are trained in cognitive behavioural therapy specifically targeted to fatigue should be offered to patients and those with chronic cancer fatigue as survivors[51, 82]. **Level of Evidence**: Sufficient*, Moderate**	**Strong**	✚

Recommendations for Complementary Therapies[2]			
6.0 **Complementary Therapies (see B.10 for details)**	6.1 Patients seeking complementary therapies in the form of herbal medicine should be advised that there is insufficient evidence demonstrating their effectiveness in reducing fatigue [30, 32, 47, 50, 54]. **Level of Evidence**: Sufficient*	**Strong**	New
	6.2 Patients should be advised that all herbal products should be used with caution as their safety may not be established and discuss their use with their oncology team as adverse effects could occur in combination with cancer treatment drugs or other drugs [30, 32, 47, 50, 54]. **Level of Evidence**: Sufficient*	**Strong**	New
	6.2 Patients should be advised that insufficient evidence is available to advise seeking Acupuncture for the treatment of fatigue [30, 47]. **Level of Evidence**: Moderate**	**Weak**	New
	6.3 Patients should be advised that there is preliminary evidence that mindfulness based interventions are likely to improve fatigue[89]. **Level of Evidence**: 2A***	**Consensus Based**	

[2] Complementary medicine interventions (i.e. yoga, acupuncture, mindfulness interventions) are defined as those used in conjunction with conventional medicine as defined by the National Institutes of Health, 2015).

Section A: Introduction

A.1 Introduction

Cancer-related fatigue (CRF) is a prevalent problem in cancer and is a side effect of treatment that often worsens during cancer treatment and can persist as a long-term problem for many patients including those in palliative care and cancer survivor populations[1, 2]. Reported prevalence rates for fatigue range from 59% to 100%[3-5]. CRF is reported as the most distressing side effect of cancer and treatment and causes greater interference with daily life than any other symptom[6, 7]. CRF also impacts on personal, social, work roles and it can have a profound negative impact on overall quality of life (QoL)[8-12]. Because its etiology is not well understood, it is frequently unrecognized and is difficult to manage in clinical practice[13].

In 2011, the Canadian Association of Psychosocial Oncology released its first pan Canadian guideline entitled, A Pan Canadian Guideline for Screening, Assessment, and Management of Cancer-Related Fatigue[27]. A concise summary of the recommendations was also produced in the form of a two-page Clinical Practice Algorithm to guide clinicians in the application of screening, assessment and management of CRF as part of routine oncology practice. This algorithm provides guidance on fatigue based on severity levels of mild (0-3), moderate (4-6) and severe (7-10) using a 0-10 Numerical Rating Scale (NRS) for symptom severity. In 2014, an expert interdisciplinary panel was convened to update the empirical evidence and adapt, revise and/or develop new recommendations for screening, assessment, management of CRF based on a review of current guidelines in the field and a systematic review of new literature published between January 2009 through November 2014.

A.2 Guideline Scope

Similar to the 2011 guideline, the scope of this 2015-Version 2 of the CRF guideline is focused on the provision of clinical practice recommendations for members of oncology interdisciplinary team (e.g. primary care physicians, oncologists, nurses, physiotherapist, occupational therapists, rehabilitation specialists), who screen, assess, and manage CRF in their daily clinical practice. Additionally, the recommendations may also help patients and families learn about the most effective strategies for managing CRF. The recommendations apply to those with CRF across the cancer trajectory, from cancer treatment to post-treatment survivorship and palliative or end-of-life care. The guideline is focused on the adult cancer population with fatigue due to cancer and/or cancer treatment.

A.3 Guideline Objective

The objective of this guideline is:

To improve the quality and consistency of the screening, assessment and management of CRF across the cancer trajectory in adults (≥18 years of age).

A.4 Research Questions

1. What are the current guideline recommendations for routine screening and assessment of CRF in adults?

2. What is the efficacy of interventions (pharmacological, non-pharmacological, and/or combinations) for reducing CRF in adults?

A.5 Definition for Cancer-Related Fatigue

The expert panel adopted the National Comprehensive Cancer Network (NCCN) definition of CRF, which states that cancer-related fatigue is a "distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" [89].

A.6 Intended Users

The intended users of this guideline are the primary oncology interdisciplinary team, and community practitioners such as family physicians and palliative care teams. The recommendations are intended to also be relevant to specialists in fatigue including psychology and psychiatry, and other members of the allied health care team (occupational therapists, rehabilitation specialists, physiotherapists) who provide counselling to patients in the management of cancer-related fatigue. Patients and their families may also find this guideline useful for understanding the current recommendations and evidence for management for cancer and/or treatment related fatigue.

A.7 Setting for Use of this Guideline

The recommendations in this guideline are intended for use in settings that provide active treatment, survivorship support, and palliative care. This guideline should be used in conjunction with recommendations for the management of other symptoms that are often experience concurrently with CRF (i.e. sleep, depression, pain).

Section B: Methods

B.1 Objectives and Research Questions

B.1.1 Objective

To improve the quality and consistency of the screening, assessment and management of CRF across the cancer trajectory in adults (≥18 years of age).

B.1.2 Research Question

1. What are the current guideline recommendations for routine screening and assessment of CRF in adults?

2. What is the efficacy of interventions (pharmacological, non-pharmacological, and/or combinations) for reducing CRF in adults?

B.2 Methods and Results

B.2.1 Methods-Screening and Assessments for CRF

Recommendations for screening and assessment for CRF were identified based on the application of the ADAPTE methodology[90, 91], a rigorous 24 step method for adapting knowledge from existing guidelines following a quality appraisal in accordance with the AGREE II convention[92]. The ADAPTE methodology is a systematic process for adapting recommendations in existing guidelines to create high quality guidelines tailored for use in a specific health care context[91, 93].

The adaptation process began with a systematic literature search to identify candidate guidelines for adaptation. The systematic search of clinical practice guideline databases, guideline developer websites, and published health literature was conducted to identify clinical practice guidelines, systematic reviews, meta-analyses, and other guidance documents addressing the screening, assessment, and care of cancer-related fatigue. The quality of guidelines identified either through grey literature or empirical data base searches were assessed by two reviewers (DH) and (HK) for this guideline. Recommendations from guidelines with rigor graded as greater than 50% were adapted or were used to clarify or refine recommendations from the original CAPO fatigue guideline of 2011. The recommendations were approved by the National Expert Fatigue Panel using an adapted Delphi consensus method by telephone or email vote.

B.2.2 Methods-Management for CRF

Our aim was to update a 2011, previous version of Pan-Canadian Practice Guideline: Screening, Assessment and Care of Cancer Related Fatigue in Adults with Cancer[27]. We developed a three-step approach:

B.2.2.1 Sources of Evidence:

1) We searched for existing evidence-based guidelines on screening, assessment, and management of CRF from 2009 to Nov 2014. We selected any guideline published since version 1 of the 2011 guideline. We compared their recommendations to version 1 of the 2011 guideline. For screening and assessment of CRF, we adopted the new recommendations, if any, not included in version 1 of the 2011 guideline after reviewing the quality of the guidelines. If there were no new recommendations in these guidelines, we adopted previous recommendations from version 1 of the 2011 guideline on screening and assessment of CRF. The adopted recommendations may have been refined to ensure substantive statements of recommendations were clear and concise.
2) We performed a systematic search for systematic reviews to identify new evidence from 2009 to 2014, and adopted, updated or developed new recommendations based on the level of evidence identified and quality of the reviews accordingly. We included all relevant systematic reviews of Randomized Control Trial (RCT) that evaluated the effects of any pharmacological and/or non-pharmacological intervention on the management of fatigue in adults with all types of cancer from 2009 to November 2014. We then used the search-end date reported in these systematic reviews to search for new RCTs published, basing our search start date on the last search year of the latest systematic review.
3) We performed a systematic search of RCTs identified beyond the *search-end date* reported in the updated systematic reviews (i.e. not included in systematic reviews identified in the previous step). Our search dates for RCTs covered from 2013, the last year searched in previous systematic reviews up to present date of November 2014 (Figure B.2.2.1.1).

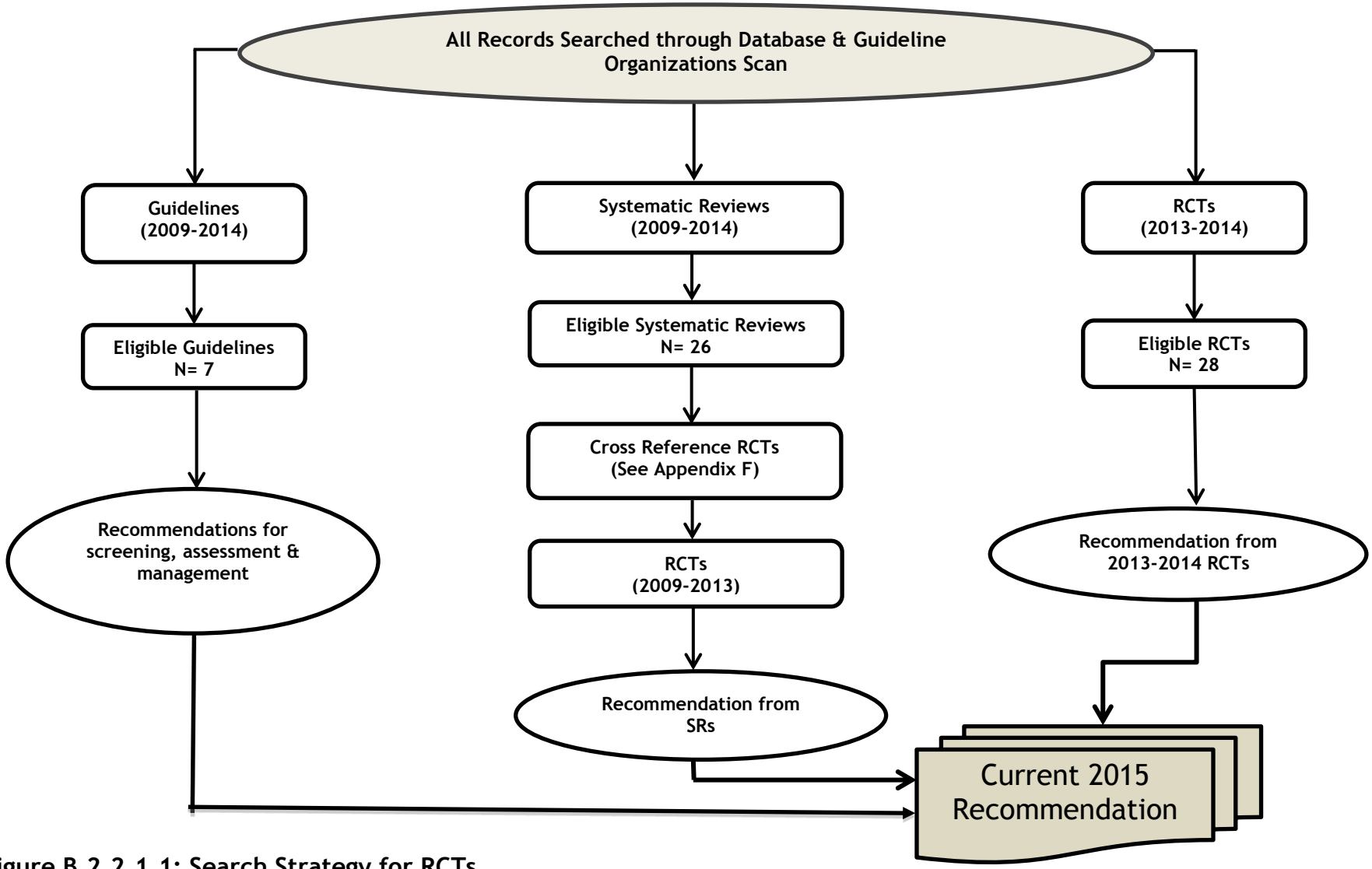

Figure B.2.2.1.1: Search Strategy for RCTs

B.2.2.2 Literature Search Strategy

For the evidence-based guidelines and systematic reviews, the search strategy was limited to studies published from 2009, to November 23, 2014. A systematic search of existing RCTs was performed since 2013 (last year searched according to the included systematic review) to November 23, 2014, where gaps were found to exist in the coverage of the systematic reviews.

The following electronic bibliographic databases were searched: MEDLINE®, Cochrane Central®, PsychINFO, Cochrane Database of Systematic Reviews, EMBASE®, and CINAHL®. The strategies used combinations of controlled vocabulary (medical subject headings, keywords) and text words. Appendix A Table A.1 details the search strategies used to capture relevant citations.

Review of reference lists of eligible studies at full text screening was performed for relevant citation. Any potentially relevant citations were cross-checked with our citation database and any that were new were retrieved and screened at full text.

In addition, a targeted environmental scan of international guideline developers and key organizations for evidence-based clinical practice guidelines, systematic reviews and ongoing trials was conducted (September, 2014) for documents about CRF. A listing of the organizations that were examined is given in appendix A Table A.2.

B.2.2.3 Study Selection Criteria [Inclusion and Exclusion Criteria (PICO)]

Types of Participants (P)

Adults (aged 18 and over) with a clinical diagnosis of cancer known to have clinically significant fatigue score >3 (moderate or severe fatigue) on a 0-10 Numeric Rating Scale or comparable scale with established cut-offs at any stage and at any point of the cancer treatment spectrum, including those undergoing curative treatment, those with advanced disease receiving palliative care, and disease-free post-cancer treatment survivors. Studies with populations without a diagnosis of any type of cancer, or did not experience clinically significant fatigue were excluded.

Types of Interventions (I)

Any pharmacological and any non-pharmacological (psychosocial, CBT, psycho-education or education, mindfulness meditation, yoga, exercise/activity, complementary medicine) interventions for the management of CRF in adult patients.

Types of Comparator (C)

Comparison condition is usual care, attention control or other comparator. Studies comparing drug treatment versus no drug treatment or versus alternative drug treatment, or both were also included.

Types of Outcomes (O)

Outcomes (either primary or secondary) included:

1) Clinically significant improvement in fatigue or
2) Clinically significant reduction in CRF (measured by severity) or
3) Differences in fatigue severity between intervention group and controls using self-reported outcome measures

Outcomes excluded:

1) Fatigue measured during the diagnostic period prior to cancer treatment;
2) Fatigue is not the outcome;
3) No validated measure of fatigue

Types of Studies

We included evidence-based guidelines based on systematic review evidence, systematic reviews, and RCTs of interventions with cancer related fatigue as a (primary or secondary) outcome.

Studies excluded:

Publications that were not RCTs, narrative reviews, or guidelines not based on systematic review evidence were excluded. Similarly, editorials, commentaries and student thesis were excluded.

Timing

There were no restrictions on study eligibility with respect to a minimum treatment interval or follow-up post treatment.

Settings

Studies that recruited patients from primary care, outpatient, and inpatient oncology, and palliative care settings were included. There were no exclusions for study setting.

Language Criteria:

All publications were in English. Non-English citations were excluded.

B.2.2.4 Selection of Clinical Practice Guideline (CPG)

We defined CPG as "systematically developed statements about specific clinical problems intended to assist practitioners and patients in making decisions about appropriate health care"[94]. We included full guidelines and consensus statements but we excluded algorithms with no background or description of the process by which the algorithm was developed, lay information, clinical knowledge summary or articles about guidelines.

B.2.2.5 Selection of Systematic Reviews (SR) and primary SR from overlapping SR

There is always the problem of having more than one systematic review that overlaps with respect to the research question and included studies. A method to remove redundant and overlapping reviews has been suggested[95]. Systematic reviews that are more recent and likely to include additional publications (relative to older systematic reviews) are preferred. Similarly, systematic reviews that are of poor methodological quality can be removed from data extraction; this would be the case if the intervention or outcomes of interest are captured in other eligible reviews. We adopted 5 steps to facilitate reasoned decision making by authors on incorporation of existing systematic reviews. We adopted a previously proposed systematic process of which the steps are depicted below (see Figure B.2.2.5.1)[95].

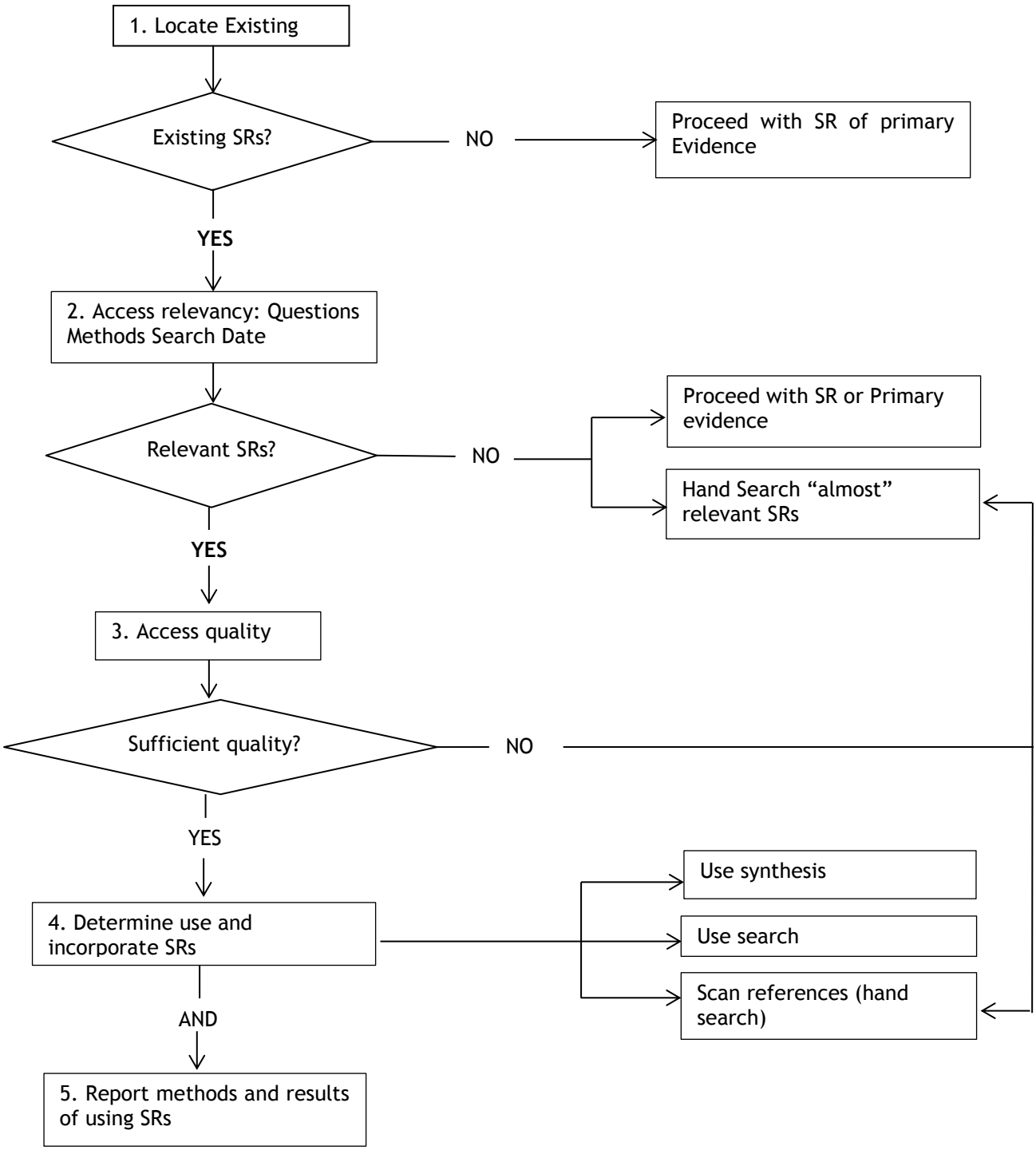

Figure B.2.2.5.1: Selection Process of Systematic Reviews

B.2.2.6 Assessment of Study Eligibility

Five reviewers (JY, RT, MW, CW, SR) working independently and in duplicate, screened all titles and abstracts and, upon retrieval of candidate studies, three team members (JY, RT, MW) reviewed the full text to determine eligibility. If the study was eligible, data were abstracted by JY and SR. Any questions arising during data abstraction were resolved by discussion with other team members.

B.2.2.7 Data Extraction and Management

Through an iterative process, we created a standardized form to extract descriptive, methodological and key variables from all eligible studies. Distiller (Ottawa, Ontario), an online reference management system for systematic reviews, was used to manage study selection and data extraction. Relevant fields of information were extracted from individual studies by trained data extractors using standardized forms and a reference guide. Prior to performing the data extraction, a calibration exercise was undertaken using a convenience sample of five included studies (RCTs and SRs). We collected data on study design, population, demographics, inclusion and exclusion criteria, measurement tool, intervention, and analytical technique. Data were tabulated and categorized according to the type of intervention. Key study elements were reviewed by a second person study investigator (DH) and methodologist (HK) (with respect to study outcomes, population characteristics, interventions, definition of prior "cancer related fatigue"), and characteristics of the intervention and outcome. Disagreements were resolved by consensus. We categorised included studies into pharmacological and non-pharmacological interventions (psychosocial and education, physical activity/exercise, and complementary medicine). Appendix E shows title and abstract, full text, and data abstraction forms.

B.3 Assessment of Methodological Quality Guidelines, Systematic Reviews and Randomized Clinical Trials

We addressed three different quality assessments:

1) We used the AGREE II to assess the variability in the quality of the guideline process[14].

2) We used AMSTAR (Assessment of Multiple Systematic Reviews) to assess the methodological quality of the systematic review[15]. AMSTAR assesses the degree to which review methods avoided bias by evaluating the methods against 11 distinct criteria, including:

1. Use of an 'a priori' design;
2. Duplicate study selection and data extraction;
3. Comprehensive searching of the literature;
4. Use of publication status as an exclusion criterion;
5. Provision of (included and excluded) studies;

6. Provision of characteristics of included studies;
7. Assessment of methodological quality of included studies;
8. Appropriate use of quality of included studies in formulating conclusions;
9. Appropriate methods for combining results of studies;
10. Assessment of publication bias; and
11. Conflict of interest (both review and included studies) stated

Each AMSTAR item was rated as yes (clearly done), no (clearly not done), can't answer, or not applicable, based on the published review report. A review that adequately met all of the 11 criteria was considered to be a review of the highest quality. Quality rating was as follows:

AMSTAR score (out of 11 criteria)	Rating
8 to 11	high quality
4 to 7	moderate quality
3 or lower	low quality

3) We selected the Risk of Bias Tool by the Cochrane Collaboration[16] to assess RCTs. The tool contains 12 items that include evaluation of the domains of randomization, blinding, co-intervention, and selective outcome reporting biases. Criteria for evaluation are standardized for these domains. Inconsistency amongst raters was minimized by providing adequate training and standardized instructions; disagreements were resolved by consensus. All tools can be viewed in Appendix E.

B.4 Quantitative Synthesis:

To perform meta-analysis, outcome measurement at the end of intervention or immediate post-treatment data (mean, standard deviation) was utilized for continuous outcome measures. The DerSimonian and Laird random effects models with inverse variance method were utilized to generate the summary measures of effect in the form of SMD for continuous outcomes[17]. The SMD was used as a summary statistic because the studies in this systematic review often assessed the same outcomes measured in a variety of ways (i.e., various studies measured CRF but they used different outcome measures such as BFI, MSFI, FACT-F, PFS etc.). In this situation, it was necessary to standardize the results of the studies before they could be compared across studies or combined in a quantitative synthesis. SMDs were calculated using change from baseline data, i.e. mean difference between pre-treatment (baseline) and post-treatment (final/end-point) scores along with its standard deviation for both intervention and control groups. The SMD effect sizes with scores of 0.2–0.5, 0.5–0.8, and >0.8 were considered as small, medium, and large effects, respectively[18]. The studies, where SD was not reported, we calculated the SD from the reported SE of the mean, or 95% CIs using the equations provided in Chapter 9 of the Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane's Q (α=0.10) and I2 statistic were employed to quantify the statistical heterogeneity

between studies, where p<0.10 indicates a high level of statistical heterogeneity between studies. The analyses were performed using Review Manager Version 5.1 software. For studies not included in the meta-analyses, findings are described narratively in the text[17, 19]. Additionally, we grouped study results: 1) according to the type of treatment categories and the corresponding comparator treatment; 2) the specific grouping of the pharmacological treatment and, 3) nonpharmacological treatment. Forest plots and summary tables were generated to display primary study outcomes of fatigue severity.

Summary tables were created for systematic reviews and CPGs stratified by country of origin, where possible.

B.5 Rating the Body of Evidence

B.5.1 Grading of Recommendations on Randomized Controlled Trials

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to determine the quality of evidence and strength of recommendations for each important outcome. GRADE has advantages over other. Advantages include: developed by a widely representative group of international guideline developers, explicit and comprehensive criteria for downgrading and upgrading quality of evidence ratings, clear separation between quality of evidence and strength of recommendations that includes a transparent process of moving from evidence evaluation to recommendations, clear, pragmatic interpretations of strong versus weak recommendations for clinicians, patients and policy-makers, explicit acknowledgement of values and preferences, and explicit evaluation of the importance of outcomes of alternative management strategies.

Once the systematic review of RCTs was available from the evidence review team, the internal panel review independently developed the recommendation statements by consensus, based on a detailed review of the evidence. In formulating recommendations, panel review considered both the benefits and harms associated with pharmacological and or non-pharmacological treatment, patient values and preferences, the quality of the evidence and, in some cases, the costs of the intervention (see Text Box 1 below). The strength of evidence is determined using the GRADE system[85-87] and the draft recommendations developed by the review panel were revised and approved by external expert reviewers.

Text Box 1: Grading of Recommendations
Recommendations are graded as either strong or weak according to the Grades of Recommendation Assessment, Development and Evaluation system (GRADE). GRADE offers two strengths of recommendation: strong and weak. The strength of recommendations is based on the quality of supporting evidence, the degree of uncertainty about the balance between desirable and undesirable effects, the degree of uncertainty or variability in values and preferences, and the degree of uncertainty about whether the intervention represents a wise use of resources.
Evidence is graded as high, moderate, low or very low based on how likely further research is to

change our confidence in the estimate of effect.			
Category Quality	**Definitions**	**Strong Recommendation**	**Weak Recommendation**
High Quality Evidence	Further research is very unlikely to change our confidence in the estimate of effect.	The work group is confident that the desirable effects of adhering to this recommendation outweigh the undesirable effects. This is a strong recommendation for or against. This applies to most patients.	The work group recognizes that the evidence, though of high quality, shows a balance between estimates of harms and benefits. The best action will depend on local circumstances, patient values or preferences.
Moderate Quality Evidence	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	The work group is confident that the benefits outweigh the risksbut recognizes that the evidence has limitations. Further evidence may impact this recommendation. This is recommendation that likely applies to most patients.	The work group recognizes that there is a balance between harms and benefits, based on moderate quality evidence, or that there is uncertainty about the estimates of the harms and benefits of the proposed intervention that may be affected by new evidence. Alternative approaches will likely be better for some patients under some circumstances.
Low Quality Evidence	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change. The estimate or any estimate of effect is very uncertain.	The work group feels that the evidence consistently indicates the benefit of this action outweighs the harms. This recommendation might change when higher quality evidence becomes available.	The work group recognizes that there is significant uncertainty about the best estimates of benefits and harms.

B.5.2 Grading of Recommendations on Systematic Reviews

We used standardised 'effectiveness statements' to rate the evidence obtained from reviews, using a further synthesis step that aims to extend a simple summary of the main results of each review. These statements were based on the rating scheme developed by the Cochrane Consumers and Communication Review Group (CC&CRG) to guide synthesis and rating of evidence across systematic reviews with complex and diverse intervention[20-22]. See the table below for a full explanation of the terms used and how these definitions were applied to developing effectiveness statements for statement of recommendations. Using standardized language and a set of decision rules that take into account results of the review, statistical significance and the quality and number of studies on which the results are based, the effectiveness

statements give bottom-line statements about the main effects of interventions assessed within each intervention category[84] (see Table B.5.2.1).

Table B.5.2.1: Terms and definitions used to formulate standardised effectiveness statements to rate evidence from reviews, adopted from Ryan,2014[84]

Summary statement	Translation
Sufficient evidence	Evidence to make a decision about the effect of the intervention(s) in relation to a specific outcome(s). This includes evidence of an effect in terms of (i) benefit or (ii) harm. Statistically significant results are considered to represent sufficient evidence on which to base decisions, but a judgement of sufficient evidence is also made based on the number of studies/participants included in the analysis for a particular outcome. A rating of sufficient evidence is often based on meta-analysis producing a statistically significant pooled result that is based on a large number of included studies/participants. This judgement may also be made based on the number of studies and/or study participants showing a statistically significant result – for example (in a narrative synthesis) a result where 12 studies of a total of 14 for a specific outcome showed a statistically significant effect of an intervention would be considered to represent sufficient evidence.
Some evidence	Less conclusive evidence to make a decision about the effects of a particular intervention(s) in relation to a specific outcome(s).This may be based on narrative syntheses of review results. In this case, the result is qualified according to the findings of the review - for example, 'some evidence' (5 studies of 9) reported a positive effect for all types of physical activity and exercise (this would be based on a more equivocal set of results than those obtained for 'sufficient evidence' above. For example, while 12/14 statistically significant studies would be classed as 'sufficient evidence', 5/9 statistically significant studies is more equivocal and would be classed as 'some evidence'). This may also be based on a statistically significant result obtained in a small number of studies; a statistically significant result obtained from studies with a small number of participants; or a statistically significant result obtained from studies of low quality.
Insufficient evidence	Not enough evidence to support decisions about the effects of the intervention(s) on the basis of the included studies. This should be interpreted as 'no evidence of effect', rather than 'evidence of no effect'. Statistically non-significant results are considered to represent insufficient evidence. Where the number of studies is small, and/or the number of participants included in the studies is small, insufficient evidence might reflect under powering of the included studies to be able to detect an effect of the intervention. Where the number of studies is large, and/or the number of participants included in these studies is large, 'insufficient evidence' may reflect underlying ineffectiveness of the intervention to affect the outcomes being examined. In such cases the intervention may additionally be described as 'generally ineffective' in order to separate such results from those cases where insufficient evidence is used to describe results but this is based on a small number of studies and/or participants (where non-significant results may reflect under powering of studies rather than ineffectiveness).
Insufficient	Not enough evidence to be able to determine whether an intervention is

evidence to determine	effective or not on the basis of the included studies. This statement is about reporting gaps in the evidence (i.e. where there are too few studies to be able to determine effects), rather than the situation of the summary statement above, which is about ineffectiveness (e.g. several studies reporting a statistically non-significant result). It is likely to arise when the numbers of included studies is very small.

B.6 Publication Bias

Although our search strategy is comprehensive and includes a grey literature search including sources for unpublished trials, there is still potential for publication bias. Publication bias is important to assess in reviews with the use of drugs (pharmacological section), as there is evidence to suggest that industry sponsorship may lead to negative trials not being published[96], that reporting of adverse events are more favorable to clinician[97], and that there may be delay in publication of negative findings[98].

B.7 Results

We identified 6[23-28] clinical practice guidelines in 7 publications[23-29], 26[30-55] unique systematic reviews and 28[56-83] randomized clinical trials in this practice guideline. We categorized systematic reviews by pharmacological and non-pharmacological interventions. We sub-grouped non-pharmacological interventions into the following categories: 1) educational and psychosocial; 2) physical activity/exercise; 3) complementary. (See PRISMA diagram in appendix A, Figure A.1)

B.7.1. Clinical Practice Guidelines

We defined CPG as "systematically developed statements about specific clinical problems intended to assist practitioners and patients in making decisions about appropriate health care"[94]. We included full guidelines and consensus statements if their was an explicit process identified that summarized the evidence that contributed to the statement of recommendation.

There were a total of 6[23-28] CPGs sponsored by unique organizations and described in 7 publications[23-29]. Table B.1 in appendix B shows the characteristics of the CPGs as a function of country of origin, scope, and intended users.

B.7.1.1 Quality Assessment of CPGs for CRF

Table B.7.1.1.1 shows the domain scores for the AGREE II ratings of the CPGs for CRF. The AGREE II is based on six domains of methodology for the guideline process and one item with an overall assessment.

All CPGs scored high for *scope and purpose* (Domain 1) (range 67 to 100 percent). *Stakeholder involvement* (Domain 2) showed scores varying from 33 to 100 percent, and the lowest score was for a CPG sponsored by Harris[24]. For the domain of *rigor of development* (Domain 3), scores varied from 52 to 86 percent; all indicated a process for updating the guideline. For the domain of *clarity of presentation* (Domain

4), scores were generally high and varied from 69 to 100 percent. This domain evaluated whether the recommendations were clear and unambiguous, such that options were clearly presented, and key recommendations easily identifiable. However, the scores for the items within this domain were based on all recommendations within the CPG and were not specific to those applicable to patients who failed to respond to antidepressants. When considering the *applicability* domain (Domain 5), scores were highly variable from 0 to 58 percent. The majority of CPGs scored poorly for two criteria within this domain: 1) consideration of potential resource implications of applying their recommendations, and 2) presenting monitoring or auditing criteria. For the domain regarding *editorial independence* (Domain 6), scores were generally highly variable except for one[26] and ranged from 58 to 100 percent. Most systems of grading the strength of the evidence included aspects of study design, number of studies, or confidence of treatment; most included a level that reflected consensus or expert opinion for some recommendations. Potential competing interests of the guideline development group were not consistently recorded. Note that although the AGREE II evaluates the methodology of the guideline process, it cannot evaluate the clinical merit (taking into account the methods for summarizing the evidence).

Table B.7.1.1.1: The AGREE II Ratings for the 6 domains in CPG applicable for Cancer-Related Fatigue in Adults

Author	Organization	Scope and Purpose (Domain 1)	Stakeholder Involvement (Domain 2)	Rigor of Development (Domain 3)	Clarity of Presentation (Domain 4)	Applicability (Domain 5)	Editorial Independence (Domain 6)
Simoff,2013[23]	American College of Chest Physicians(ACCP)	100%	94%	52%	72%	21%	100%
Harris,2012[24]	American Cancer Society	67%	33%	44%	94%	0%	100%
Schmitz,2010[25]	American College of Sports Medicine	94%	100%	86%	100%	58%	100%
NCCN,2014[26]	National Comprehensive Cancer Network (NCCN)	94%	94%	79%	100%	21%	58%
Howell,2011[27]	Canadian Partnership Against Cancer (CPAC) and Canadian Association of Psychosocial Oncology (CAPO)	83%	89%	67%	69%	25%	100%
Bower,2014[28]	American Society of Clinical Oncology	100%	100%	62%	100%	31%	96%

**Note that the recommended number of reviewers ranges from two to four; however, if two independent reviewers are consistent in their scoring, no further review is necessary.*

B.7.1.2 Supporting Evidence for Screening in Guidelines

Four out of six guidelines reviewed were consistent in making a recommendation that all cancer patients should be screened for presence and severity of fatigue using a valid, quantitative or semi-quantitative (mild, moderate, severe) measure and established cut-off points for differentiating between mild, moderate and severe levels of fatigue. Additionally, all of the guidelines made recommendations that a Numerical Rating Scale (0-no fatigue to 10-worst fatigue) provided an appropriate screen for fatigue severity and if the score was moderate to severe fatigue[26-28] that a focused and comprehensive assessment of contributing factors should be completed. All guidelines made very similar recommendations that all patients should be screened for fatigue at intervals throughout treatment and this should include regular screening of post-treatment survivors in follow-up care and those with advanced disease receiving palliative or end of life care. For most of the guidelines a specific review of evidence of the effectiveness of screening as an intervention was not completed. However, given the prevalence and impact of cancer fatigue on the daily functioning of cancer patients and their overall quality of life and adaptation to treatment, the expert panel reached consensus that recommendations for screening were essential to be included in the 2015 revision of the CAPO fatigue guideline. The recommendations are similar to those in the 2011 guideline but we did make some refinements to the statements of recommendations to ensure consistency with other guidelines and to enhance clarity. Most of the guidelines suggested further assessment should follow a positive screen for moderate or severe fatigue[26-28] whereas other suggested this next step be taken if fatigue was present and reported as mild[28]. The NCCN[26] has designated a two-step process of screening for presence of fatigue followed by an assessment of severity, whereas most others use a numerical rating scale to screen for presence and severity of fatigue. The following recommendations for screening are identified for this guideline based on expert opinion of the panel and informed by recommendations made in other guidelines reviewed[24, 26-28].

B.7.1.3 Supporting Evidence for Assessment in Guidelines

Four guidelines made recommendations for assessment of fatigue that included assessment of a wide range of contributing factors, medical history and laboratory evaluation. The components of the assessment were similar across guidelines with some guidelines stating a strong recommendation for fitness testing and review of patient activity levels. All of the guidelines recommended including assessment of patients current disease status, type and length of treatment, capacity to induce fatigue, patient's response to treatment, organs affected by fatigue, onset, pattern, duration, change over time, associated or alleviating factors, and interference with function. Contributing factors such as, anxiety, sleep disturbance, nutrition, activity level, medication, alcohol/substance abuse, anemia and comorbidities should also be assessed and documented[24, 26-28].

B.7.2 Systematic Reviews

We identified 26 unique systematic reviews in this practice guideline and these are described in table C.3, C.4, C.5 and C.6,in appendix C by type of intervention in adults with CRF[30-55]. We further categorized included systematic reviews by pharmacological and non-pharmacological interventions. We sub-grouped non-pharmacological interventions into the following categories: 1) educational and psychosocial; 2) physical activity/exercise; 3) complementary. We describe these systematic reviews including their quality rating by intervention type, in detail. Two review authors (DH, HK) independently assessed the methodological quality of included systematic reviews using the AMSTAR instrument[15, 18]. Differences were resolved by discussion to reach consensus.

We did not extract data from reviews with considerable overlap in objectives and scope, or those with serious methodological flaws and poor quality (rating of less than 4 of possible 11 points) using the AMSTAR assessment tool[15, 18].

B.7.3 Randomized Clinical Trials (RCTs)

Applying our eligibility criteria led to the inclusion of 28 randomized clinical trials[56-83] describing the results of intervention for the management of CRF. We further categorized included RCTs by pharmacological and non-pharmacological interventions. We sub-grouped non-pharmacological interventions into the following categories: 1) physical activity/exercise; 2) education and psychosocial interventions including CBT and 3) complementary. We describe these RCTs including their quality rating by intervention type in detail. Each included trial was independently assessed for risk of bias using the criteria described in the Cochrane Hand-book version 5.1.0[19] by the authors with any disagreements resolved by discussion or consultation to the third party.

B.8. Characteristics of Eligible Studies on Pharmacological Interventions

A total of 9 reviews met our inclusion criteria and were incorporated in the review[31, 35, 37, 40-42, 44, 48, 55]. From those reviews two[31, 41] reviews were not extracted data from reviews with considerable overlap in objectives and scope, or those with serious methodological flaws and poor quality (rating of less than 4 of possible 11 points) using the AMSTAR assessment tool. Table C.3 in appendix C shows characteristics of eligible reviews.

B.8.1 Methodological Quality of Included SRs

All seven reviews are considered of high quality (AMSTAR ≥8). See Table C.1 for the AMSTAR rating of the included SRs in Appendix C.

B.8.2 Results of Included Systematic Reviews

A high quality Cochrane review focused on pharmacological therapy for the management of cancer related fatigue and included randomized controlled trials published between January 2007 and 2009 with comparsions of placebo, usual care, or non-pharmacological intervention in adult patients[42]. Of the 50 RCTs that met inclusion criteria, 31 studies with robust measures of fatigue involving a total of n=7104 patients was included in the analyses. Studies were analysed by drug class including psychostimulants (methylphenidate, modafinil), haemopoietic growth factors, and antidepressants. There was a high degree of statistical and clinical heterogeneity in the trials. Of the drugs studied, methylphenidate showed a trend in benefit in fatigue over placebo in a few RCTs with small sample sizes and in one large trial a small treatment effect compared to placebo was shown, primarily in those with advanced disease. However, the author suggested that widespread use was not recommended and large scale RCTs are still required to confirm preliminary results and establish effectiveness of methylphenidate for management of cancer-related fatigue. Recent safety data point to increased adverse side effects with methylphenidate (e.g. vertigo, anxiety, nausea) and close monitoring in those with advanced. Side effects were also associated with haemopoietic growth factors and as such they are not recommended for treatment of cancer related fatigue[42]. Another Cochrane review on pharmacological treatments for fatigue associated with palliative care (search date up to June 2009), identified two studies that tested methylphenidate in patients with advanced cancer, both showing slightly superior effect compared to placebo[40]. In a 2011 systematic review and meta-analysis[37] of the effect of psychostimulants for the management of cancer related fatigue, 5 studies involving n=426 patients were identified including 4 which assessed of methylphenidate and one that assessed dexamphetamine. The review points to limitations of included studies particularly their small sample size, considerable clinical heterogeneity, differences in patient populations and treatment duration, that preclude firm conclusions regarding the effectiveness of psychostimulants in cancer-related fatigue. However, a trend is observed in the majority of the studies towards benefit of methylphenidate for management of cancer related fatigue[37]. A similar and more recent systematic review and meta-analysis[48] focusing on the effect of methyphenidate in patients with cancer-related fatigue, identified 5 RCTs involving n=498 patients with different types of cancer. A more recent review of methylphenidate, showed some improvement in fatigue, but recommended that the evidence was tentave and provisional with better outcomes observed with prolonged duration of treatment[48]. However, further confirmation in larger trials needed before recommending this treatment and the safety of use is not established.

In a 2014 systematic review[55] of RCTs for management of persistent post-treatment fatigue in thyroid cancer survivors, 1086 citations and 25 full text papers were reviewed and 4 papers reporting results of 3 RCTs were included. Trial duration ranged from 10 weeks to 6 months. Two of the RCTs tested pharmacological (exogenous hormonal) interventions in thyroidectomized thyroid cancer survivors on

levothyroxine treatment, including: a) the comparison of combination levo-tri-iodothyronine with levothyroxine compared to levothyroxine alone in a secondary analysis of cross-over design trial and b) reduction in the degree of thyrotropin suppression by reduction of levothyroxine dosage, compared to maintenance of TSH (thyroid-stimulating hormone) suppression in a parallel design trial[55].

Conclusion: Existing reviews on pharmacological interventions are largely heterogeneous with small samples and do not offer robust data for firm conclusions about the effectiveness of various drug classes for management of cancer-related fatigue. The majority of studies of pharmacological interventions have examined psychostimulants, in particular, methylphenidate. They suggest that this drug may be effective in the management of cancer-related fatigue. However, caution has been raised to restrict their use to patients with advanced cancer on active treatment for short time periods and with close monitoring and supervision of physicians with expertise in its use. No class of pharmacological interventions show robust evidence for effectiveness in treating cancer related fatigue.

B.8.3 Results from RCTs

We identified 9 RCTs examining the effectiveness of various pharmacological interventions including modafinil, methyphenidate, hormone therapy, dexamethasone, and antioxidant co-enzyme Q10 compared to usual care and placebo. Table D.3 in appendix D shows characteristics of included RCTs on Pharmacological interventions.

Modafinil

We identified 8 RCTs testing efficacy of pharmacological interventions on cancer-related fatigue. Three of these evaluated the efficacy of the psychostimulant modafinil in the management of fatigue in patients with cancer. We pooled the results of two of these studies[79, 83], the third[57] was not included due to heterogeneity and small sample size. Pooled results of two placebo-controlled double-blind RCTs with a pooled sample of 291 patients showed modafinil to have no effect on cancer-related fatigue. The third RCT involving 37 patients also showed no effect of modafinil compared to placebo on fatigue, depression or health related quality of life[57] (see Figure B.8.4.1).

Methyphenidate

Two RCTs assessed efficacy of methylphenidate versus placebo for cancer-related fatigue reduction[58, 77]. One evaluated a 4-week methylphenidate-placebo or placebo-methylphenidate intervention on n=38 patients with breast cancer. Low-dose methylphenidate did not lead to an improvement in cancer-related fatigue[77]. The second study involving n=141 patients with advanced cancer assessed efficacy of methylphenidate versus placebo as well as the effect of a combined intervention including methylphenidate plus a nursing telephone intervention. There were no

significant differences improvement in fatigue between the two groups receiving methyphenidate or placebo[58] (see Figure B.8.4.1). Clinically, the use of psychostimulants (e.g. modafinil, methylpenidate) must balance expected harms against unproven benefits. Treatment decisions for individual patients must consider performance status, and the intent and duration for any treatment considered.

Hormone therapy

One RCT evaluated the efficacy of abiraterone acetate on CRF in n=797 patients with castration-resistant metastatic prostate cancer who were randomized to treatment with either abiraterone acetate and prednisone or placebo and prednisone. In patients with clinically significant fatigue at baseline, abiraterone acetate and prednisone yielded clinically meaningful improvement in fatigue compared to prednisone alone[71]. It is uncertain if this improvement was dependent upon the superior reduction of tumour burden and/or disease progression with abiraterone and prednisone compared with placebo and prednisone[71]. Results cannot be extrapolated beyond the study population, since abiraterone is an active agent in management of this cancer.

One double-blind placebo-controlled RCT assessed the effect of testosterone replacement for fatigue in 29 hypogonaldal men with advanced cancer. Four weeks of testosterone replacement did not lead to significant improvement in cancer-related fatigue[62].

Dexamethasone

One RCT evaluated the effect of dexamethasone versus placebo on cancer-related fatigue in n=84 men and women with advanced cancer who had three or more CRF-related symptoms that were at least moderate in severity (i.e. fatigue, nausea, loss of appetite, pain, depression, anxiety, or sleep disturbance). Patients were randomly assigned to dexamethasone 4 mg twice per day for 14 days or placebo. Dexamethasone was more effective than placebo in improving cancer-related fatigue, on the FACIT-F (Functional Assessment of Chronic Illness Therapy-Fatigue) subscale and FACIT-F total quality of life subscale in patients with advanced cancer at 15 days[74]. Long-term outcomes (on fatigue or effect on co-morbidities) using this approach are not known, but long-term use of this high-dose corticosteroid is associated with potiential patient harms. An important limitation of the study was that adrenal insufficiency was not ruled out prior to the study, so it is possible that some of the patients' symptoms and hence response to treatment, may have been related to a therapeutic response to treatment of cortisol deficiency.

Antioxidant co-enzyme Q10

There was 1 RCT which evaluated the effectiveness of supplementation with conventional doses of CoQ10 to relieve cancer-related fatigue in n=236 newly diagnosed patients with breast cancer with planned adjuvant chemotherapy. Patients reported low levels of fatigue at study entry. A 24-week oral supplementation of 300

mg of CoQ10 did not result in improvements in self-reported fatigue compared to placebo[65].

Paullinia cupana

One study by del Giglio[63], examined the effectiveness of purified dry extract of Paullinia cupana, an Amazonian plant that has previously been shown to be effective in treating chemotherapy-related fatigue in patients with breast cancer in a 3-week intervention in 40 patients with various solid tumours, including breast, colorectal, lung, and ovarian tumours (no discrimination of stage was made). Brief fatigue inventory (BFI) scores improved or stabilized in the majority of patients. Paullinia cupana 18 extract may possibly help therefore be effective in treatment of fatigue in patients with solid tumors receiving chemotherapy but studies were small and larger studies required. As well, there may be potiential drug/herb interactions.

Conclusion: Randomized trials of various pharmacological interventions have produced mixed findings. Trials evaluating modafinil and methylphenidate did not find any benefit over placebo for management of cancer-related fatigue. Similarly, supplementation with CoQ10 did not result in improvement of fatigue. However, two trials, one evaluating dexamethasone and the other evaluating combined abiraterone acetate and prednisone therapy reported improvement of cancer-related fatigue compared to placebo. Studies conducted in more-specific cancer populations or at particular stages in the cancer journey may not be generalizable to wider populations and must be interpreted with caution.

Methodological Quality

The results of the methodological quality assessment are described in the Tables of Quality Assessment (Table D.1 in appendix D) see Figure. B.8.3.1.

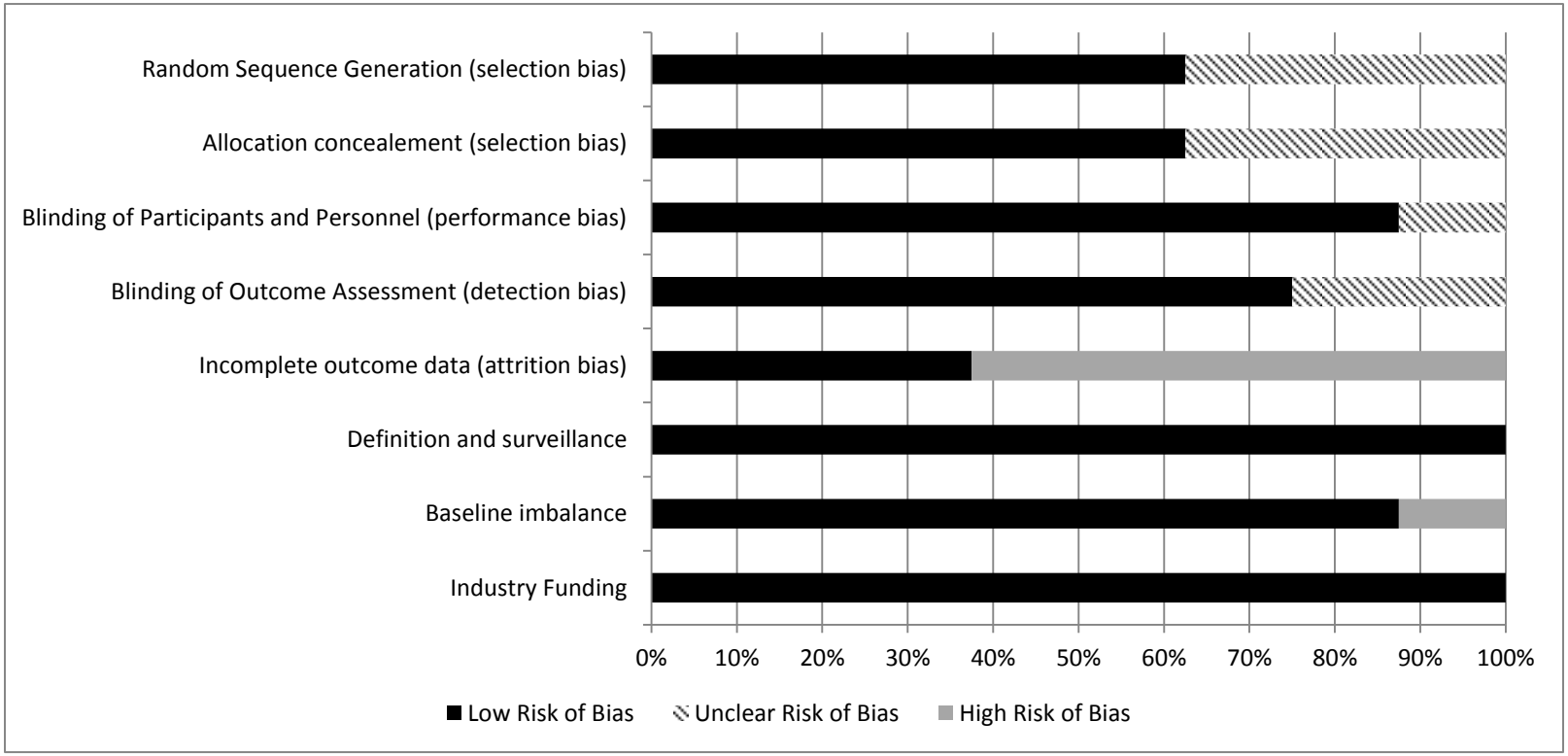

Figure B.8.3.1: Risk of Bias Graph: Review Authors' Judgment about Pharmacological Interventions

B.8.4 Meta-analysis

Of nine identified trials, we could pool results of only 2 trials due to significant heterogeneity in 7 trials. Two studies tested modafinil in CRF patients[79, 83]. One of these trials[57] did not have the required data to be pooled. Meta-analysis was possible for two studies in CRF comparing modafinil to placebo; the results show there was no significant effect of modafinil (0.0133; 95%CI 0.2546 to 0.2811) Figure B.8.4.1.

Of nine identified trials, we could pool results of only 2 trials due to significant heterogeneity in 7 trials. Three studies tested modafinil in CRF patients[57, 79, 83]. One of the trials [57] did not have the data required for quantitative synthesis. Meta-analysis of two studies showed that there was no statistically significant difference in CRF assessed using continuous outcome measures between the modafinil and placebo groups (SMD = 0.0133; 95%CI -0.2546 to 0.2811). Figure B.8.4.1. shows the result of pooled analysis on modafinil on section 1.1.1. Section 1.1.2 depicts result of one study with the effect size of dexamethasone and section 1.1.3 details results of one study on methylphenidate; these are not pooled analyses.

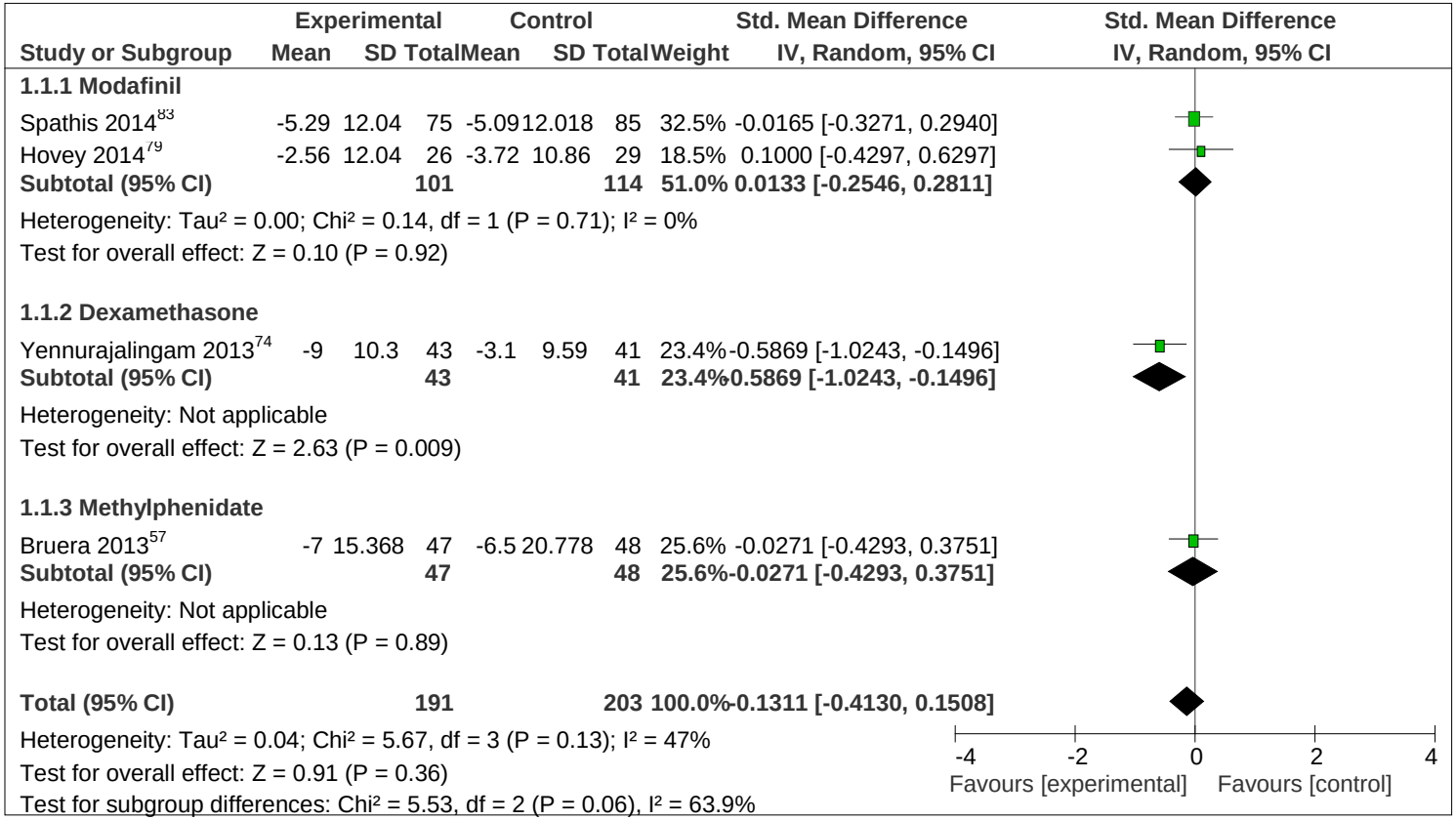

Figure B.8.4.1: Effect of Pharmacological Interventions on CRF

Table B.8.4.1: GRADE Tables for Effect of Pharmacological Interventions on CRF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pharmacotherapy	Control	Relative (95% CI)	Absolute		
Effect of Modafinil on CRF (measured with: CRF tools; Better indicated by lower values)												
2	randomised trials	no serious risk of bias[1]	no serious inconsistency[2]	no serious indirectness[3]	serious[4]	none[5]	101	114	-	SMD 0.01 higher (0.25 lower to 0.28 higher)	▫▫▫▫ MODERATE	CRITICAL
Effect of Dexamethasone on CRF (measured with: CRF tools; Better indicated by lower values)												
1	randomised trials	no serious risk of bias[6]	no serious inconsistency[7]	no serious indirectness[8]	no serious imprecision[9]	none[5]	43	41	-	SMD 0.59 lower (1.02 to 0.15 lower)	▫▫▫▫ HIGH	CRITICAL
Effect of Methylphenidate on CRF (measured with: CRF tools; Better indicated by lower values)												
1	randomised trials	serious[10]	no serious inconsistency[7]	no serious indirectness[11]	serious[12]	none[5]	47	48	-	SMD 0.03 lower (0.43 lower to 0.38 higher)	▫▫▫▫ LOW	CRITICAL

Pharmacotherapy for CRF

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Pharmacotherapy				
Effect of Modafinil on CRF		The mean effect of Modafinil on CRF in the intervention groups was		215 (2 studies)	⊕⊕⊕⊖ **moderate**[1,2,3,4,5]	SMD 0.01 (-0.25 to 0.28)

CRF tools (FACIT-F, CIS)		**0.01 standard deviations higher** (0.25 lower to 0.28 higher)			
Effect of Dexamethasone on CRF CRF tools (FACIT-F)		The mean effect of Dexamethasone on CRF in the intervention groups was **0.59 standard deviations lower** (1.02 to 0.15 lower)	84 (1 study)	⊕⊕⊕⊕ **high**[5,6,7,8,9]	SMD -0.59 (-1.02 to -0.15)
Effect of Methylphenidate on CRF CRF tools (FACIT-F)		The mean effect of Methylphenidate on CRF in the intervention groups was **0.03 standard deviations lower** (0.43 lower to 0.38 higher)	95 (1 study)	⊕⊕⊖⊖ **low**[5,7,10,11,12]	SMD -0.03 (-0.43 to 0.38)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Across studies, there was high risk of bias associated with selective reporting (50%),Given that most of the information is from studies at low risk of bias, this body of evidence was not downgraded for serious study limitations.
[2] The statistical heterogeneity is minimal [Chi2=0.14, df=1 (P=0.71); I2=0%] and the confidence intervals overlap. This body of evidence was not downgraded for inconsistency.
[3] Two RCTs provided data for this outcome. Both studies included mixed gender population in adult population. The intervention arm received modafinil 200 mg per day. The control group received placebo. One study was conducted in UK, and one study in Australia. All studies were published in 2013 and 2014. The length intervention across two studies ranged from 18 days to 28 days. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded.
[4] The sample size is not adequate i.e. < 300 (101 intervention arm, 114 control arm) and the pooled effect estimate is imprecise with confidence intervals including the null value "0" [SMD= 0.0133 (-0.2546, 0.2811)]. This body of evidence was downgraded due to serious concerns regarding imprecision.
[5] There were too few studies to assess publication bias.
[6] There was lack of certainty associated with sequence generation and allocation concealment. Given that most of the information is from studies at low risk of bias, this body of evidence was not downgraded for serious study limitations.
[7] Inconsistency could not be assessed due to single study in this group.
[8] One RCT provided data for this outcome. The study included mixed gender population in adult population. The intervention arm received dexamethasone. The control group received placebo. The study was conducted in USA and was published in 2013. The length of intervention was 14 days. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded.
[9] The sample size is not adequate i.e. < 300 (43 intervention arm, 41 control arm) but the pooled effect estimate is precise with a narrow confidence interval [SMD= -0.5869 (-1.0243, -0.1496)]. This body of evidence was not downgraded for imprecision.
[10] There was lack of certainty associated with allocation concealment, blinding of outcome assessment, incomplete outcome data and high risk of bias associated with selective reporting. Given that most of the information is at moderate risk of bias, this body of evidence was downgraded for serious study limitations.
[11] One RCT provided data for this outcome. The study included mixed gender population in adult population. The intervention arm received methylphenidate. The control group received placebo. The study was conducted in USA and was published in 2013. The length of intervention was 14 days. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded.
[12] The sample size is not adequate i.e. < 300 (47 intervention arm, 48 control arm) and the pooled effect estimate is imprecise with confidence intervals including the null value "0" [SMD= -0.0271 (-0.4293, 0.3751)]. This body of evidence was downgraded due to serious concerns regarding imprecision.

B.8.5 Conclusion:

Existing reviews on pharmacological interventions are largely heterogeneous with small samples and do not offer robust data for firm conclusions about the effectiveness of various drug classes for management of CRF. The majority of studies of pharmacological interventions have examined psychostimulants, in particular, methylphenidate[40, 42, 48]. They suggest that this drug may be effective in the management of CRF. However, caution has been raised to restrict the use to patients with advanced cancer on active treatment for short time periods and with close monitoring of physicians skilled in prescribing this drug i.e. palliative care specialists. No class of pharmacological interventions show robust evidence for effectiveness in treating CRF. Current evidence is based on few preliminary studies and more research is needed for any conclusions to be drawn regarding effectiveness. Randomized trials of various pharmacological interventions have produced mixed findings. Trials evaluating modafinil and methylphenidate did not find any benefit over placebo for management of CRF. Similarly, supplementation with CoQ10 did not result in improvement of fatigue. However, two trials, one evaluating dexamethasone and the other evaluating combined abiraterone acetate and prednisone therapy reported statisistically significant improvements in CRF compared to placebo. However, the dose for these were not identified and these were in patients with advanced prostate cancer and not generalizeable to other populations; the safety of these drugs was not specifically assessed in these studies and the effect observed may have been as a result of discontinuing chemotherapy.

B.8.6 Recommendation

We formulated standardized ‘effectiveness statements’ to rate the evidence arising from reviews on pharmacological interventions for management of CRF, using these statements were based on the rating scheme developed by the CC&CRG to help synthesise and rate the evidence across eligible systematic reviews[84].

We assessed the overall SOE across the literature using the rating approach as specified by the GRADE tables.

B.9 Characteristics of Eligible Studies on Non-Pharmacological Interventions

We categorized included systematic reviews and randomised controlled trials from non-pharmacological interventions into: 1) physical activity/exercise 2) education and psychosocial including CBT 3) complementary medicine.

B.9.1 Physical Activity/Exercise Interventions

A total of 16 reviews met our inclusion criteria and were assessed. These included[31, 34-36, 38, 39, 41, 43-46, 49, 51-53, 55]. Data from six[31, 38, 41, 43, 45, 46] reviews were not extracted considering overlap in objectives and scope, or those with serious methodological flaws and poor quality (rating of less than 4 of possible 11 points) using the AMSTAR assessment tool. See Table C.4 in appendix C shows characteristics of eligible reviews.

B.9.1.1 Methodological Quality of Included SRs

Six of the included reviews are considered of high quality (AMSTAR ≥8), 3 of moderate quality ((AMSTAR 4 - 7.9) and 5 SR scores below 4 points. See Table C.2 for the AMSTAR rating of the included SRs in appendix C.

B.9.1.2 Results of Included Systematic Reviews

In this updated review of systematic reviews of exercise interventions in cancer patients and survivors (during and after active treatment), we reviewed data from 10 new systematic reviews (including[34-36, 39, 44, 49, 51-53, 55]). In these systematic reviews, various types of exercise interventions in various types of oncology populations were reviewed, and all of them cited positive evidence from randomized controlled trials or pooled analyses of randomized controlled trial data, suggesting fatigue reduction benefit[34, 36, 39, 44, 49, 51-53, 55].

The major findings of these reviews are summarized in Table C.4 in appendix C and methodologic grading is summarized using the AMSTAR system in Table C.2. All recent systematic reviews of randomized controlled trials or pooled analyses of randomized controlled trial data in cancer patients or survivors, suggested a significant benefit of strategies for increasing physical activity (of various types), in reducing fatigue[34, 36, 39, 44, 49, 51-53, 55]. Statistically significant heterogeneity of treatment effect was observed among some of the pooled analyses[39, 52, 53]. We did not look for head-to-head comparisons comparing different physical activity programs as part of this review, so we cannot make any regarding superiority of any particular program over others.

The impact of duration of exercise program on degree of fatigue reduction was examined in one meta-analysis, which reported that interventions ≤ 8weeks in duration were associated with statistically significant reduction in fatigue, but in longer interventions (>8 weeks) similar associations were not observed[53]. Long-term, post-trial adherence with exercise regimens for cancer patients or survivors cannot be reliably extrapolated from these systematic reviews, as most of the trials included in

these reviews had relatively short follow-up periods. More long-term outcome research is needed, to inform lifelong successful maintenance of physical activity in cancer survivors.

B.9.1.3 Conclusion

In summary, there is high quality evidence from multiple systematic reviews and meta-analyses, indicating that strategies for increasing physical activity are associated with a reduction in fatigue in cancer patients and survivors.

B.9.1.4 Results from RCTs

We identified ten[56, 59, 60, 68, 70, 73, 75, 76, 80, 81] RCTs examining the effectiveness of various interventions including multimodal mind-body program, supervised exercise, aquatic exercise, incremental walking and home-based strength training, and non-traditional exercise compared to usual care.

Cancer post treatment survivors

Among cancer survivors, three studies conducted by[59, 70, 81] tested different types of exercise programs (walking, aquatic exercise, yoga) and used various measures of fatigue [PFS, Multidimensional Fatigue Symptom Inventory Short Form (MFSI-SF), Visual Analogue Scale (VAS)] and all 3 reported a significant reduction in fatigue in patients with a previous diagnosis of breast cancer.

Exercise in patients undergoing treatment for early stage cancer

Four studies examined effectiveness of exercise in patients with early stage cancer. Two studies[68, 76], both with populations of patients with breast cancer (n=163 and n=41 respectively), reported that cardiovascular and whole body conditioning in patients receiving radiotherapy reduced fatigue. A study[80] involving 67 patients with breast cancer receiving chemotherapy did not find strength training and daily brisk walking for 30 minutes as measured using Schwartz Cancer Fatigue Scale – version 6 (SCFS-6) to significantly reduce fatigue. Another study[73], which included 138 patients with prostate, breast, colorectal or other solid tumors receiving chemotherapy, radiotherapy or a combination treatment reported that a 30 minute home based brisk walking program with 5 minutes warm-up and 5-minutes cool-down 5 times per week reduced cancer fatigue.

Advanced cancer populations:

Three studies included populations of patients with advanced cancer[56, 60, 75] with solid tumours or hematologic cancers receiving chemotherapy (n=213) examined the effectiveness of a supervised mixed high and low intensity training at the gym, 6 hours per week for 9 weeks. They found reduced fatigue in patients receiving the intervention compared to usual care. Another study which included n=100 men with locally advanced or metastatic prostate cancer receiving long-term Androgen-Deprivation Therapy (ADT)[75] reported that a 12-week program of supervised aerobic

exercise for 30 minutes plus 1 activity/week (walking, cycling, gym exercise) in first 6 weeks and 2 activities/week in second 6 weeks using FACT-F to measure fatigue, significantly reduced cancer fatigue. A further study[60] that included n=66 patients with stage IV lung or colorectal cancer not residing in hospice reported that a home-based exercise intervention with upper and lower body exercise plus brisk walking for 4 weeks reduced fatigue.

B.9.1.5 Methodological Quality of Included RCTs

The results of the methodological quality assessment are described in the Tables of Quality Assessment (Table D.2 in appendix D). There are some flaws in terms of methodological reporting in 6 out of 10 trials and were assessed as high risk of bias. For example, even though blinding is rated as high quality, it cannot really be maintained in this type of intervention (Figure B.9.1.5.1).

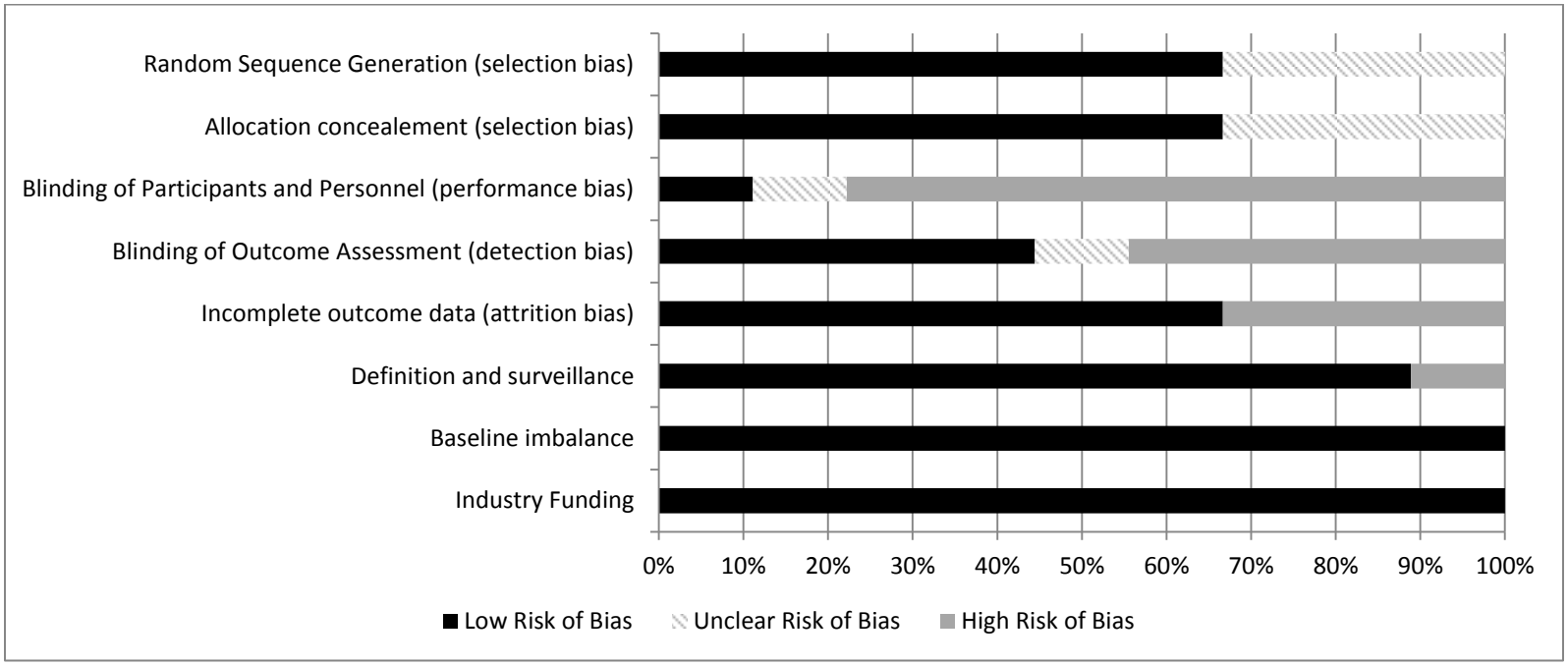

Figure B.9.1.5.1: Risk of Bias Graph: Review Authors' Judgment about each Risk of Bias item presented as Percentages across all Included RCT-Physical Activity/Exercise Intervention

B.9.1.6 Meta-analysis

The SMD effect sizes with scores of 0.2–0.5, 0.5–0.8, and >0.8 were considered as small, medium, and large effects, respectively[18]. Meta-analysis was possible for all 10 studies comparing physical activity and exercise including (aerobic exercise, strength training, flexibility exercises, alternative treatment/exercise regime for fatigue associated with cancer, resistance training exercise, therapeutic exercise, balancing activity, home based supervised exercise) in CRF with usual care and reporting continuous outcome indicators[56, 59, 60, 68, 70, 73, 75, 76, 80, 81]. Meta-analysis showed a statistically significant reduction (p=0.0005) in CRF in the intervention group as compared to the control group with a medium magnitude of effect (SMD = -0.5343; 95% CI -0.8062, -0.2625), although there was a high degree of statistical heterogeneity in treatment effect (I^2=81%, p<0.00001) (Figure. B.9.1.6.2).

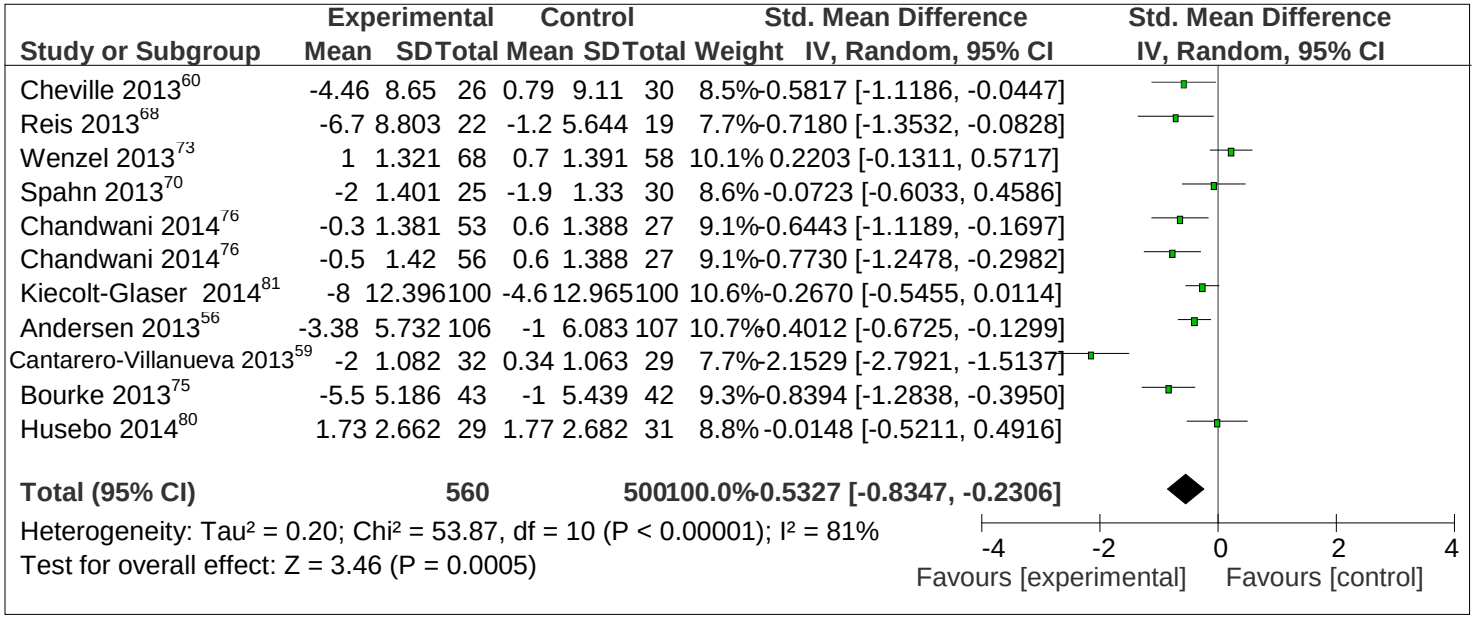

Figure B.9.1.6.2: Estimate of Overall Efficacy of Physical Activity/Exercise Intervention (immediate post response/treatment)

Table B.9.1.6.1: GRADE Tables for Effect of Exercise based Interventions on CRF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise based interventions	Control	Relative (95% CI)	Absolute		
Cancer related Fatigue (measured with: CRF tools; Better indicated by lower values)												
11	randomised trials	serious[1]	no serious inconsistency[2]	no serious indirectness[3]	no serious imprecision[4]	none[5]	631	566	-	SMD 0.5343 lower (0.8062 to 0.2625 lower)	▫▫▫▫ MODERATE	CRITICAL

Exercise based interventions for CRF

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Exercise based interventions				
Cancer related Fatigue CRF tools		The mean cancer related fatigue in the intervention groups was **0.5343 standard deviations lower** (0.8062 to 0.2625 lower)		1197 (11 studies)	⊕⊕⊕⊖ **moderate**[1,2,3,4,5]	SMD -0.53 (-0.81 to -0.26)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] Across studies, there was a lack of certainty (unclear ratings) regarding sequence generation (34%), allocation concealment (34%) and blinding of outcome assessment (11%), and high risk of bias associated with incomplete outcome reporting (33%), blinding of outcome assessment (45%). Given that most of the information is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.
[2] The statistical heterogeneity is high [Chi2=54.69, df=11 (P<0.000001); I2=80%] but the direction of the effect is consistent across most studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.
[3] Eleven RCTs provided data for this outcome. Six studies included mixed gender in adult population, while 4 included women and 1 included men. The type of intervention varied across studies including yoga, stretch, multimodal mind body programs, walking and supervised training exercises. The control group across all studies was usual care. Three studies were conducted in US, one in UK, one study in Germany, one study in Denmark, one study in Netherlands, one study in Spain and one study in Norway. All studies were published in 2013 and 2014. The length of follow-up across all studies ranged from 1 week to 6 months. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded.
[4] The sample size is adequate (631 intervention arm, 566 control arm) and the pooled effect estimate is precise with a narrow confidence interval [SMD= -0.5343 (-0.8062, -0.2625)]. This body of evidence was not downgraded for imprecision.
[5] There were too few studies to assess publication bias.

B.9.1.7 Conclusion

Overall, we found that exercise moderately reduced CRF among all type of cancer patients diagnosed with fatigue regardless of stage of treatment; significant benefit shown (p=0.0005). There is a large degree of heterogeneity of benefit, among pooling trials from various oncology populations, using various physical activity strategies. Thus, physical activity exercises should be used in the management of cancer-related fatigue in all types of cancer.

B.9.1.8 Recommendation

We formulated standardized 'effectiveness statements' to rate the evidence arising from reviews on physical activity and exercise for management of CRF. Using these, statements were based on the rating scheme developed by the CC&CRG to help synthesize and rate the evidence across eligible systematic reviews[84].

We assessed the overall SOE across the literature using the rating approach as specified by the GRADE tables.

B.9.2 Psychosocial/Education Intervention

We identified 7 systematic reviews[31, 33, 35, 38, 41, 45, 51] and 2 RCTs[67, 72]. From those seven reviews, 4[31, 38, 41, 45] reviews were not extracted considering overlap in objectives and scope, or those with serious methodological flaws and poor quality (rating of less than 4 of possible 11 points) using the AMSTAR assessment tool. Table C.5 in appendix C shows characteristics of eligible reviews.

B.9.2.1 Methodological Quality of Included SRs

Two out of five reviews are considered of high quality (AMSTAR ≥8), and 3 reviews were not synthesized because of low quality (scores below 4 points). See Table C.2 for the AMSTAR rating of the included SRs in Appendix C.

B.9.2.2 Results of Included Systematic Reviews

Three systematic reviews[33, 35, 51] were included that examined the effectiveness of education and/or psychosocial interventions that reported mixed results.

The interventions included in the Larkin et al. 2014[51] review and the Goendorp (2010)[33] reviews were diverse and included patient education interventions and psychosocial interventions inclusive of interpersonal counseling, psycho-educational interventions, and cognitive behavioural therapy targeting depression or psychological distress with fatigue as a secondary outcome.

In the Goendorp review[33], twenty-seven studies met the inclusion criteria with a total of 33324 participants. All were during cancer treatment, in a variety of different stages and malignancies but most studies were in breast cancer. The sample size of the 27 included studies varied between 30 and 396. Quality of studies was deemed to be moderate. Seven of the 27 studies reported a significant effect on fatigue (0.05 level) but effect sizes varied between 0.17 to 1.07. In five studies the interventions were specifically focused on fatigue. Four were effective. Most of the interventions were delivered by a nurse (11/27) and in most studies additional information was given to participants in the form of written materials or audiotapes. Most studies measured the effect immediately following the intervention and a few measured the effects within one month or 6 weeks of intervention completion.

Goendorp found that 4 of 5 RCTs that targeted fatigue as a primary outcome were effective. In three studies the effect was maintained at follow up. Effectiveness of interventions specific for fatigue was significantly higher (80%) compared to interventions not specific for fatigue (14%). The five interventions were brief with 3 individual sessions given by oncology nurses. Nature of these interventions was such that participants were provided with education about fatigue, were taught self-care and coping techniques about fatigue and learned about activity management (balancing rest with activity). Other 22 studies showed only 3 to be effective in reducing fatigue and had a more general approach. These interventions targeted psychological distress, mood and physical symptoms and had variation in duration and content. Goendorp concluded that psychosocial interventions that specifically target fatigue are likely to be effective but the stability of the effect made it difficult to

conclude that psychosocial interventions are effective in reducing fatigue, particularly since the interventions varied making it difficult to clearly describe the effectiveness of any one particular type of intervention approach or mode of delivery compared to another. Seven of the included studies (ones deemed to be effective) reported a significant effect of the interventions on fatigue at 0.05 level. The effect sizes varied between 0.17 and 1.07. Of the seven studies that found a significant effect of the interventions on fatigue, three found significant time by group interaction effects at follow up on at least one instrument that measured fatigue. The follow up period was short – up to one month in most studies. Of the seven studies two studies found a significant effect immediately post-intervention but these results were not maintained at longer follow up periods.

Of the 20 remaining studies (not effective) 17 had no significant effects of the intervention on fatigue, although in four of these 17 studies the authors concluded that the results were in the expected direction or significant on a 0.1 level. Three of the 20 studies found a significant effect of the intervention when measured with a t-test immediately post-interventions. In the first study, it was reported that the difference between the intervention group and control group disappeared after controlling for demographic variables and fatigue at baseline. In the second study, a statistically significant difference in the pre versus post test scores was found, where control patients become more fatigued. However no significant results on treatment by repeated measures of interaction were found on fatigue. In addition when looking at the results, fatigue scores were higher in the experimental group compared to the control group at baseline and post intervention. In the third study, significant results on fatigue was found on the within group analysis and the between group analysis but reported no significant result of the analysis of covariance on fatigue.

The Larkin (2014)[51] review identified 7 studies of non-pharmacological interventions (n=600) in men with fatigue either due to prostate cancer or treatment. The studies reviewed included exercise, exercise with diet and lifestyle modifications, education and cognitive behavioural therapy. Of the two studies included that investigated education interventions, the results were mixed. An intervention of a brief nursing intervention providing education to participants was not effective, whereas a more intensive and prostate cancer specific education did show effects in reducing fatigue but was not statistically significant. Similarly, a cognitive behavioural intervention also showed reductions in fatigue but the results were not statistically significant and interpersonal counseling showed no effect when compared to a health education control. The results of the Larkin review suggest that education and psychosocial interventions are likely to be effective in reducing fatigue but the conclusions are not definitive.

B.9.2.3 Results of Included RCTs

We identified one RCT[67] (n=261) of an 8-week patient education program conducted in post-treatment survivors that was identified as a psycho-educational intervention and compared to a wait-list control group. The intervention included

facilitated group sessions designed to increase participants' knowledge of fatigue, increase participation in physical activity, managing emotional distress and depression and peer support. The main intervention components were delivered weekly over 6 weeks with two additional sessions delivered at 3 months and 6 months post-completion of the main sessions[67]. The results of this study showed effectiveness of intensive psycho-educational interventions (90 minutes/session) in reducing perceived cancer-related fatigue ($F=76.510$, $p < 0.001$) for cancer patients following therapy completion[67]. Secondary outcomes also showed significant improvements in all measures, including QoL, general self-efficacy, exercise self-efficacy, physical activity, anxiety, depression and fatigue knowledge[67]. The effect could be maintained 6 months following participation[67].

A second RCT[72] (n=60) was reviewed that was comprised of an intensive, multidisciplinary self-care education program whereby nutrition experts, a mental health nurse counsellor, and a physiotherapist who counselled patients on self-management of fatigue which included maintenance of physical activity during active treatment for lung cancer. The intervention dose was approximately 3 sessions ranging from 30 to 60 minutes with patients counselled in behaviour change and practice of behaviours. The intervention decreased fatigue in patients with lung cancer who are receiving chemotherapy[72]. The trial group showed a lower fatigue score compared to the control group ($p = 0.036$) and higher nutritional status score ($p=0.002$)[72].

A third RCT[82] (n=200) that focused specifically on Cognitive Behavioural Therapy (CBT) was identified that targeted fatigue in women with breast cancer undergoing radiotherapy. CBT plus hypnosis (CBTH) was compared with an attention control group described as an empathic intervention. CBT plus hypnosis significantly reduced fatigue scores at end of radiotherapy; 4 week follow-up; and 6 month follow-up in comparison to an empathic-attention control group.

CBTH, when delivered prior to radiotherapy and twice per week during radiotherapy by a doctoral-level psychologist, is efficacious in improving fatigue in patients with breast cancer undergoing radiotherapy.

A randomized trial[61] of systematic monitoring and treatment of physical symptoms investigated the effectiveness of monitoring and protocolized treatment of physical symptoms to alleviate fatigue in 152 patients with advanced cancer. The patient-tailored treatment (PTT) of symptoms involved four appointments with a nurse who assessed fatigue symptoms; patients with a moderate score received nonpharmacological interventions and those with a high score received a medical intervention for symptoms. The intervention resulted in significant improvement over time for general fatigue compared to placebo. Nurse-monitoring and protocolized treatment of physical symptoms in patients with advanced cancer seems to be effective in reducing cancer related fatigue.

B.9.2.4 Methodological Quality of Included RCTs

The results of the methodological quality assessment are described in the Tables of Quality Assessment (Table D.2 in appendix D). There are some flaws in terms of methodological reporting in both trials and were assessed as high risk of bias. For example, even though blinding is high it cannot really be maintained in this type of intervention (Figure B.9.2.4.1).

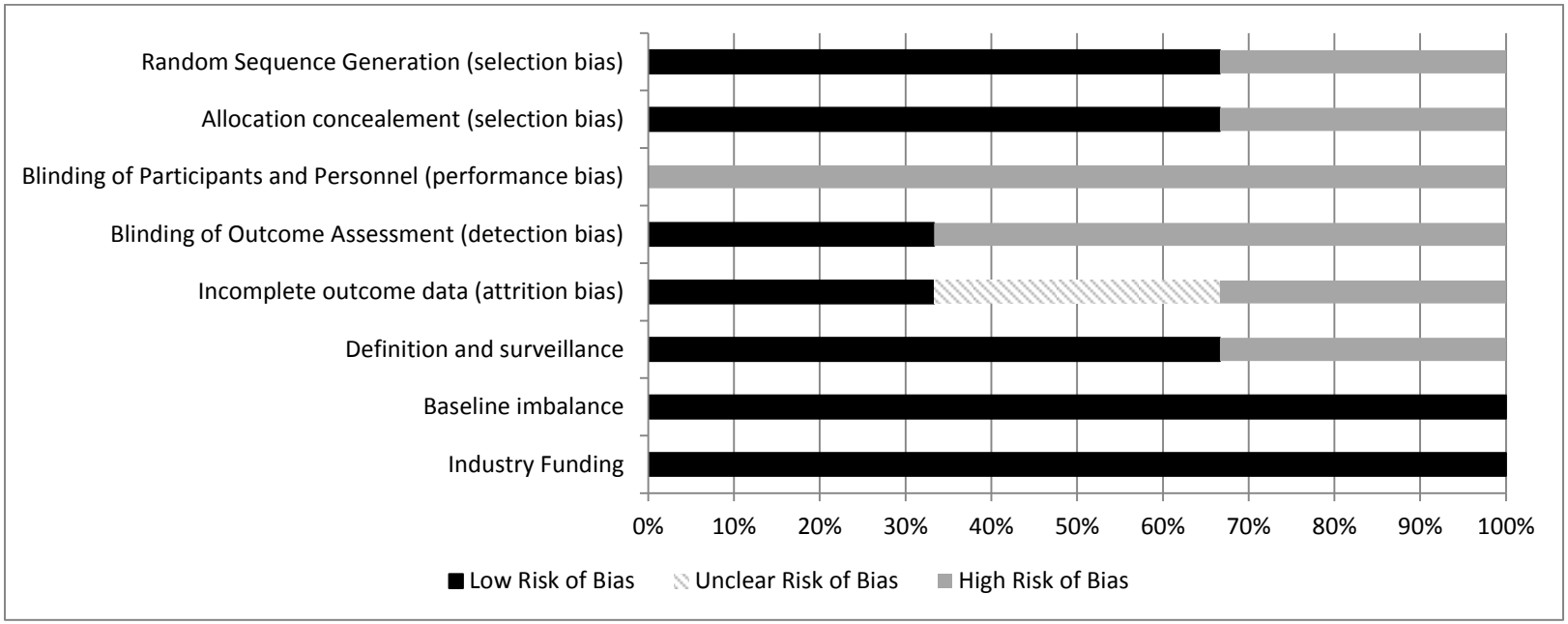

Figure B.9.2.4.1: Risk of Bias Graph: Review Authors' Judgment about Psychosocial/Education Interventions

B.9.2.5 Meta-analysis

We were not able to pool the three trials due to lack of required data so we reported the trial by Wangnum et al.[72] narratively and only 1 study[67] in GRADE and forest plots that showed a significant reduction (p<0.00001) in CRF in the structured patient education program group as compared to the control group with a medium magnitude of effect (SMD = -1.80001; 95% CI -2.1047, -1.4956), (Figure. B.9.2.5.1). Figure 9.2.5.1 depicts result of one study with the effect size of the structured patient education program group this is not a pooled analysis.

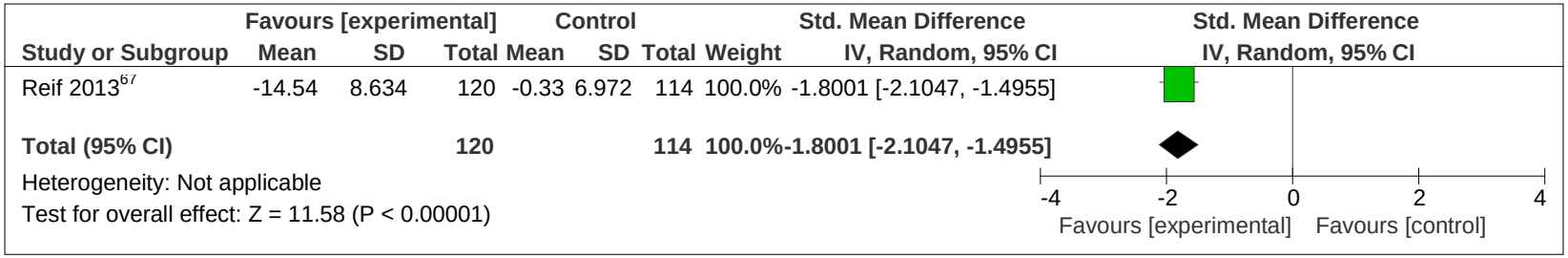

Figure. B.9.2.5.1: Results of one study of Structured Patient Psychosocial/Education Intervention

Table B.9.2.6.1: GRADE Tables for Effect of Psychosocial/Education based Interventions on CRF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Education based interventions	Control	Relative (95% CI)	Absolute		
Cancer related Fatigue (follow-up mean 6 months; measured with: CRF tools; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency[2]	no serious indirectness[3]	no serious imprecision[4]	none[5]	120	114	-	SMD 1.8 lower (2.1 to 1.5 lower)	▫▫▫▫ MODERATE	CRITICAL

Education based interventions for CRF

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Education based interventions				
Cancer related Fatigue CRF tools Follow-up: mean 6 months		The mean cancer related fatigue in the intervention groups was **1.8001 standard deviations lower** (2.1047 to 1.4955 lower)		234 (1 study)	⊕⊕⊕⊖ **moderate**[1,2,3,4,5]	SMD -1.8 (-2.1 to -1.5)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] There was a high risk of bias associated with incomplete outcome reporting blinding of outcome assessment. Given that most of the information is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.
[2] Inconsistency could not be assessed due to single study in this group.
[3] One RCT provided data for this outcome. The study included mixed gender population in adult population. The intervention arm received structured patient education program. Patients in the control group (CG) were put on a waiting-list. The study was conducted in Germany and published in 2013. The length of follow-up was 6 months. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded.
[4] The sample size is not adequate i.e. < 300 (120 intervention arm, 114 control arm) but the pooled effect estimate is precise with a narrow confidence interval [SMD= -1.8001 (-2.1047, -1.4955)]. This body of evidence was not downgraded for imprecision.
[5] There were too few studies to assess publication bias.

Table B.9.2.6.2: GRADE Tables for Effect of Cognitive-Behavioral Therapy on CRF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive-Behavioral Therapy Plus Hypnosis	Control	Relative (95% CI)	Absolute		
Effect of Cognitive-Behavioral Therapy Plus Hypnosis on CRF (measured with: CRF tools (FACIT-F); Better indicated by lower values)												
1	randomised trials	no serious risk of bias[1]	no serious inconsistency[2]	no serious indirectness[3]	no serious imprecision[4]	none[5]	100	100	-	SMD 0.83 lower (1.11 to 0.54 lower)	▫▫▫▫ HIGH	CRITICAL

Cognitive-Behavioral Therapy Plus Hypnosis for CRF

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Cognitive-Behavioral Therapy Plus Hypnosis				
Effect of Cognitive-Behavioral Therapy Plus Hypnosis on CRF CRF tools (FACIT-F)		The mean effect of cognitive-behavioral therapy plus hypnosis on CRF in the intervention groups was **0.83 standard deviations lower** (1.11 to 0.54 lower)		200 (1 study)	⊕⊕⊕⊕ **high**[1,2,3,4,5]	Cohen's d = -0.83 (-1.11 to -0.54)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Given that most of the information is at low risk of bias across all domains, this body of evidence was not downgraded for serious study limitations.
[2] Inconsistency could not be assessed due to single study in this group.
[3] One RCT provided data for this outcome. The study included mixed gender population in adult population. The intervention arm received Cognitive-Behavioral Therapy Plus Hypnosis. The control group received no treatment. The study was conducted in USA and was published in 2014. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded.
[4] The sample size is not adequate i.e. < 300 (100 intervention arm, 100 control arm) but the effect estimate is precise with a narrow confidence interval [Cohen's d= -0.83 (-1.11, -0.54)]. This body of evidence was not downgraded for imprecision.
[5] There were too few studies to assess publication bias.

B.9.2.6 Conclusion:

Multidisciplinary (psychological nurse, physical therapist, nutritionist) self-care education strategy should be adopted as the standard guideline for caring for patients with lung cancer who are receiving chemotherapy.

Cognitive behavioural therapy and intensive and disease-specific psycho-education are valuable interventions for helping manage cancer-related fatigue in men with prostate cancer.

Education programs (covering topics such as dimensions of fatigue, etiology and treatment of fatigue, time and energy management, healthy sleep, positive reinforcement techniques to enhance enjoyment of life, coping with emotions, implementing new strategies, and opportunity to exchange experiences) designed for cancer survivors after treatment had a positive impact on perceived fatigue and other secondary variables.

Education and counselling are feasible and likely to be effective in reducing CRF and enhancing QoL in breast cancer patients. At a minimum, preparing information on CRF and its management for patients with breast cancer before treating cancer treatments that may contribute to CRF may be helpful. A variety of educational methods such as telephone support, comprehensive coping strategy, combined stress management and physical activity, or even nurse-in-home visits can be used to inform patients on self-management of CRF.

There is limited evidence that general psychosocial interventions that are not targeted specifically to fatigue are effective in reducing fatigue. Educational interventions of a minimum of 3 sessions that target improvement in patients' understanding and knowledge of fatigue through targeted education sessions, focus on self-care, and activity management appear to reduce fatigue but the effect sizes are small. It is unclear if similar effects would be found for post-treatment survivors as most studies were conducted in patients on active treatment and primarily in breast cancer. More intensive interventions i.e. psychoeducation and cognitive behavioural therapy also targeted to fatigue are effective in reducing fatigue and the effect is maintained for longer periods of follow-up.

B.9.2.7 Recommendations

1. All patients should receive a patient education program (that includes dimensions of fatigue, etiology and treatment of fatigue, time and energy management, healthy sleep, positive reinforcement techniques to enhance enjoyment of life, coping with emotions, use of resources to overcome barriers when implementing new strategies, and opportunity to exchange experiences) as a strategy in reducing CRF. Health professionals need to collaborate to educate patients and decrease the risk of cancer-related fatigue.
2. Early detection and thorough evaluation of fatigue, its co-existing causes (i.e., anemia, mood disorders and sleep disturbances) and co-morbidities (i.e.,

endocrine disorders, metabolic, cardiovascular and liver diseases) are recommended specially in elderly cancer patient population.

3. Health care providers should continue to screen regularly for fatigue during follow-up visits and when clinically relevant. For patients on active treatment or long-term follow up, provide patient/family education and counseling, and general strategies for managing fatigue (e.g., monitor fatigue levels, energy conservation, set priorities and realistic expectations, finding meaning in life and promoting dignity of patient).
4. Healthcare providers should consider non-pharmacologic supportive-strategies (CBT, psycho-educational therapies, supportive expressive therapies) as adjunctive interventions to pharmacologic interventions in improving CRF.
5. Cognitive behavioural therapy and psycho-educational interventions that specifically target fatigue should be offered through designated fatigue clinics with trained staff.
6. Health care professionals should provide targeted education (minimum of 3 sessions) that includes elements of education about fatigue, teaching of self-care and coping about fatigue, teaching of activity management (balancing activity and rest). The overall SOE across the literature using the rating approach as specified by the GRADE tables.

B.9.3 Complementary Therapies

We identified 6 systematic reviews[30, 32, 38, 47, 50, 54] and 5 RCTs[63, 64, 66, 69, 78]. Table C.6 in appendix C shows characteristics of eligible SRs and Table D.6 in appendix D shows characteristics of eligible RCTs.

A total of 6 reviews met our inclusion criteria and were incorporated in the review[30, 32, 38, 47, 50, 54]. From those 6 reviews one review[38] was not extracted considering overlap in objectives and scope, or those with serious methodological flaws and poor quality (rating of less than 4 of possible 11 points) using the AMSTAR assessment tool. Table C.6 in appendix C shows characteristics of eligible reviews.

B.9.3.1 Methodological Quality of Included SRs

Five of the reviews are considered of high quality (AMSTAR ≥8). See Table C.2 for the AMSTAR rating of the included SRs in appendix C.

B.9.3.2 Results of Included Systematic Reviews

There is insufficient evidence with low quality and quantity of RCTs to draw firm conclusions regarding the effectiveness of acupuncture for cancer related fatigue. Pooled estimates of effect sizes for acupuncture on cancer related fatigue based on seven RCTs were not statistically significant with some studies having serious methodological flaws[30, 47].

A systematic review of complementary interventions for treatment of cancer related fatigue included studies evaluating effectiveness of acupuncture, massage, yoga, and relaxation training. The trials included varied greatly in quality. This review indentified only limited evidence for a beneficial effect of ginseng and hypnosis, and no evidence for effectiveness of vitamins in treating cancer related fatigue. Overall, the review concluded that there was insufficient evidence in support of any type of complementary medicine in management of cancer related fatigue[32].

With regard to Chinese herbal medicine, no firm conclusions about safety or efficacy can be drawn from the body of literature published to date. According to the Sue et al.[50] systematic review which looked at 10 RCTs, all studies had methodological flaws and heterogeneity in the herbal components studied. A recently published systematic review[54] of 4 RCTs examining the use of moxibustion found that the risk of bias was high and that there were significant methodological flaws.

B.9.3.3 Results of Included RCTs

With regard to acupuncture, it is not possible to make any recommendations with regard to the effectiveness of acupuncture for the treatment of CRF. Generally speaking, the results have been mixed. Three RCTs were reviewed[64, 66, 69], Deng et al. tested true acupuncture against sham acupuncture in 34 and 40 patients respectively with mixed cancer types and a cross-over design. They found that acupuncture did not result in reduction of fatigue at 6 months, as measured by the BFI and that there was no difference between true versus sham acupuncture. Molassiotis and her colleagues examined maintenance acupuncture administered by an acupuncturist (n=65) versus

self-administered (n=67) versus no further acupuncture (n=65) beyond an initial 2 week intervention. They found no statistically significant differences among the groups and no further improvements beyond the initial 2-week intervention.

The third RCT[69] was a feasibility study. Acupuncture was compared to sham acupuncture and a control group. Improvements in fatigue were noted at 2 weeks in the acupuncture group versus the sham acupuncture and control groups.

Although the results of this and other earlier studies are promising, all three RCTs in our review time frame suffered from methodological flaws or, in the case of Smith et al. were too small to draw firm conclusions about the efficacy of acupuncture.

A pilot RCT of the effect of healing touch on fatigue in 41 cancer patients undergoing radiotherapy that included a 45 minute session or sham therapy once a week during radiation therapy. Although this intervention was deemed to be feasible, results do not support a beneficial effect of healing touch therapy for cancer related fatigue[78].

In one study by del Giglio[63] examined the effectiveness of purified dry extract of Paullinia cupana, an Amazonian plant that has previously been shown to be effective in treating chemotherapy-related fatigue in patients with breast cancer in a 3-week intervention in 40 patients with various solid tumours, including breast, colorectal, lung, and ovarian tumours (no discrimination of stage was made). BFI scores improved or stabilized in the majority of patients. Paullinia cupana 18 extract may therefore be effective in treatment of fatigue in patients with solid tumors receiving chemotherapy but studies were small and larger studies required.

B.9.3.4 Methodological Quality of Included RCTs

The results of the methodological quality assessment are described in the Tables of Quality Assessment (Table D.2 in Appendix D). There are a few flaws in terms of methodological reporting in 5 eligible trials and were assessed as high risk of bias. For example, even though blinding is high it cannot really be maintained in this type of intervention (Figure B.9.3.4.1).

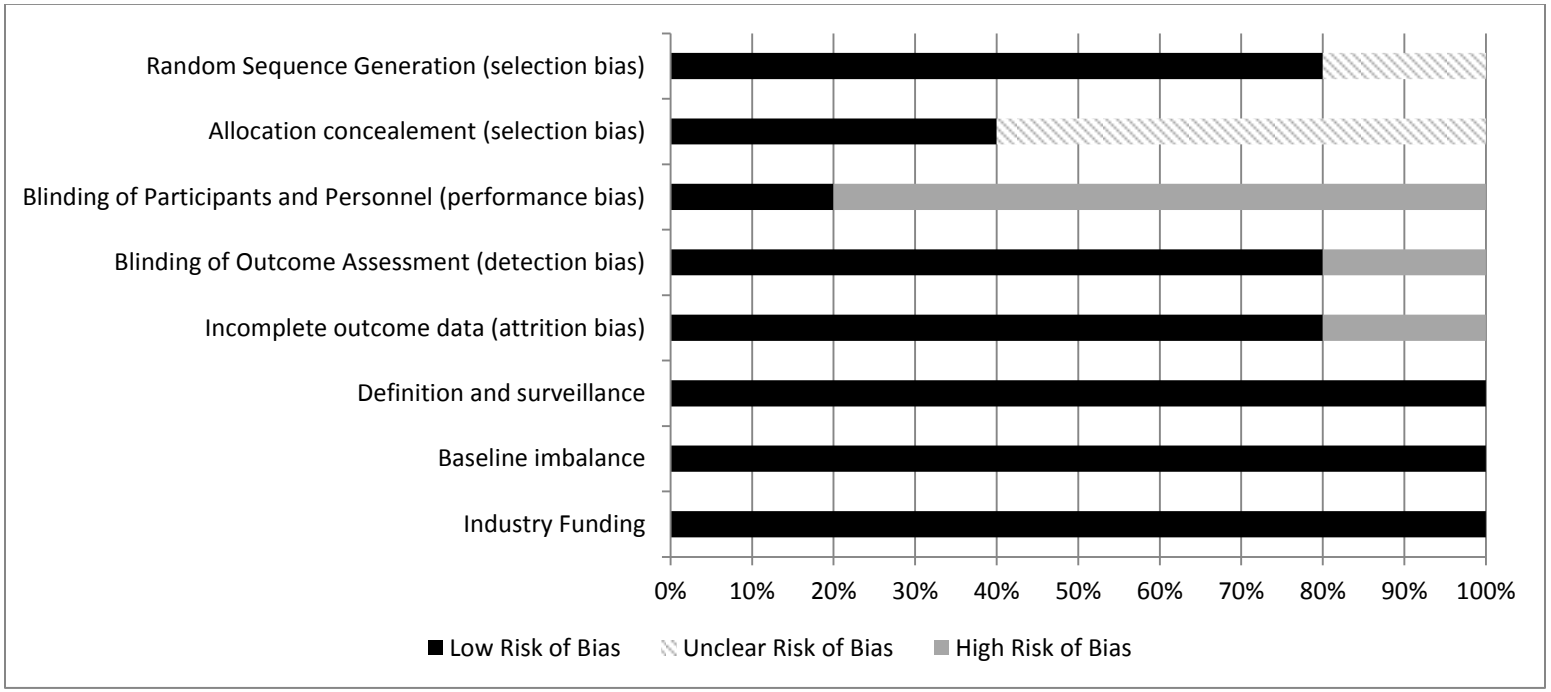

Figure B.9.3.4.1: Risk of Bias Graph: Review Authors' Judgment about Complementary Therapies

B.9.3.5 Meta-analysis

The SMD effect sizes with scores of 0.2–0.5, 0.5–0.8, and >0.8 were considered as small, medium, and large effects, respectively[18]. Meta-analysis was possible for 3 out of 5 studies comparing acupuncture in CRF with usual care and reporting continuous outcome indicators[64, 69, 78]. Meta-analysis showed no significant reduction in CRF in the intervention group as compared to the control (Figure. B.9.3.5.1).

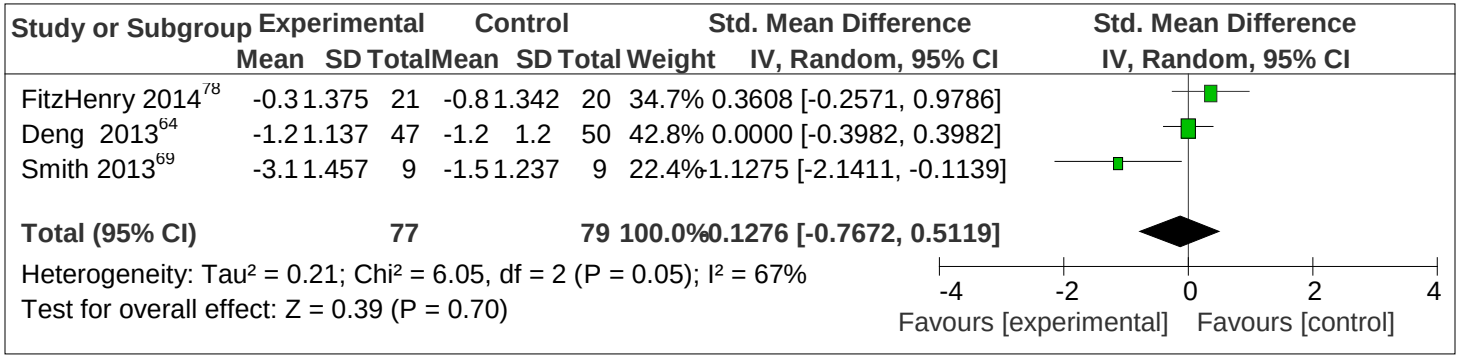

Figure B.9.3.5.1: Meta-analysis of Studies Comparing Acupuncture in CRF Compared to Usual Care

Table B.9.3.5.1: GRADE Tables for Effect of Complementary Therapies on CRF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Complementary interventions	Control	Relative (95% CI)	Absolute		
Cancer related Fatigue (measured with: CRF tools; Better indicated by lower values)												
3	randomised trials	no serious risk of bias[1]	no serious inconsistency[2]	no serious indirectness[3]	serious[4]	none[5]	77	79	-	SMD 0.13 lower (0.77 lower to 0.51 higher)	▫▫▫▫ MODERATE	CRITICAL

Complementary interventions for CRF

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Complementary interventions				
Cancer related Fatigue CRF tools		The mean cancer related fatigue in the intervention groups was **0.1276 standard deviations lower** (0.7672 lower to 0.5119 higher)		156 (3 studies)	⊕⊕⊕⊖ **moderate**[1,2,3,4,5]	SMD -0.13 (-0.77 to 0.51)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Across studies, there was a lack of certainty (unclear ratings) regarding sequence generation (20%) and allocation concealment (60%), and high risk of bias

associated with incomplete outcome reporting (20%), blinding of outcome assessment (20%). Given that most of the information is from studies at low risk of bias, this body of evidence was not downgraded for serious study limitations.
[2] The statistical heterogeneity is moderate [Chi2=8.05, df=2 (P=0.05); I2=67%] but the direction of the effect is consistent across most studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.
[3] Three RCTs provided data for this outcome. One study included mixed gender population in adult population while 2 included women. The intervention arm received acupuncture in two studies and healing touch in one study. The control group received sham therapy across all three studies. Two studies were conducted in US, and one study in Australia. All studies were published in 2013 and 2014. The length of follow-up across four studies ranged from 3 weeks to 6 month. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded.
[4] The sample size is not adequate i.e. < 300 (77 screening arm, 79 control arm) and the pooled effect estimate is imprecise with confidence intervals inducing the null value "0" [SMD= -0.1276 (-0.7672, 0.5119)]. This body of evidence was downgraded due to serious concerns regarding imprecision.
[5] There were too few studies to assess publication bias.

B.9.3.6 Recommendation

We formulated standardized 'effectiveness statements' to rate the evidence arising from reviews on complementary interventions for management of CRF, using these statements were based on the rating scheme developed by the CC&CRG to help synthesize and rate the evidence across eligible systematic reviews[84].

We assessed the overall SOE across the literature using the rating approach as specified by the GRADE tables.

Guideline Implementation

To promote the uptake of the guideline across Canada and maximize its dissemination, various steps will be developed and implemented. This includes producing practice protocols for health care professionals, patient versions, translation of the guideline into French, and workshops with key health providers. An important consideration when selecting the interprofessional panel, is the ability of the panel members to disseminate and implement the guideline in their respective jurisdictions. The partnership with the Canadian Association of Psychosocial Oncology will also ensure greater exposure for the guideline and support its implementation. In addition, the guideline will be published in a peer-reviewed journal, and posted on the websites of the Canadian Partnership Against Cancer (Cancer Journey Advisory Group) and the Canadian Association of Psychosocial Oncology. Further, the guidance will be disseminated through cancer advocacy survivorship groups, including the Canadian Cancer Action Network and the Canadian Cancer Society, and a summary of the guideline will act as an implementation tool, which will be distributed widely. It is recommended that the implementation of the guidelines in clinical practice follow a systematic knowledge translation process and use best practice strategies tailored to the local contextual health care setting to facilitate uptake.

Much variability in resources across the various Canadian health jurisdictions exists but the potential resource implications of applying the recommendations is unclear as no relevant evidence was identified. Although the resources needed to implement the recommendations are unknown, there are also the resources consumed to offer current services to consider, and it is clear that increasing the health and well being of cancer survivors is an important and worthwhile investment. The guideline recommendations were developed for implementation in a variety of health settings, and criteria to monitor or audit the organization of care or clinical practice are clearly defined throughout the document. In many cases, whether or not the services are offered forms the initial criteria to assess services. With reorganization of services, subsequent program evaluations will be essential for optimizing care for cancer survivors.

Current Research Limitations and Future Direction

Existing studies on the effectiveness of various interventions to manage cancer-related fatigue are limited by different methodological shortcomings such as small

sample size, lack of blinding, and short study duration. Further trials with more robust methodology are clearly required to ascertain the most effective interventions to alleviate fatigue in patients with cancer. Improving methodological quality of future studies and consensus on issues such as minimum accepted duration of trials and clinically meaningful change in symptoms are needed to better evaluate effectiveness of interventions and to facilitate inter-study comparisons.

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Section C: Appendices

Appendix A: Search Strategies, Environmental Scan, PRISMA Chart, & Abbreviations and Acronyms

Table A.1: Fatigue Search Strategy

Search Strategy	
Medline	
Cancer	
1	neoplasm*.hw.
2	exp Neoplasms/
3	cancer*.mp.
4	tumor*.mp.
5	tumour*.mp.
6	carcin*.mp.
7	neoplas*.mp.
8	lymphoma*.mp.
9	melanoma*.mp.
10	melanotic*.mp.
11	metasta*.mp.
12	exp Medical Oncology/
13	exp Radiation Oncology/
Fatigue	
14	exp fatigue/

Search Strategy	
15	Asthenia/
16	Muscle Weakness/
17	Fatigue Syndrome, Chronic/
18	Fatigue?.mp.
19	Exhausted.mp.
20	Exhaustion.mp.
21	Lethargy.mp.
22	Lassitude.mp.
23	Languidness.mp.
24	Vitality.mp.
25	vigor.mp.
26	Neurasthenia/
27	weariness.mp.
28	weary.mp.
29	weakness.mp.
30	weakening.mp.
31	lethargic.mp.
32	tired*.mp.
33	lacklustre.mp.
34	asthenic.mp.
35	asthenia.mp.
36	apathy.mp.
37	apathetic.mp.
38	apathetic.mp.
39	sleepiness.mp.
40	drowsy.mp.
41	drowsiness.mp.
42	drained.mp.
43	(loss adj3 energy).mp.
44	(lost adj3 energy).mp.
45	(lack* adj3 energy).mp.

Search Strategy	
46	adynami?.mp.
47	undynami?.mp.
48	or/14-47
49	or/1-13
50	48 and 49
SRs	
51	review/
52	(medline or medlars or pubmed or grateful med or CINAHL or scisearch or psychinfo or psycinfo or psychlit or psyclit or handsearch* or hand search* or manual* search* or electronic database* or bibliographic database* or embase or lilacs or scopus or web of science).mp.
53	51 and 52
54	meta-analysis.mp.
55	meta-analysis as topic/
56	meta-analysis/
57	systematic review*.tw.
58	cochrane database*.jn.
59	or/53-58
Combined Results	
60	50 and 59
61	limit 60 to (english language and yr="2009 -Current")
Guidelines	
51	guideline.pt.
52	exp guideline/
53	guideline?.mp.
54	51 or 52 or 53
Combined Results	
55	50 and 54
56	limit 55 to (english language and yr="2009 -Current")
57	remove duplicates from 56
EMBASE	
Cancer	

Search Strategy	
1	neoplasm*.hw.
2	exp Neoplasm/
3	exp oncology/
4	exp cancer staging/
5	cancer*.mp.
6	tumor*.mp.
7	tumour*.mp.
8	carcin*.mp.
9	101eoplasm*.mp.
10	lymphoma*.mp.
11	melanoma*.mp.
12	melanotic*.mp.
13	metasta*.mp.
14	exp Medical Oncology/
15	exp Radiation Oncology/
Fatigue	
16	exp fatigue/
17	asthenia/
18	exp muscle weakness/
19	Fatigue?.mp.
20	Exhausted.mp.
21	Exhaustion.mp.
22	Lethargy.mp.
23	Lassitude.mp.
24	Languidness.mp.
25	Vitality.mp.
26	vigor.mp.
27	Neurasthenia/
28	weariness.mp.
29	weary.mp.
30	weakness.mp.

Search Strategy	
31	weakening.mp.
32	lethargic.mp.
33	tired*.mp.
34	lacklustre.mp.
35	asthenic.mp.
36	asthenia.mp.
37	apathy.mp.
38	apathetic.mp.
39	apathetic.mp.
40	sleepiness.mp.
41	drowsy.mp.
42	drowsiness.mp.
43	drained.mp.
44	(loss adj3 energy).mp.
45	(lost adj3 energy).mp.
46	(lack* adj3 energy).mp.
47	adynami?.mp.
48	undynami?.mp.
49	or/1-15
50	or/16-48
SRs	
51	meta analysis/
52	"systematic review"/
53	meta-analysis.tw.
54	systematic review.tw.
55	51 or 52 or 53 or 54
Combined Results	
56	49 and 50 and 55
57	limit 56 to (english language and yr="2009 -Current")
58	limit 57 to embase
59	remove duplicates from 58

Search Strategy	
Guidelines	
51	exp practice guideline/
52	guideline?.mp.
53	51 or 52
Combined Results	
54	49 and 50 and 53
55	limit 54 to (english language and yr="2009 -Current")
56	limit 55 to embase
57	limit 56 to (book or book series or conference abstract or conference paper or conference proceeding or "conference review" or erratum or letter or note or report or short survey or trade journal)
58	56 not 57
59	remove duplicates from 58
Cochrane	
Cancer	
1	cancer*.mp.
2	tumor*.mp.
3	tumour*.mp.
4	carcin*.mp.
5	neoplas*.mp.
6	lymphoma*.mp.
7	melanoma*.mp.
8	melanotic*.mp.
9	non small cell.mp.
10	nonsmall cell.mp.
11	(nonsmall adj2 cell).mp.
12	nsclc.mp.
13	adenocarcin*.mp.
14	osteosarcom*.mp.
15	phyllodes.mp.
16	cystosarcom*.mp.
17	fibroadenom*.mp.

Search Strategy	
18	hepatoma*.mp.
19	hepatoblastom*.mp.
20	plasmacytoma*.mp.
21	myeloma?.mp.
22	blastoma*.mp.
23	lymphangioma*.mp.
24	lymphangiomyoma*.mp.
25	lymphangiosarcoma*.mp.
26	lymphoblastoma*.mp.
27	lymphocytoma*.mp.
28	lymphosarcoma*.mp.
29	lymphoma?.mp.
30	immunocytoma?.mp.
31	angiosarcoma*.mp.
32	astrocytoma*.mp.
33	neuroma?.mp.
34	cytoma?.mp.
35	gist.mp.
36	neurocytoma?.mp.
37	oncolog*.mp.
38	staging.mp.
39	squamous cell?.mp.
40	cytosarcoma*.mp.
41	sarcoma*.mp.
42	hodgkin*.mp.
43	non-hodgkin*.mp.
44	nonhodgkin*.mp.
45	incidentaloma?.mp.
46	retinoblastoma?.mp.
47	plasmacytoma*.mp.
48	cholangiocarcinoma*.mp.

Search Strategy	
49	leiomyoblastoma*.mp.
50	leiomyocarcinoma*.mp.
51	leiomyosarcoma*.mp.
52	melanosis.mp.
53	(hutchinson* adj2 freckle*).mp.
54	melanoameloblastom*.mp.
55	melanoblastom*.mp.
56	melanocarcin*.mp.
57	melanomalign*.mp.
58	naevocarcin*.mp.
59	nevocarcin*.mp.
60	adamantinom*.mp.
61	ameloblastom*.mp.
62	adenosquam*.mp.
63	teratoma*.mp.
64	leukemia*.mp.
65	metaplas*.mp.
Fatigue	
66	Fatigue?.mp.
67	Exhausted.mp.
68	Exhaustion.mp.
69	Lethargy.mp.
70	Lassitude.mp.
71	Languidness.mp.
72	Vitality.mp.
73	vigor.mp.
74	weariness.mp.
75	weary.mp.
76	weakening.mp.
77	lethargic.mp.
78	tired*.mp.

Search Strategy	
79	lacklustre.mp.
80	asthenic.mp.
81	asthenia.mp.
82	apathy.mp.
83	apathetic.mp.
84	apathetic.mp.
85	sleepiness.mp.
86	drowsy.mp.
87	drowsiness.mp.
88	drained.mp.
89	(loss adj3 energy).mp.
90	(lost adj3 energy).mp.
91	(lack* adj3 energy).mp.
92	adynami?.mp.
93	undynami?.mp.
94	or/1-65
95	or/66-93
SRs *****	
Combined Results	
96	94 and 95
97	limit 96 to last 5 years
98	remove duplicates from 97
PsycINFO	
Cancer	
1	exp neoplasms/
2	exp oncology/
3	cancer*.mp.
4	tumor*.mp.
5	tumour*.mp.
6	carcin*.mp.

Search Strategy	
7	neoplas*.mp.
8	lymphoma*.mp.
9	melanoma*.mp.
10	melanotic*.mp.
11	metasta*.mp.
Fatigue	
12	fatigue/
13	exp asthenia/
14	chronic fatigue syndrome/
15	Fatigue?.mp.
16	Exhausted.mp.
17	Exhaustion.mp.
18	Lethargy.mp.
19	Lassitude.mp.
20	Languidness.mp.
21	Vitality.mp.
22	vigor.mp.
23	Neurasthenia/
24	weariness.mp.
25	weary.mp.
26	weakness.mp.
27	weakening.mp.
28	lethargic.mp.
29	tired*.mp.
30	lacklustre.mp.
31	asthenic.mp.
32	asthenia.mp.
33	apathy.mp.
34	apathetic.mp.
35	apathetic.mp.
36	sleepiness.mp.

Search Strategy	
37	drowsy.mp.
38	drowsiness.mp.
39	drained.mp.
40	(loss adj3 energy).mp.
41	(lost adj3 energy).mp.
42	(lack* adj3 energy).mp.
43	adynami?.mp.
44	undynami?.mp.
45	or/12-44
46	or/1-11
SRs	
47	exp meta analysis/
48	exp literature review/
49	metanalys:.mp.
50	(systematic overview: or systematic review:).mp.
51	(methodologic: overview: or methodologic: review:).mp.
52	(collaborative: overview: or collaborative: review:).mp.
53	integrative research review:.mp.
54	research integration.mp.
55	(handsearch: or hand search: or manual search:).mp.
56	mantel haenszel.mp.
57	peto.mp.
58	(dersimonian or der simonian).mp.
59	fixed effect:.mp.
60	meta analysis.sh.
61	meta-anal*.tw.
62	metaanal*.tw.
63	(systematic* and (review* or overview*)).tw.
64	(critical* and apprais*).tw.
65	literature review.sh.
66	or/47-65

Search Strategy	
Combined Results	
67	45 and 46 and 66
68	limit 67 to (english language and yr="2009 -Current")
Guidelines	
47	Treatment guidelines/
48	guideline*.tw.
49	Best practices/
50	or/47-49
Combined Results	
51	45 and 46 and 50
52	limit 51 to (english language and yr="2009 -Current")
CINAHL	
SRs	
#	Query
S1	MW neoplasm*
S2	(MH "Neoplasms+")
S3	(MH "Oncology+")
S4	(MH "Neoplasm Staging")
S5	cancer*
S6	tumor*
S7	tumour*
S8	carcin*
S9	neoplas*
S10	metasta*
S11	oncolog*
S12	malignan*
S13	lymphoma*
S14	melanoma*.
S15	melanotic
S16	non small cell
S17	nonsmall n2 cell

Search Strategy	
S18	nsclc
S19	adenocarcin*
S20	osteosarcom*.
S21	phyllodes
S22	cystosarcom*.
S23	fibroadenom*.
S24	hepatoma*
S25	hepatoblastom*
S26	plasmacytoma*
S27	myeloma?
S28	blastoma*
S29	lymphangioma*
S30	lymphangiomyoma*
S31	lymphangiosarcoma*
S32	lymphoblastoma*
S33	lymphocytoma*
S34	lymphosarcoma*
S35	lymphoma?
S36	immunocytoma?
S37	angiosarcoma*
S38	astrocytoma?
S39	neuroma?
S40	cytoma?
S41	gist
S42	neurocytoma?
S43	staging
S44	squamous cell?
S45	cytosarcoma*
S46	sarcoma*
S47	hodgkin*
S48	non-hodgkin*

Search Strategy	
S49	nonhodgkin*
S50	incidentaloma?
S51	retinoblastoma?
S52	plasmacytoma*
S53	cholangiocarcinoma*
S54	leiomyoblastoma*
S55	leiomyocarcinoma*
S56	leiomyosarcoma*
S57	melanosis
S58	hutchinson* n2 freckle*
S59	melanoameloblastom*
S60	melanoblastom*
S61	melanocarcin*
S62	melanomalign*
S63	naevocarcin*
S64	nevocarcin*
S65	adamantinom*
S66	ameloblastom*
S67	adenosquam*
S68	teratoma*
S69	leukemia*
S70	metaplas*
S71	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70
S72	(MH "Fatigue+")
S73	(MH "Asthenia")
S74	(MH "Muscle Weakness")
S75	Fatigue?.

Search Strategy	
S76	(MH "Fatigue (Saba CCC)")
S77	(MH "Fatigue (NANDA)")
S78	Exhausted
S79	Exhaustion
S80	"Lethargy"
S81	"Lassitude"
S82	Languidness
S83	Vitality
S84	vigor
S85	"Neurasthenia"
S86	weariness
S87	weary
S88	weakness
S89	weakening
S90	lethargic
S91	tired*.
S92	lacklustre
S93	asthenic
S94	asthenia
S95	apathy
S96	apathetic
S97	apathetic
S98	sleepiness
S99	drowsy
S100	drowsiness
S101	drained
S102	loss n3 energy
S103	lost n3 energy
S104	lack* n3 energy
S105	adynami?
S106	undynami?

Search Strategy	
S107	S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102 OR S103 OR S104 OR S105 OR S106
S108	(MH "Clinical Trials+")
S109	PT Clinical trial
S110	TX clinic* n1 trial*
S111	TX (singl* n1 blind*)
S112	TX (singl* n1 mask*)
S113	TX (doubl* n1 blind*)
S114	TX (doubl* n1 mask*)
S115	TX (tripl* n1 blind*)
S116	TX (trebl* n1 blind*)
S117	TX (trebl* n1 mask*)
S118	TX randomi* control* trial*
S119	(MH "Random Assignment")
S120	TX placebo*
S121	TX (random* n2 allocat*)
S122	(MH "Placebos")
S123	S108 OR S109 OR S110 OR S111 OR S112 OR S113 OR S114 OR S115 OR S116 OR S117 OR S118 OR S119 OR S120 OR S121 OR S122
S124	S71 AND S107 AND S123
Guidelines	
#	Query
S1	MW neoplasm*
S2	(MH "Neoplasms+")
S3	(MH "Oncology+")
S4	(MH "Neoplasm Staging")
S5	cancer*
S6	tumor*
S7	tumour*
S8	carcin*

Search Strategy	
S9	neoplas*
S10	metasta*
S11	oncolog*
S12	malignan*
S13	lymphoma*
S14	melanoma*.
S15	melanotic
S16	non small cell
S17	nonsmall n2 cell
S18	nsclc
S19	adenocarcin*
S20	osteosarcom*.
S21	phyllodes
S22	cystosarcom*.
S23	fibroadenom*.
S24	hepatoma*
S25	hepatoblastom*
S26	plasmacytoma*
S27	myeloma?
S28	blastoma*
S29	lymphangioma*
S30	lymphangiomyoma*
S31	lymphangiosarcoma*
S32	lymphoblastoma*
S33	lymphocytoma*
S34	lymphosarcoma*
S35	lymphoma?
S36	immunocytoma?
S37	angiosarcoma*
S38	astrocytoma?
S39	neuroma?

Search Strategy	
S40	cytoma?
S41	gist
S42	neurocytoma?
S43	staging
S44	squamous cell?
S45	cytosarcoma*
S46	sarcoma*
S47	hodgkin*
S48	non-hodgkin*
S49	nonhodgkin*
S50	incidentaloma?
S51	retinoblastoma?
S52	plasmacytoma*
S53	cholangiocarcinoma*
S54	leiomyoblastoma*
S55	leiomyocarcinoma*
S56	leiomyosarcoma*
S57	melanosis
S58	hutchinson* n2 freckle*
S59	melanoameloblastom*
S60	melanoblastom*
S61	melanocarcin*
S62	melanomalign*
S63	naevocarcin*
S64	nevocarcin*
S65	adamantinom*
S66	ameloblastom*
S67	adenosquam*
S68	teratoma*
S69	leukemia*
S70	metaplas*

Search Strategy	
S71	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70
S72	(MH "Fatigue+")
S73	(MH "Asthenia")
S74	(MH "Muscle Weakness")
S75	Fatigue?.
S76	(MH "Fatigue (Saba CCC)")
S77	(MH "Fatigue (NANDA)")
S78	Exhausted
S79	Exhaustion
S80	"Lethargy"
S81	"Lassitude"
S82	Languidness
S83	Vitality
S84	vigor
S85	"Neurasthenia"
S86	weariness
S87	weary
S88	weakness
S89	weakening
S90	lethargic
S91	tired*.
S92	lacklustre
S93	asthenic
S94	asthenia
S95	apathy
S96	apathetic
S97	apathetic

Search Strategy	
S98	sleepiness
S99	drowsy
S100	drowsiness
S101	drained
S102	loss n3 energy
S103	lost n3 energy
S104	lack* n3 energy
S105	adynami?
S106	undynami?
S107	S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102 OR S103 OR S104 OR S105 OR S106
S108	S71 AND S107
S109	guideline*
S110	standard*
S111	position paper
S112	clinical protocol*
S113	(clinical OR medical) N1 criteri*
S114	(clinical OR medical) N1 polic*
S115	clinical N1 pathway
S116	critical N1 pathway
S117	care map*
S118	algorithm*
S119	(MH "Practice Guidelines")
S120	PT practice guidelines
S121	PT nursing interventions
S122	S109 OR S110 OR S111 OR S112 OR S113 OR S114 OR S115 OR S116 OR S117 OR S118 OR S119 OR S120 OR S121
S123	S108 AND S122
S124	S108 AND S122

Table A.2: Environmental Scan Search Strategy

Database/Source (Website)	No of Retrieved papers
National Guidelines Clearinghouse (NCG) (www.g-i-n.net)	21
NCCN-SAGE Directory of Cancer Guidelines, Canadian Partnership Against Cancer (www.cancerview.ca)	1
National Comprehensive Cancer Network (NCCN) (www.nccn.org	1
National Institute for Health and Clinical Excellence (NICE) (http://www.nice.org.uk/)	4
Scottish Intercollegiate Guideline Network (SIGN) (http://www.sign.ac.uk/)	2
Cancer Care Ontario (https://www.cancercare.on.ca/)	2
Vancouver Island Health Authority (http://www.viha.ca/)	0
Fraser Health, British Columbia (http://www.fraserhealth.ca/)	0
Cancer Care Nova Scotia (http://www.cancercare.ns.ca/en/home/default.aspx)	0
American Society of Clinical Oncology (ASCO) (http://www.asco.org/)	1
Multinational Association of Supportive Care in Cancer (MASCC) (www.mascc.org)	0

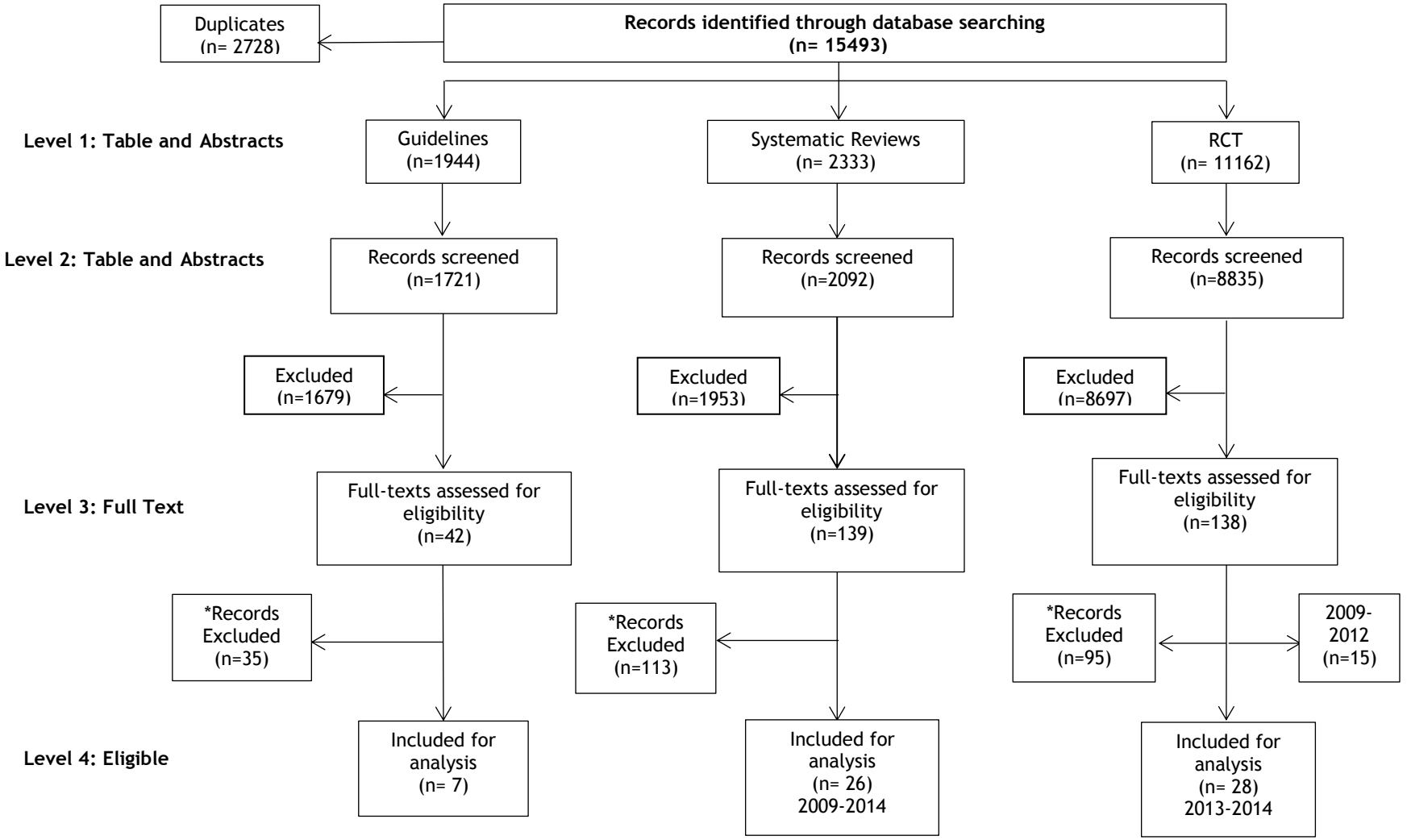


Figure A.1. PRISMA Flow diagram of Guidelines, Systematic Reviews, and RCT by Systematic Literature Search

***See Appendix F**

Table A.3: Abbreviations and Acronyms

Abbreviation	Term description
ACCP	American College of Chest Physicians
ACS	American Cancer Society
ACSM	American College of Sport Medicine
ADT	Androgen-Deprivation Therapy
AE	Adverse Event
AGREE	Appraisal of Guidelines for Research and Evaluation
AMSTAR	Assessment of Multiple Systematic Reviews
ASCO	American Society of Clinical Oncology
AT	Acupuncture
AT+EA	Electro-acupuncture
BFI	Brief Fatigue Inventory: Nine-item numeric scale validated for use in mixed cancer population reasonable psychometric properties but limited ongoing use cut-off scores to differentiate between mild, medium, and severe fatigue, but it has not been validated and is likely to be ofuse for screening purposes only. Dimensions: severity and interference
BFI-C	Brief Fatigue Inventory Chinese
CAM	Complementary & Alternative Medicine
CAPO	Canadian Association of Psychosocial Oncology
CBT	Cognitive Behavioral Therapy
CBTH	CBT + Hypnosis
CC&CRG	Cochrane Consumers and Communication Review Group
CCO	Cancer Care Ontario
CFS	Cancer Fatigue Scale
Chemo	Chemotherapy
CHM	Chinese Herbal Medicine
CI	Confidence Interval

CIS	Checklist Individual Strenght
CIS-fat	Checklist Individual Strenght- Fatigue
CoQ10	Co-emzyme Q10
CPAC	Canadian Partnership Against Cancer
CPG	Clinical Practice Guideline
CRF	Cancer-related fatigue
CTI	Control Telephone Intervention
EORTC	European Organization for Research and Treatment Care
EPA	Eicosapentaenoic acid
ESASr	*Edmonton Symptom Assessment System Revised*
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FACT	Functional Assessment of Cancer Therapy
FACT-F	Functional Assessment of Cancer Therapy-Fatigue 13-item standalone questionnaire that is part of larger FACIT series of quality-of-life and tumor-specific symptom questionnaires studied in mixed cancer population. Dimension: severity
FAQ	Fatigue Assessment Questionnaire
FSI	Fatigue Symptom Inventory: 13-item scale Validated in breast cancer population and mixed cancers Reasonable psychometric properties, but there is some concern regarding its test/retest reliability Dimensions: severity, duration, and interference.
FSS	Fatigue Severity Scale
GFPFMFRA	Reduced Motivation Subscale, General Fatigue, Physical Fatigue, Mental Fatigue and Reduced Activity.
GFS	General Fatigue Scale
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HADS	Hospital Anxiety and Depression Scale
JBI	Joanna Briggs institute

KPS	Karnofsky Performace Scale
L-T4	Levothyroxine
LASA	Linear Analo-Cancer Therapy
MASCC	Multinational Association of Supportive Care in Cancer
MD	Mean Difference
MDASI	MD Anderson Symptom Invetory
MFI	Multidimensional Fatigue Inventory: 20-item scale Designed for use in patients with cancer. Validated in Army trainees and physicians undertaking shift work as well as in patients with cancer. Dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity
MMMB	Multimodal mind-body
Mo	Months
MSFI	Multidimensional Fatigue Symptom Inventory
MSFI	Multidimensional Fatigue Symptom Inventory Short Form
NCCN	National Comprehensive Cancer Network
NOS	Newcastle-Ottawa Scale Used to assess the quality of nonrandomised studies in meta- analyses.
NR	Not Reported
NRS	Numerical Rating Scale
NTI	Nursing Telephone Intervention
ONS	Oncology Nursing Society
OT	Occupational Therapist
PAQFA	Physical Activity Questionnaire
PEDro	Physiotherapy Evidence Database scale
PFS	The Piper Fatigue Scale
POMS	Profile of Mood States

POMS-F	Profile of Moods States Fatigue subscale: 65-item questionnaire with seven-item fatigue subscale assessed in both non cancer and cancer populations. Has defined minimum clinically significant difference. Dimension: severity
PPT	Protocolized Patien-tailored treatment
PTT	Patient-tailored treatment
pts	patients
QoL	Quality of Life
RCT	Randomized Controlled Trial
RPFS	Revised PFS
SCFS	Schwartz Cancer Fatigue Scale
SCFS-6	Schwartz Cancer Fatigue Scale - version 6
SD	Standard Deviation
SE	Standard Error
SF-36	The Short Form Survey
SMD	Standardized Mean Difference
SOE	Strength of Evidence
SR	Systematic Reviews
TC	Thyroid Cancer
TSH	Thyroid Stimulating Hormone
TOI-F	Trial Outcome Index-Fatigue
UC	Ulcerative Colitis
VAS	Visual Analogue Scale
VAS-F	Visual Analogue Scale of Fatigue
Yrs	Years

Appendix B: Summary and Characteristics of Included Guidelines

Table B.1: Summary of Recommendations of Included Guidelines

Author, Year Organization/guideline publisher Country	Guideline: (Title) Intended users: Scope:	Recommendation(s) (additional information for referral to another CPG database) Level of Evidence
Schmitz,2010[25] American College of Sports Medicine USA	Guideline: American College of Sports Medicine Roundtable on Exercise Guidelines for Cancer Survivors Indented users: Health and fitness professionals Scope: The 2009 ACSM Roundtable focused on adult cancers and sites where most evidence had been assembled (i.e. breast, prostate, colon, hematologic, and gynecologic cancers), and reviewed the safety and efficacy of exercise training during and after adjuvant cancer therapy to provide guidelines.	General contraindications for starting an exercise program common across all cancer sites: Do not exercise individuals who are experiencing extreme fatigue, anemia, or ataxia. Exercise training-induced improvement can be expected concerning aerobic fitness, muscular strength, QoL, and fatigue in breast, prostate, and hematologic cancer survivors. Exercise is effective in reducing the burden of several specific cancers, including demonstrated benefits related to physical function, QoL, and cancer-related fatigue. There is scant literature on the potential effects of exercise on common problems experienced by gynecologic cancer survivors, including poor QoL, fatigue, peripheral neuropathy, and obesity. **Level of Evidence**: level[1] B
Howell,2011[27] Canadian	Guideline: A Pan-Canadian Practice Guideline: Screening, Assessment and Care of Cancer Related Fatigue	**Screening:** 1. Health care professional should screen for the presence of fatigue from the point of diagnosis and onwards routinely.

[1] Evaluation of evidence conducted as outlined by the National Heart, Lung, and Blood Institute: A (overwhelming data from RCTs), B (few RCTs exist or they are small and results are inconsistent), C (results stem from uncontrolled, nonrandomized, and/or observational studies), and D (evidence insufficient for categories A to C).

Author, Year Organization/guideline publisher Country	Guideline: (Title) Intended users: Scope:	Recommendation(s) (additional information for referral to another CPG database) Level of Evidence
Partnership Against Cancer (CPAC) and Canadian Association of Psychosocial Oncology (CAPO)[2] Canada	in Adults with Cancer Indented users: Canadian healthcare authorities, program leaders, administrators, and healthcare practitioners Scope: The goal of this guideline is to inform Canadian health authorities and professional healthcare practitioners about optimum assessment following screening and interventions for managing fatigue in adult cancer patients.	2. All patients should be screened for fatigue at initial visit, and clinically indicated. 3. Screening should be done with reliable tools including reportable scores that are clinically meaningful and have established cut-offs. 4. For inpatients a rating of mild, moderate or severe may be used. **Level of Evidence**: NCCN 2A **Assessment:** 1. Individuals should have a comprehensive and focused assessment to identify the nature and extent of fatigue symptoms if fatigue rating is moderate or severe (ESASr is greater than 4). 2. Medical and substance-induced causes of fatigue should be ruled out, and assessment should be a shared responsibility in the clinical team. 3. Assessment should include a history of fatigue (disease status, pre-treatment activity levels, fatigue onset, pattern, duration, changes over time, interference with function and daily living), contributing risk factors, physical exam, and a review of symptoms and self-assessment of causes contributing to fatigue. 4. Open communication should be promoted among patient, family and clinical team to facilitate discussions experiences of fatigue and its effects on daily functioning. 5. Clinical team must decide when referral to trained professional is needed. **Level of Evidence**: NCCN 2A **Treatment and Care Options:**

[2] CAPO is the steward of this guideline, which is a result of a collaborative partnership between the CPAC and the CAPO.

Author, Year Organization/guideline publisher Country	Guideline: (Title) Intended users: Scope:	Recommendation(s) (additional information for referral to another CPG database) Level of Evidence
		1. Address all medical and substance-induced treatable contributing factors (e.g., pain, depression, anxiety, anemia, sleep disturbance, nutrition, activity level, medication side-effects, and comorbidities). 2. Unless contraindicated, actively encourage all patients to engage in a moderate level of physical activity (e.g. aerobic exercise such as fast walking, cycling or swimming, and resistance training such as weight training) during and after cancer treatment (e.g., 30 minutes of moderate intensity activity on most days). 3. Additional non-pharmacologic interventions include nutrition consultation, optimizing sleep quality, psychosocial interventions (e.g., cognitive behavioural therapy, stress management or support groups), relaxation, massage, and attention restoring therapy (e.g., exposure to natural environments). 4. For patients on active treatment or long-term follow-up, provide patient/family education and counseling (e.g. information about known pattern of fatigue during and following treatment), and general strategies for managing fatigue (e.g. self-monitoring of fatigue levels, energy conservation, setting priorities, scheduling activities at times of peak energy, postponing nonessential activities, etc.). 5. All patients should be offered specific education about fatigue prior to the start of treatment and when fatigue is identified, plus advice on strategies (e.g., physical activity, energy conservation, stress reduction and distraction) to manage fatigue. 6. At this time, the use of pharmacologic agents to treat cancer-related fatigue is considered experimental and therefore is not recommended (e.g., psychostimulants, sleep medications, trials of low-dose corticosteroids such as prednisone or dexamethasone) except for selected patients at the end of life with severe fatigue. 7. Promote ongoing self-monitoring of fatigue levels as a late or long-

Author, Year Organization/guideline publisher Country	Guideline: (Title) Intended users: Scope:	Recommendation(s) (additional information for referral to another CPG database) Level of Evidence
		term cancer or treatment problem in post treatment survivors. 8. For those on active treatment and for those with advanced, progressive disease, repeat ESASr screening and assessment as needed to determine any change in both subjective and objective aspects of fatigue. **Level of Evidence**: NCCN 2A
Harris,2012[24] American Cancer Society USA	Guideline: Clinical practice guidelines for breast cancer rehabilitation: syntheses of guideline recommendations and qualitative appraisals Indented users: Consumers, rehabilitation clinicians, and health care funding agencies Scope: The overall goal of this article was to identify and review CPGs related to the assessment and management of physical impairment outcomes of having had breast cancer and/or from the interventions used to treat the disease.	Table 6. Relevant Guideline Recommendations for Cancer-Related Fatigue. **Screening and Assessment** Screen every patients for fatigue at regular intervals using a 10 point scale (a score ≥ 4 = moderate fatigue). Patients with moderate to severe fatigue should be queried about their activity level, including changes in exercise or activity patterns and the influence of deconditioning. Patients with fatigue should also be screened for contributing factors to fatigue. Before recommending exercise program, health care providers and exercise experts should assess the conditioning levels of patients. **Level of Evidence**: Category 2A **Interventions for Patients on Active Treatment:** **Education and Counseling of Patient** Education about fatigue and its natural history should be offered to all cancer patients but is particularly essential for patients beginning potentially fatigue-inducing treatments (e.g., radiation, chemotherapy, or biotherapy). In addition to education, the National Comprehensive Cancer Network panel recommends counseling for patients about general strategies (energy concentration and distraction) useful in coping with fatigue.

Author, Year Organization/guideline publisher Country	Guideline: (Title) Intended users: Scope:	Recommendation(s) (additional information for referral to another CPG database) Level of Evidence
		Educational interventions (including teaching, counseling, support, anticipatory guidance about fatigue patterns, coping skills training, and coaching) are ‘‘likely to be effective’’ in supporting positive coping in patients with fatigue and in reducing fatigue levels. **Level of Evidence**: Category 2A **Physical Activity/Exercise** It is reasonable to encourage all patients to engage in a moderate level of physical activity during and after cancer treatment, (e.g. 30 minutes of moderate activity most days of the week). Exercising several times per week (including walking, cycling, resistance exercise, or a combination of aerobic and resistance exercise) can be effective in reducing fatigue during and following cancer treatment. Some patients may require referrals to exercise specialists in fields such as physical therapy, physical medicine, or rehabilitation for assessment and an exercise prescription. **Level of Evidence**: Category 2A **Interventions for Patients After Treatment:** Maintain optimal level of activity. Consider initiation of exercise program of both endurance and resistance exercise. It is reasonable to encourage all patients to engage in a moderate level of physical activity during and after cancer treatment, (e.g. 30 minutes of moderate activity most days of the week). Consider referral to rehabilitation: physical therapy, occupational therapy, physical medicine. The exercise program should be individualized based on the patient’s age, sex, type of cancer, and physical fitness level. The program should begin

Author, Year Organization/guideline publisher Country	Guideline: (Title) Intended users: Scope:	Recommendation(s) (additional information for referral to another CPG database) Level of Evidence
		at a low level of intensity and duration, progress slowly, and be modified as the patient's condition changes. **Level of Evidence**: Category 2A **Other Considerations for Cancer-Related Fatigue:** The guidelines for fatigue are best implemented by an interdisciplinary institutional committee, including representatives from the fields of medicine, nursing, social work, physical therapy, and nutrition. **Level of Evidence**: Category 2A
Simoff,2013[23] American College of Chest Physicians (ACCP) USA	Guideline: Symptom management in patients with lung cancer: Diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines Indented users: Physicians Scope: The goal of this guideline is to provide the reader recommendations for the management of many of the symptom complexes that patients with lung cancer may experience example: pain, dyspnea, depression, fatigue, etc. based on evidence supported by scientific study.	14.1.3. In lung cancer patients with depression, anxiety, excessive daytime sedation and fatigue, medications such as antidepressants, anxiolytics and psychostimulants are recommended to decrease the morbidity associated with these symptoms. **Level of Evidence**:Grade 1C

Author, Year Organization/guideline publisher Country	Guideline: (Title) Intended users: Scope:	Recommendation(s) (additional information for referral to another CPG database) Level of Evidence
NCCN,2014[26] National Comprehensive Cancer Network (NCCN) USA	Guideline: (NCCN) Clinical Practice Guidelines in Oncology: cancer-related fatigue. Version I.2014 Indented users: Health care professionals This guideline synthesizes the available research and clinical experience on CRF and provides recommendations for patient care (children, adolescents, and adults) Scope: CRF is defined as "a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning".	**Screening** Every patient (inpatient, outpatient, survivors) must be screened for the presence or absence of fatigue. If fatigue is present a quantitative or semi quantitative assessment should be performed and documented such as numeric rating scale (0= no fatigue and 10= worst fatigue). Patients may rate fatigue as mild, moderate or severe. If mild or absent levels of fatigue is documented then patients and family should receive education and management strategies for fatigue. Periodic re-screening and re-evaluation are recommended. **Level of Evidence**: Category 2A[3] **Assessment** When fatigue is rated moderate to severe, history and physical exam should be conducted. Including components such as patients' current disease status, type and length of treatment, capacity to induce fatigue, patient's response to treatment, organs affected by fatigue, onset, pattern, duration, changeover time, associated or alleviating factors, and interference with function. It is also important that an in-depth self-assessment should be conducted. Contributing factors such as, anxiety, sleep disturbance, nutrition, activity level, medication, alcohol/substance abuse anemia and comorbidities should also be assessed and documented. **Level of Evidence**: Category 2A **Interventions for Active Treatment** *Education and counseling of patient and family:* Provide patient and family with information about known pattern of fatigue during and

[3] Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Author, Year Organization/guideline publisher Country	Guideline: (Title) Intended users: Scope:	Recommendation(s) (additional information for referral to another CPG database) Level of Evidence
		following treatment. Provide reassurance that treatment-related fatigue is not necessarily an indicator of disease progression. *General strategies for management of fatigue:* - Self-monitoring of fatigue levels - Energy conservation (set priorities and realistic expectations, pace, delegate, schedule activities at times of peak energy, labor-saving devices, postpone nonessential activities, limit naps to <1 hour to not interfere with night-time sleep quality, structured daily routine, attend to one activity at a time) - Use distraction (e.g. games, music, reading, socializing) - Find meaning in current situation (emphasis on meaningful interactions; promote dignity of patient). **Level of Evidence**: Category 2A *Non-pharmacologic interventions:* 1. Physical activity– Maintain optimal level of activity; Consider starting and maintaining an exercise program, as appropriate per health care provider, of both endurance (walking, jogging, or swimming) and resistance (light weights) exercises; Consider referral to rehab (physical therapy, occupational therapy, and physical medicine); Caution: bone metastases, thrombocytopenia, anemia, fever or active infection, limitations secondary to metastases or other illnesses. **Level of Evidence**: Category 1[4] 2. Physically based therapies o Massage therapy

[4] Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Author, Year Organization/guideline publisher Country	Guideline: (Title) Intended users: Scope:	Recommendation(s) (additional information for referral to another CPG database) Level of Evidence
		Level of Evidence: Category 1 3. Psychosocial interventions ▪ CBT/behavioural therapy **Level of Evidence**: Category 1 ▪ Psycho-educational therapies/Educational therapies **Level of Evidence**: Category 1 ▪ Supportive expressive therapies **Level of Evidence**: Category 2A 4. Nutrition consultation **Level of Evidence**: Category 2A 5. CBT for sleep (stimulus control, sleep restriction, sleep hygiene). *Pharmacologic interventions:* Consider psychostimulants (methylphenidate or modafinil) after ruling out other causes of fatigue; Treat for pain, emotional distress, and anemia as indicated per NCCN Guidelines; Optimize treatment for sleep dysfunction, nutritional deficit/imbalance, and comorbidities. **Level of Evidence:** Category 2A **Interventions for Post-Treatment** *Education and counseling of patient and family:* Information about known pattern of fatigue during and following treatment. *General strategies for management of fatigue:* - Monitor fatigue levels - Energy conservation (set priorities and realistic expectations, pace, schedule activities at times of peak energy, limit naps to <1 hour to not interfere with night-time sleep quality, structured daily routine, attend to one activity at a time) - Use distraction (e.g. games, music, reading, socializing)

Author, Year Organization/guideline publisher Country	Guideline: (Title) Intended users: Scope:	Recommendation(s) (additional information for referral to another CPG database) Level of Evidence
		- Find meaning in current situation (emphasis on meaningful interactions; promote dignity of patient). **Level of Evidence**: Category 2A *Non-pharmacologic interventions:* 6. Physical activity– Maintain optimal level of activity; Consider starting and maintaining an exercise program, as appropriate per health care provider, of both endurance and resistance exercises; Consider referral to rehab (physical therapy, OT, and physical medicine); Caution: late effects of treatment (e.g. cardiomyopathy). **Level of Evidence**: Category 1 7. Psychosocial interventions **Level of Evidence**: Category 1 ▪ CBT/behavioral therapy **Level of Evidence**: Category 1 ▪ Mindfulness-based stress reduction ▪ Psycho-educational therapies/Educational therapies **Level of Evidence**: Category 1 ▪ Supportive expressive therapies **Level of Evidence**: Category 1 8. Nutrition consultation **Level of Evidence**: Category 2A 9. CBT for sleep (stimulus control, sleep restriction, sleep hygiene). **Level of Evidence**: Category 1 *Pharmacologic interventions:* Consider psychostimulants (methylphenidate or modafinil) after ruling out other causes of fatigue; Treat for pain, emotional distress, and anemia as indicated per NCCN Guidelines;

Author, Year Organization/guideline publisher Country	Guideline: (Title) Intended users: Scope:	Recommendation(s) (additional information for referral to another CPG database) Level of Evidence
		Optimize treatment for sleep dysfunction, nutritional deficit/imbalance, and comorbidities. **Level of Evidence**: Category 2A **Interventions for End of Life** *Education and counseling of patient and family:* Information about known pattern of fatigue during and following treatment (expected end-of-life symptom; may vary in intensity). *General strategies for management of fatigue:* - Energy conservation (set priorities and realistic expectations, pace, delegate, schedule activities at times of peak energy, labor-saving and assistive devices (including wheelchairs, walkers, and commodes), eliminate nonessential activities, structured daily routine, attend to one activity at a time, conserve energy for valued activities) - Use distraction (e.g. games, music, reading, socializing) - Find meaning in current situation (emphasis on meaningful interactions; promote dignity of patient). *Non-pharmacologic interventions:* 10. Physical activity – Optimal level of activity with careful consideration of constraints (bone metastases, thrombocytopenia, anemia, fever or active infection, assessment of safety issues i.e. risk of falls, stability) 11. Psychosocial interventions. *Pharmacologic interventions:* Consider psychostimulants (methylphenidate or modafinil) after ruling out other causes of fatigue; Consider corticosteroids (prednisone or dexamethasone); Treat for pain, emotional distress, and anemia as indicated per NCCN Guidelines; Optimize treatment for sleep dysfunction and comorbidities. **Level of Evidence**: Category 2A

Author, Year Organization/guideline publisher Country	Guideline: (Title) Intended users: Scope:	Recommendation(s) (additional information for referral to another CPG database) Level of Evidence
Bower,2014[28] American Society of Clinical Oncology USA	Guideline: Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation Indented users: Health care professional, family, caregivers, and patients Scope: The goal for this guideline was to present screening assessment, and treatment approaches for the management of adult cancer survivors who are experiencing symptoms of fatigue after completion of primary treatment.	**Screening** • Screen for the presences of fatigue from the point of diagnosis onwards and after completion of primary treatment at least annually. • Screening should be performed and documented using a quantitative or semi-quantitative assessment. **Level of Evidence**: NR **Comprehensive and Focused Assessment** • Perform fatigue history, assess disease status and refer patient to appropriate trained professional. • Perform laboratory evaluation if presence of other symptoms and severity of fatigue. **Level of Evidence**: NR **Treatment and Care Options** • Patients should be offered specific education about fatigue after treatment, advice to help manage fatigue and if treated; patient should be evaluated on regular basis to determine if treatment is effective or reassessed. **Physical Activity** • Physical activity can help reduce fatigue for cancer survivors. Therefore all patients are encouraged to engage in moderate level of physical activity. • Walking programs are safe for cancer survivors, patients should consult their physician before beginning without formal exercise test needed. • Survivors with high risk of injury and patients with server fatigue

Author, Year Organization/guideline publisher Country	Guideline: (Title) Intended users: Scope:	Recommendation(s) (additional information for referral to another CPG database) Level of Evidence
		should be referred to a physical therapist or exercise specialist. **Psychosocial Interventions** • CBT/behavioral therapy, psychoeducational/educational therapies can reduced cancer-related fatigue for cancer survivors. • Survivors should be referred to psychosocial providers who specialize in cancer and are trained to deliver empirically based intervention. **Mind-Body Interventions** • Yoga, acupuncture can reduce cancer-related fatigue for cancer survivors. • Survivors should be referred to practitioner who specialize in cancer and use protocols that are empirically valid for cancer survivors. **Level of Evidence**: NR **Pharmacological Interventions** Pyschostimulants and wakefulness agents can be used to manage fatigue for patients with advance disease or receiving active treatment. **Level of Evidence**: NR

*** Definitions for NCCN Categories:**The specific definitions of the NCCN categories for recommendations are *included below:*
Category 1*: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate;*
Category 2A*: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate;*
Category 2B*: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate;*
Category 3*: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.*
For the 'uniform NCCN consensus' defined in Category 1 and Category 2A, a majority Panel vote of at least 85% is required. For the 'NCCN consensus' defined in Category 2B, a Panel vote of at least 50% (but less than 85%) is required. Lastly, for recommendations where there is strong Panel disagreement regardless of the quality of the evidence, NCCN requires a vote from at least three Panel Members (representing at least three different Member Institutions) to include and designate a recommendation as Category 3. The large majority of the recommendations put forth in the Guidelines are Category 2A. Where categories are not specified within the Guidelines, the default designation for the recommendation is Category 2A

Appendix C: Summary and Characteristics of Included Systematic Reviews

Table C.1: Quality Assessment (AMSTAR) of Included Systematic Reviews- Pharmacological Intervention

Author, Year	1. Was an 'a priori' design provided?	2. Was there duplicate study selection and data extraction?	3. Was a comprehensive literature search performed?	4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	5. Was a list of studies (included and excluded) provided?	6. Were the characteristics of the included studies provided?	7. Was the scientific quality of the included studies assessed and documented?	8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	9. Were the methods used to combine the findings of the studies appropriate?	10. Was the likelihood of publication bias assessed?	11. Were conflicts of interest stated?	Score
Giacalone,2013[31]	Yes	No	No	No	No	Yes	No	No	No	No	No	2/11
Payne,2012[35]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	10/11
Minton,2011[37]	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	8/11
Peuckmann,2010[40]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11/11
Dy and Apostol,2010[41]	Yes	No	No	No	No	No	No	No	No	No	Yes	2/11
Minton,2010[42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11/11
Gong,2014[48]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	8/11
Minton,2014[44]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11/11
Sawka,2014[55]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	8/11

Table C.2: Quality Assessment (AMSTAR) of Included Systematic Reviews- Non-Pharmacological Intervention

Author, Year	1. Was an 'a priori' design provided?	2. Was there duplicate study selection and data extraction?	3. Was a comprehensive literature search performed?	4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	5. Was a list of studies (included and excluded) provided?	6. Were the characteristics of the included studies provided?	7. Was the scientific quality of the included studies assessed and documented?	8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	9. Were the methods used to combine the findings of the studies appropriate?	10. Was the likelihood of publication bias assessed?	11. Were conflicts of interest stated?	Score
Physical Activity/Exercise												
Giacalone,2013[31]	Yes	No	No	No	No	Yes	No	No	No	No	No	2/11
Cramp and Byron-Daniel,2012[34]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	10/11
McMillan and Newhouse,2011[36]	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	No	7/11
Storic,2013[46]	Yes	No	Yes	No	No	Yes	No	No	NA	No	No	3/11
Wanchai,2011[38]	Yes	No	No	No	No	Yes	No	No	No	No	No	2/11
Brown,2011[39]	Yes	No	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	7/11
Kuchinski,2009[43]	Yes	No	No	No	No	Yes	No	No	No	No	No	2/11
Minton,2014[44]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11/11
Paramanandam and Dunn,2013[49]	Yes	No	No	No	No	Yes	Yes	Yes	No	No	No	4/11
Dy and Apostol,2010[41]	Yes	No	No	No	No	No	No	No	No	No	Yes	2/11
Larkin,2014[51]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	8/11
Zou,2014[53]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	9/11
Tomlinson,2014[52]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	8/11
Sawka,2014[55]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	8/11
Alcântara-Silva,2013[45]	Yes	No	No	No	No	No	No	No	No	No	Yes	2/11
Payne,2012[35]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	10/11

Author, Year	1. Was an 'a priori' design provided?	2. Was there duplicate study selection and data extraction?	3. Was a comprehensive literature search performed?	4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	5. Was a list of studies (included and excluded) provided?	6. Were the characteristics of the included studies provided?	7. Was the scientific quality of the included studies assessed and documented?	8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	9. Were the methods used to combine the findings of the studies appropriate?	10. Was the likelihood of publication bias assessed?	11. Were conflicts of interest stated?	Score
Psychosocial/Education												
Wanchai,2011[38]	Yes	No	No	No	No	Yes	No	No	No	No	No	2/11
Dy and Apostol,2010[41]	Yes	No	No	No	No	No	No	No	No	No	Yes	2/11
Larkin,2014[51]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	9/11
Giacalone,2013[31]	Yes	No	No	No	No	Yes	No	No	No	No	No	2/11
Payne,2012[35]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	10/11
Goedendorp,2009[33]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11/11
Alcântara-Silva,2013[45]	Yes	No	No	No	No	No	No	No	No	No	Yes	2/11
Complementary Therapies												
Posadzki,2013[30]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	10/11
Wanchai,2011[38]	Yes	No	No	No	No	Yes	No	No	No	No	No	2/11
Zeng,2014[47]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	9/11
Su,2014[50]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11/11
Lee,2014[54]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	10/11
Finnegan-John,2013[32]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	8/11

Characteristics of Systematic Review

Table C.3: Characteristics of Included Systematic Reviews -Pharmacological Intervention

Author, Year Country	Range of search date Target population/ treatment stage Type of cancer/ Cancer site	Interventions vs. Comparison	Total # of Ps in intervention group vs. Ps in control group	Type of outcomes evaluated/ assessment tools (outcome)	Meta-Analysis/ effect size	Review limitation Overall conclusion	Quality of review Recommendations
Psychostimulants							
Minton, 2010[42] UK	2007-2009 ≥18 yrs with cancer at any disease/treatment stage (including curative treatment, palliative care, and disease-free survivors) Any	Psycho-stimulants (methyl-phenidate) vs. Placebo	410 (205 vs. 205)	Fatigue/NR (Primary)	**Fatigue score change:** -SMD (95% CI) = 0.28 (-0.48, -0.09), P = 0.0046	Small sample sizes. Methylphenidate seems to reduce CRF in cancer patients.	GRADE: 4/high. Methylphenidate: use in a dose of 10 to 20 mg/day depending on response. Contra-indications to this drug should be reviewed before prescribing.
Gong, 2014[48] China	Inception-2013 ≥18 yrs with cancer Any	Methyl-phenidate vs. Placebo	126 vs. 143	Fatigue/ FACT-F (Primary)	**Effects on CRF (FACT-F):** MD (95% CI), -3.13 (-5.55, -.71); P = 0.01	Limited RCT data; small sample size; subjective fatigue assessment; inconsistent fatigue measurements; fatigue poorly defined; poorly defined	NR No recommendation can be made at this time.
Gong,2014[48]	Inception-2013	Methyl-phenidate vs.	72 vs. 76	Fatigue/BFI	**Effects of on CRF**		

Author, Year Country	Range of search date Target population/ treatment stage Type of cancer/ Cancer site	Interventions vs. Comparison	Total # of Ps in intervention group vs. Ps in control group	Type of outcomes evaluated/ assessment tools (outcome)	Meta-Analysis/ effect size	Review limitation Overall conclusion	Quality of review Recommendations
China	≥18 yrs with cancer Any	Placebo		(Primary)	**(BFI):** MD (95% CI), -0.69 (-1.81, 0.43); P = 0.23	concomitant conditions; side effect of methylphenidate unknown given short-term treatment administration. Existing trials of methylphenidate on CRF provided limited evidence for the use of methylphenidate to treat CRF.	
Gong, 2014[48] China	Inception-2013 ≥18 yrs with cancer Any	**(a)** Methyl-phenidate (short-time treatment) vs. Placebo	72 vs. 74	Fatigue/FACT-F, BFI (primary)	**Effects of methyl-phenidate on CRF:** MD (95% CI), -2.49 (-6.01, 1.03); P = 0.17		
		(a) Methyl-phenidate (short-term treatment) vs. Placebo	72 vs. 74	Fatigue/FACT-F, BFI (Primary)	**Effects of methyl-phenidate on CRF:** MD (95% CI), -2.49 (-6.01, 1.03), P = 0.17		
		(b) Methyl-phenidate (long-time treatment)	54 vs. 69	Fatigue/ FACT-F, BFI (Primary)	**Effects of methyl-phenidate on CRF:**		

Author, Year Country	Range of search date Target population/ treatment stage Type of cancer/ Cancer site	Interventions vs. Comparison	Total # of Ps in intervention group vs. Ps in control group	Type of outcomes evaluated/ assessment tools (outcome)	Meta-Analysis/ effect size	Review limitation Overall conclusion	Quality of review Recommendations
		vs. Placebo			MD (95% CI), -3.70 (-7.03, -0.37), P = 0.03		
		Total (a + b)	126 vs. 143	Fatigue/ FACT-F, BFI (Primary)	**Effects of methyl-phenidate on CRF:** MD (95% CI), -3.13 (-5.55, -0.71); P = 0.01		
Peuckmann, 2010[40] Germany	Inception-2009 Males & Females ≥18 yrs, palliative care (not cancer specific) patients with fatigue Any	Methyl-phenidate vs. Placebo (in cancer-related fatigue population)	72 vs. 74	Fatigue/BFI, FACIT-F, ESASr, Multidimen-sional Assessment of Fatigue, Fatigue Symptom Checklist (Primary)	**3 Methyl-phenidate in advanced cancer:** SMD (95% CI), 0.49 (0.15, 0.83); P = 0.0042	Clinically significant fatigue was not statistically examined; limited evidence base. Existing evidence shows a slightly superior effect of methylphenidate on CRF reduction compared to placebo.	No overall GRADE; reviewed articles were individually assessed. No recommend-ation can be made at the time.

Author, Year Country	Range of search date Target population/ treatment stage Type of cancer/ Cancer site	Interventions vs. Comparison	Total # of Ps in intervention group vs. Ps in control group	Type of outcomes evaluated/ assessment tools (outcome)	Meta-Analysis/ effect size	Review limitation Overall conclusion	Quality of review Recommendations
Minton, 2014[44] UK	Inception-2013 NR Any	Methyl-penidate vs. Placebo	Total: 710	Fatigue/NR (Not specified)	SMD (95% CI), -0.22 (-0.38, -0.06); P = 0.007	Small sample sizes; a short follow-up duration (< 2 weeks). Further clinical trials are needed to investigate the benefits of methylphenidate. So far, evidence suggests methylphenidate is effective for CRF.	NR No concrete recommendation can be made at this time.
Minton, 2011[37] UK	Inception-2009 Not specified Any	Psycho-stimulants (including methyl-phenidate/ dexampheta-mine) vs. Placebo	205 vs. 205	Fatigue/ FACT-F, BFI (Primary)	**Effects of psycho-stimu-lants on CRF:** SMD (95% CI), -0.28 (1.48, -.09); P = .005; **Fre-quency of adverse**	Quality of source data; limited evidence base. There is preliminary evidence for the use of psychostimulants to treat CRF. There were no differences in the frequency of	NR Further research is needed before their use can be recommended more widely.

Author, Year Country	Range of search date Target population/ treatment stage Type of cancer/ Cancer site	Interventions vs. Comparison	Total # of Ps in intervention group vs. Ps in control group	Type of outcomes evaluated/ assessment tools (outcome)	Meta-Analysis/ effect size	Review limitation Overall conclusion	Quality of review Recommendations
					events between methyl-phenidate and placebo: Combined odds ratio (95% CI), 1.24 (0.42, 3.62); P = 0.70	adverse events between methylphenidate and placebo.	
Antidepressants							
Minton, 2010[42] UK	2007-2009 ≥18 yrs with cancer at any disease/treatment stage (including curative treatment, palliative care, and disease-free survivors) Any	Anti-depressants vs. Placebo	Total: 643 (321 vs.322)	Fatigue/NR (Primary)	**Fatigue score change:** SMD (95% CI) = -0.08 (-0.24, 0.07); P = 0.29	Limited trials available. Benefit of antidepressants for the treatment of CRF not shown.	Jadad average: 4 (reasonable quality). The use of antidepressants with different mechanisms of action may improve fatigue.

Author, Year Country	Range of search date Target population/ treatment stage Type of cancer/ Cancer site	Interventions vs. Comparison	Total # of Ps in intervention group vs. Ps in control group	Type of outcomes evaluated/ assessment tools (outcome)	Meta-Analysis/ effect size	Review limitation Overall conclusion	Quality of review Recommendations
Haemopoietic growth factors							
Minton, 2010[42] UK	2007-2009 ≥18 yrs with cancer at any disease/treatment stage (including curative treatment, palliative care, and disease-free survivors) Any	Haemo-poietic growth factors vs. No treat-ment (placebo controlled trials)	2115 (1203 vs. 912)	Fatigue/NR (Primary)	**I Erythro-poetin or darbo-poetin versus no treatment :** SMD (95% CI) = -0.23 (-0.32, -0.14); P < 0.00001	Lack of consistency in reporting trials; missing necessary data for meta-analysis. Haemopoietic growth factors are associated with increased adverse outcomes.	Jadad average: 4 (reasonable quality). Use is not recommended.
Progestational steroids							
Minton, 2010[42] UK	2007-2009 ≥18 yrs with cancer at any disease/treatment stage (including curative treatment, palliative care, and disease-free survivors)	Progest-ational steroid vs. Placebo	633 (317 vs. 316) [Megestro-lacetate alone: 427 (214 vs. 213)]	Fatigue/NR (Primary)	**Fatigue score change: SMD (95% CI) = -0.49 [-1.74, 0.75];** P = 0.44 **Megestrol - acetate alone: -**	A high degree of heterogeneity. No difference between progestational steroids and placebo in their effectiveness for treating CRF.	Jadad average: 4 (reasonable quality). N/A

Author, Year Country	Range of search date Target population/ treatment stage Type of cancer/ Cancer site	Interventions vs. Comparison	Total # of Ps in intervention group vs. Ps in control group	Type of outcomes evaluated/ assessment tools (outcome)	Meta-Analysis/ effect size	Review limitation Overall conclusion	Quality of review Recommendations
	Any				**0.66** (-2.60, 1.28); P = 0.51		
Erythropoetin							
Minton, 2010[42] UK	2007-2009 ≥18 yrs with cancer at any disease/treatment stage (including curative treatment, palliative care, and disease-free survivors) Any	Erythro-poietin vs. Control	All trials: 2978 (1927 vs.1051) Placebo controlled trials: 1273 (699 vs. 574)	Fatigue/NR (Primary)	**Diff-erence in fatigue score:** **All trials:** SMD (95% CI) = -0.36 (-0.46, -0.26); P < 0.00001; **Placebo cont-rolled:** -0.28 (-0.39, -0.17); P < 0.00001	N/A Erythropoetin is effective in managing CRF.	Jahad score: average of 3. Cannot be recommended due to safety concerns and side effects.
Darbopoetin							

Author, Year Country	Range of search date Target population/ treatment stage Type of cancer/ Cancer site	Interventions vs. Comparison	Total # of Ps in intervention group vs. Ps in control group	Type of outcomes evaluated/ assessment tools (outcome)	Meta-Analysis/ effect size	Review limitation Overall conclusion	Quality of review Recommendations
Minton, 2010[42] UK	2007-2009 ≥18 yrs with cancer at any disease/treatment stage (including curative treatment, palliative care, and disease-free survivors) Any	Darbopoetin vs. Control	Total: 964 (567 vs. 397)	Fatigue/NR (Primary)	**Fatigue score change:** SMD (95% CI) = -0.13 (-0.27, 0.00); P = 0.050	N/A Darbopoetin is effective in managing CRF.	Jadad average score of 4. Can not be recommended due to safety concerns and side effects.
Modafinil							
Minton, 2014[44] UK	Inception – 2013 NR Any	Modafinil vs. Placebo	Total: 790	Fatigue/NR (Not specified)	SMD (05% CI), -0.06 (-0.20, -0.08); p= 0.73	Small sample sizes; a short follow-up duration (2 weeks or less). No statistically significant effect over placebo.	NR Modafinil cannot be recommended for routine clinical use.
Levothyroxine (L-T4)							

Author, Year Country	Range of search date Target population/ treatment stage Type of cancer/ Cancer site	Interventions vs. Comparison	Total # of Ps in intervention group vs. Ps in control group	Type of outcomes evaluated/ assessment tools (outcome)	Meta-Analysis/ effect size	Review limitation Overall conclusion	Quality of review Recommendations
Sawka, 2014[55] Canada	Inception-2014 Thyroid cancer survivors ≥ 18 yrs, whose disease was of any histologic subtype and who had completed primary treatment; any disease stage/ status Thyroid Cancer (TC)	Study A: Tri-iodo-thyronine with L-T4 vs. L-T4 Study B: L-T4 vs. maintenance of TSH suppression	Study A: 15 TC patients Study B: 24 TC patients	Study A: PMS, Fatigue-Inertia subscale, Vigour-activity subscale, VAS for "tired" symptoms Study B: MFI-20 subscale, GFPFMFRA[5] (At least one quantitative measure of fatigue in respective intervention and control arms, at one or more time points after randomization)	0/NR	Search strategy did not specifically search for QoL as an outcome; restricted RCTs; evidence is limited for drawing conclusions. There is paucity of RCTs to guide evidence-based management of persistent post-treatment fatigue in TC survivors.	Cochrane Risk of Bias Tool[6]: Some limitations in reporting of the methods of all the trials; all trials lacked comprehensive reporting of adverse event details. N/A
Eicosapentaenoic Acid							

[5] GFPFMFRA: Reduced Motivation Subscale, General Fatigue, Physical Fatigue, Mental Fatigue, and Reduced Activity.

[6] For detailed critical appraisal results of included studies, refer to Table 3 in the article.

Author, Year Country	Range of search date Target population/ treatment stage Type of cancer/ Cancer site	Interventions vs. Comparison	Total # of Ps in intervention group vs. Ps in control group	Type of outcomes evaluated/ assessment tools (outcome)	Meta-Analysis/ effect size	Review limitation Overall conclusion	Quality of review Recommendations
Payne, 2012[35] UK	Inception - 2010 Adults 18 years or older with an advanced progressive illness known to have clinically significant fatigue and/or weight loss in the latter stages of illness. Lung/neck, not limited to these/ All stages	Eico-sapentaenoic acid (EPA) and any drug therapy for the management of cancer-related fatigue vs. exercise, interventions by breast care nurses and psychosocial interventions	Total 17342 (116 studies)	Primary/ Not specified Fatigue	Not performed	Exercise interventions can lead to an improvement in fatigue in people with cancer, however, this beneficial effect is still to be proven for those in advanced stages of their illness.	1-specific exercise interventions might best manage fatigue in advanced stages of cancer. 2- Due to the heterogeneity of the included reviews, unable to provide any definitive recommendations for practice. 3- More research, both in terms of primary studies and more robust methodology, is required to ascertain the best interventions to manage fatigue in advanced illness. There is a need for standardised

Author, Year Country	Range of search date Target population/ treatment stage Type of cancer/ Cancer site	Interventions vs. Comparison	Total # of Ps in intervention group vs. Ps in control group	Type of outcomes evaluated/ assessment tools (outcome)	Meta-Analysis/ effect size	Review limitation Overall conclusion	Quality of review Recommendations
							reporting of these symptoms and the minimum acceptable duration of studies. 4- Researchers could improve the applicability of recommendations by including subgroup analysis.

Table C.4: Characteristics of Included Systematic Reviews - Non-Pharmacological (Physical Activitiy/Exercise Intervention)

Author, Year Country	Search date Target population/ Treatment stage Type of cancer/Cancer site	Intervention vs. Comparison	# Ps in intervention group vs. control group	Outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/Effect size	Review limitation Overall conclusion	Quality of review Recommendations
Physical Activity/Exercise							
Brown, 2011[39] USA	See Supplementary Appendix 1 ≥18 yrs, any cancer type, stage of diagnosis, and type or stage of treatment (including post-treatment) Any, Breast, Prostate, Lymphoma, Colorectal, Leukemia	Exercise vs. Usual control	3254 (only pooled data reported)	fatigue/NR (Others - not specified)	Weighted mean effect size[7] (95% CI): **CRF modulation in mixed cancer type**: 0.01 (-0.18, 0.20), p = .257; **in all cancers:** 0.31 (0.22, 0.40), p < 0.001	Limited generalizability since most interventions targeted breast and prostate cancer survivors. Authors combined theories of behaviour change and adaptation models into a single category. Adherence to the exercise interventions was	PEDro[8]: mean = 6.8. Exercise interventions for adult cancer survivors should be individualized based on the targeted health outcome and possibly cancer type. Exercise interventions should be multi-dimensional,
		Exercise vs. Usual control	NR	fatigue/NR (Others - not specified)	**CRF modulation in breast cancer**: 0.39 (0.27, 0.51), p = .010)		
		Exercise vs. Usual control	NR	fatigue/NR (Others - not specified)	**CRF modulation in prostate cancer**: 0.42 (0.27, 0.57), p = 0.533		

[7] Random-effects means. Weighted mean effect size values are positive when the exercise intervention was successful in reducing CRF compared with standard care.
[8] PEDro: Physiotherapy Evidence Database scale.

Author, Year Country	Search date Target population/ Treatment stage Type of cancer/Cancer site	Intervention vs. Comparison	# Ps in intervention group vs. control group	Outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/Effect size	Review limitation Overall conclusion	Quality of review Recommendations
		Exercise vs. Usual control	NR	fatigue/NR (Others - not specified)	**CRF modulation in lymphoma**: 0.20 (-0.03, 0.43), p = 0.509	not evaluated because most studies did not report this information. "We confirm … that moderate resistance exercise reduces CRF among adult cancer survivors, particularly breast and prostate cancer survivors and those of older age… the most efficacious exercise interventions were based on behavior change and adaptation theory."	combining sound exercise as well as behavioural science.
		Exercise vs. Usual control	NR	fatigue/NR (Others - not specified)	**CRF modulation in colorectal cancer:** 0.06 (-0.38, 0.49), p = NR		
		Exercise vs. Usual control	NR	fatigue/NR (Others - not specified)	**CRF modulation in leukemia**: 0.78 (-0.14, 1.70); p = NR		
Paramanan	2001-2012	All types of physical	192	fatigue/ FACT-F,	0/NR	Possible subjective bias in study	Quality ranged from 50% to

Author, Year Country	Search date Target population/ Treatment stage Type of cancer/Cancer site	Intervention vs. Comparison	# Ps in intervention group vs. control group	Outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/Effect size	Review limitation Overall conclusion	Quality of review Recommendations
dam and Dunn, 2013[49] UK	Male & Female, adults with lung cancer, any tumour stage/type of cancer treatment. Ps may have been receiving treatment/be in long-term follow-up/ receiving palliative care. Lung	exercise (e.g. aerobic, strength training, flexibility exercises) vs. No exercise/ usual care/ alternative treatment for CRF		EORTC, MFI, VAS; 13-item Fatigue Scale (Primary)		selection and data extraction. Limited numbers of quality studies available in this area. Language (English only) limitation. Exercise is beneficial and safe in lung CRF; however, the studies examined are small, without any control group, and lack clinically significant effect.	83.33%[9]. Patients eligible for exercise enhancement according to the NCCN guidelines can be advised to undergo exercise testing and prescription in an individual basis.[10] This should be done under the supervision of qualified professionals either in rehabilitation clinics or in community-based settings.

[9] Quality was assessed using a generic quantitative appraisal tool developed by Law et al. and modified by Machotka et al. (2009).

[10] As per ACSM roundtable on exercise guidelines for cancer survivors' recommendations.

Author, Year Country	Search date Target population/ Treatment stage Type of cancer/Cancer site	Intervention vs. Comparison	# Ps in intervention group vs. control group	Outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/Effect size	Review limitation Overall conclusion	Quality of review Recommendations
Cramp and Byron-Daniel, 2012[34] UK	Inception-2011 Adults (of any age); Males & Females; any tumour type/stage/ treatment (actively receiving treatment, long-term follow-up or palliative care) Any	Exercise vs. No exercise control	1460 vs. 1186	Fatigue/ FACT-F (Main outcome)	**Fatigue (all data):** SMD [95% CI], -0.27 [-0.37, -0.17]; P < 0.00001	Clinical and statistical heterogeneity; limited data availability/ suitability for meta-analysis. Exercise is more effective than the control intervention in managing CRF.	2-3[11]. Exercise programme may be delivered in conjunction with psychosocial therapies, stress management, nutrition therapy, sleep therapy, etc. Further work is necessary to determine the most effective parameters of exercise for fatigue management.
		Exercise vs. No exercise control	819 vs. 637	Fatigue/ FACT-F (Main outcome)	**Fatigue (during anti-cancer therapy)**: SMD [95% CI], -0.23 [-0.33, -0.12]; P = 0.000021	Clinical and statistical heterogeneity; limited data availability/ suitability for meta-analysis. Exercise during cancer treatment is more effective in	

[11] Oxford Quality Score.

Author, Year Country	Search date Target population/ Treatment stage Type of cancer/Cancer site	Intervention vs. Comparison	# Ps in intervention group vs. control group	Outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/Effect size	Review limitation Overall conclusion	Quality of review Recommendations
						managing CRF than receiving control intervention.	
		Exercise vs. No exercise control	272 vs. 267	Fatigue/ FACT-F (Main outcome)	**Fatigue (post anti-cancer therapy)**: SMD [95% CI], -0.44 [-0.79, -0.09]; Heterogeneity: P = 0.013	Clinical and statistical heterogeneity; limited data availability/ suitability for meta-analysis. Exercise following cancer treatment is more effective in managing CRF than receiving control intervention.	
		Exercise vs. No exercise control	672 vs. 511	Fatigue/ FACT-F (Main outcome)	**Fatigue (breast cancer):** SMD [95% CI], 0.35 [-0.51, -0.19]; P = 0.000014	Clinical and statistical heterogeneity; limited data availability/ suitability for meta-analysis. Exercise is more	

Author, Year Country	Search date Target population/ Treatment stage Type of cancer/Cancer site	Intervention vs. Comparison	# Ps in intervention group vs. control group	Outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/Effect size	Review limitation Overall conclusion	Quality of review Recommendations
						effective than the control intervention in managing CRF in breast cancer populations.	
		Exercise vs. No exercise control	239 vs. 176	Fatigue/ FACT-F (Main outcome)	**Fatigue (prostate cancer):** SMD [95% CI], -0.45 [-0.78, -0.11]; P = 0.0093	Clinical and statistical heterogeneity; limited data availability/ suitability for meta-analysis. Exercise is more effective than the control intervention in managing CRF in prostate cancer populations.	
		Exercise vs. No exercise control	114 vs. 106	Fatigue/ FACT-F (Main outcome)	**Fatigue (haematological malignancies):** SMD [95% CI], -0.15 [-0.42, 0.11]; P =	Clinical and statistical heterogeneity; limited data availability/	

Author, Year Country	Search date Target population/ Treatment stage Type of cancer/Cancer site	Intervention vs. Comparison	# Ps in intervention group vs. control group	Outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/Effect size	Review limitation Overall conclusion	Quality of review Recommendations
					0.26	suitability for meta-analysis. Exercise was no more effective than the control intervention in managing CRF in populations with haematological malignancies.	
		Exercise (aerobic training) vs. No exercise control	832 vs. 701	Fatigue/ FACT-F (Main outcome)	**Fatigue (aerobic training):** SMD [95% CI], -0.22 [-0.34, -0.10]; P = 0.00025	Clinical and statistical heterogeneity; limited data availability/ suitability for meta-analysis. Aerobic exercise is beneficial in the management of fatigue both during and after cancer treatment.	

Author, Year Country	Search date Target population/ Treatment stage Type of cancer/Cancer site	Intervention vs. Comparison	# Ps in intervention group vs. control group	Outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/Effect size	Review limitation Overall conclusion	Quality of review Recommendations
		Exercise (resistance training) vs. No exercise control	237 vs. 164	Fatigue/ FACT-F (Main outcome)	**Fatigue (resistance training):** SMD [95% CI], -0.18 [-0.39, 0.02]; P = 0.074	Clinical and statistical heterogeneity; limited data availability/ suitability for meta-analysis. Resistance training is no more effective than the control intervention in CRF management.	
		Exercise (mind-body exercise) vs. No exercise control	117 vs. 77	Fatigue/ FACT-F (Main outcome)	**Fatigue (mind-body exercise):** SMD [95% CI], -0.10 [-0.39, 0.19]; P = 0.49	Clinical and statistical heterogeneity; limited data availability/ suitability for meta-analysis. Mind-body exercise is no more effective than the control	

Author, Year Country	Search date Target population/ Treatment stage Type of cancer/Cancer site	Intervention vs. Comparison	# Ps in intervention group vs. control group	Outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/Effect size	Review limitation Overall conclusion	Quality of review Recommendations
						intervention in CRF management.	
McMillan and Newhouse, 2011[36] Canada	Not found[12] ≥18, all tumour types, disease stages, and treatment types Any	Exercise vs. Usual care	759 vs. 667	fatigue/FACT-F, PFS, BFI, LASA; SCFS (Primary or Secondary)	**Pooled exercise data (effects on CRF)**: SMD (95% CI), 0.28 [0.17, -0.38]; p < 0.00001	Limited evidence base. Exercise has beneficial effect on CRF.	Not specified[13]. Exercise should be considered as a treatment option to manage CRF. But the causes of CRF remain elusive, making targeted exercise prescriptions difficult.
		Aerobic exercise vs. Usual care	509 vs. 499	fatigue/FACT-F, PFS, BFI, LASA; SCFS (Primary or Secondary)	**Aerobic exercise (effects on CRF):** SMD (95% CI), 0.25 (0.12, 0.38); p < 0.001	Limited evidence base. Aerobic exercise programs had a small but statistically significant beneficial effect in reducing CRF.	
		Resistance training vs. Usual care	204 vs. 175	fatigue/FACT-F, PFS, BFI, LASA; SCFS	**Resistance training (effects on CRF):** SMD (95% CI), 1.66 (-0.41,	Limited evidence base. Resistance training	

[12] Emailed author to confirm.
[13] Authors stated: "methodological quality was not an inclusion criteria."

Author, Year Country	Search date Target population/ Treatment stage Type of cancer/Cancer site	Intervention vs. Comparison	# Ps in intervention group vs. control group	Outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/Effect size	Review limitation Overall conclusion	Quality of review Recommendations
				(Primary or Secondary)	3.73); p > 0.05	had a positive effect, but did not reach statistical significance.	
		Mixed (aerobic-resistance) exercise regime vs. Usual care	46 vs. 96	fatigue/FACT-F, PFS, BFI, LASA; SCFS (Primary or Secondary)	**Aerobic-resistance (effects on CRF):** SMD (95% CI), 0.22 (-0.006, 0.51); p > 0.05	Limited evidence base. Mixed programs displayed a positive effect, but did not reach statistical significance.	
Minton, 2014[44] UK	Inception - 2013 NR Any	Exercise vs. Control (not specified)	3000	Refer to the source/ referenced systematic review (Refer to the source/ referenced systematic review)	Overall effect size (refer to the referenced systematic review): -0.27 (95% CI -0.37 to -0.17)	Trial quality and contamination between groups undergoing interventions not specifically addressed. Research mainly carried out in best and prostate cancer patients/receiving treatment.	Refer to the source/referenced systematic review. Sufficient evidence exists to encourage exercise for CRF alleviation, particularly in those with earlier disease or on

Author, Year Country	Search date Target population/ Treatment stage Type of cancer/Cancer site	Intervention vs. Comparison	# Ps in intervention group vs. control group	Outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/Effect size	Review limitation Overall conclusion	Quality of review Recommendations
						Evidence found in favour of exercise. Only aerobic exercise had an effect and not resistance training.	active treatment. Recommendation cannot be made about frequency, duration or intensity.
Tomlinson, 2014[52] Canada	Inception-2012 Male & Female adults and children with cancer in active treatment or follow-up Any	Exercise vs. Usual care/non-exercise intervention	2057 vs. 1943	Fatigue/ FACT-F, Centre for Epidemio-logic Studies -Depression; EORTC QoL Question-naire Core 30-insomnia subscale (Primary or secondary)	**Fatigue reduction after exercise vs. control for cancer patients:** SMD (95% CI), -0.45(-0.57, -0.32); P < 0.00001	English publications only; heterogeneous vis-à-vis patient- and intervention-related factors; none of the studies were double-blinded; difficult to isolate exercise effects since several studies delivered other non-pharma intervention; one paediatric study. Exercise had a moderate effect on	Jadad score: Median score for study quality was 2 (range: 0-5). Exercise should be incorporated into the routine management of CRF, at least for adult cancer patients. The type of exercise may be tailored to the specific population.

Author, Year Country	Search date Target population/ Treatment stage Type of cancer/Cancer site	Intervention vs. Comparison	# Ps in intervention group vs. control group	Outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/Effect size	Review limitation Overall conclusion	Quality of review Recommendations
						the reduction of fatigue for patients with cancer.	
Larkin, 2014[51] Australia	1990-2012 Males≥18 yrs with prostate cancer at any disease stage; active treatment/ completed within the last 12 mo.; any previous treatment/ comorbidities; fatigue from cancer or its treatment. Prostate	Physical activity[14] vs. Usual care/other non-pharma-cologic inter-ventions	408	Fatigue/ FACT-F, FSS, PFS-Revised (Primary)	0/NR	NR Physical activity appears to show the greatest benefit; other non-pharmacological interventions like education and CBT have demonstrated benefit and should also be considered as a strategy in treating CRF.	JBI[15]: High (scored≥5). N/A

[14] Of the 5 included studies on physical activity: 2 = combined resistance + aerobic exercise; 1 = resistance exercise; 1 = aerobic exercise; 1 = aerobic vs. resistance exercise.
[15] JBI: Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Randomized and Pseudo-Randomized Studies.

Author, Year Country	Search date Target population/ Treatment stage Type of cancer/Cancer site	Intervention vs. Comparison	# Ps in intervention group vs. control group	Outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/Effect size	Review limitation Overall conclusion	Quality of review Recommendations
Zou, 2014[53] China	Inception-2013 Females ≥ 18 yrs diagnosed with breast cancer undergoing chemotherapy Breast	Aerobic exercise vs. Usual care	522 vs. 492 (from 12 clinical comparative studies)	Fatigue/ FACIT-F, Revised PFS (RPFS) (Main)	A. Differences in RPFS and FACIT-F scores of breast cancer patients in the aerobic exercise and usual care groups: **a) RPFS scores, 6 included studies: SMD (95% CI), -0.82 (-1.04, -0.60); P < 0.001;** b) FACIT-F scores, 6 included studies: SMD (95% CI), 0.09 (-0.07, 0.25); P = 0.224 B. Subgroup analysis by ethnicity for the differences in RPFS and FACIT-F scores	Relatively small sample size; possible recall/selection bias; lack of access to original data from the included studies. Aerobic exercise may improve CRF in breast cancer patients receiving chemotherapy, especially among Asian populations: A. RPFS scores of breast cancer patients in the intervention group were significantly lower than those in the control group; b) but no significant	Newcastle-Ottawa Scale (NOS) criteria: High (mostly >= 8). N/A

Author, Year Country	Search date Target population/ Treatment stage Type of cancer/Cancer site	Intervention vs. Comparison	# Ps in intervention group vs. control group	Outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/Effect size	Review limitation Overall conclusion	Quality of review Recommendations
					of breast cancer patients in the aerobic exercise and UC groups: **a) RPFS scores: *Asian* (3 studies), SMD (95% CI), -1.08 (-1.35, -0.82); P < 0.001)** *Caucasian* (3 studies), SMD (95% CI), -0.29 (-0.67, 0.09); P = 0.138 *Overall* (6 studies), SMD (95% CI), -0.82 (-1.04, -0.60); P < 0.001 **b) FACIT-F scores: *Asian* (1 study), SMD (95% CI), 1.20 (0.70, 1.71); P < 0.001**	difference in FACIT-F scores between the two groups. B. Subgroup analysis by ethnicity showed significant differences in RPFS and FACIT-F scores between intervention and control among Asian populations, but no significant difference between the two groups in Caucasian populations.	

Author, Year Country	Search date Target population/ Treatment stage Type of cancer/Cancer site	Intervention vs. Comparison	# Ps in intervention group vs. control group	Outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/Effect size	Review limitation Overall conclusion	Quality of review Recommendations
					Caucasian (5 studies), SMD (95% CI), 0.04 (-0.26, 0.35); P = 0.775) *Overall* (6 studies), SMD (95% CI), 0.27 (-0.16, 0.70); P = 0.224 C. Subgroup analysis by exercise time for the differences in RPFS and FACIT-F scores of breast cancer patients in the aerobic exercise and UC groups: **a) RPFS scores: ≤ *8 weeks* (4 studies), SMD (95% CI), -0.87 (-1.10, -**	C. Subgroup analysis based on exercise time showed significant difference of RPFS scores between intervention and	

Author, Year Country	Search date Target population/ Treatment stage Type of cancer/Cancer site	Intervention vs. Comparison	# Ps in intervention group vs. control group	Outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/Effect size	Review limitation Overall conclusion	Quality of review Recommendations
					0.64); P < 0.001 *> 8 weeks* (2 studies), SMD (95% CI), -0.41 (-1.09, 0.27); P = 0.240 *Overall* (6 studies), SMD (95% CI), -0.82 (-1.04, -0.60); P < 0.001 b) FACIT-F scores: *≤ 8 weeks* (2 studies), SMD (95% CI), 0.76 (-0.15, 1.57); P = 0.101 *> 8 weeks* (4 studies), SMD (95% CI), 0.01 (-0.33, 0.35); P = 0.946 *Overall* (6 studies), SMD (95% CI), 0.27 (-0.16, 0.70); P =	control in the ≤ 8-week subgroup, but not in the > 8-week subgroup; b) also, there was no difference in FACIT-F scores between the intervention and control groups in both the ≤ 8-week and >8-week subgroups.	

Author, Year Country	Search date Target population/ Treatment stage Type of cancer/Cancer site	Intervention vs. Comparison	# Ps in intervention group vs. control group	Outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/Effect size	Review limitation Overall conclusion	Quality of review Recommendations
					0.224		
Sawka, 2014[55] Canada	Inception-2014 Thyroid cancer survivors ≥ 18 yrs, whose disease was of any histologic subtype and who had completed primary treatment; any disease stage/status Thyroid Cancer (TC)	Exercise	36[16]	Chalder Fatigue Scale, Qualification of Fatigue, Vitality domain of Short Form-36 ("At least one quantitative measure of fatigue in respective intervention and control arms, at one or more time points after	0/NR	Search strategy did not specifically search for QoL as an outcome; restricted RCTs; evidence is limited for drawing conclusions. There is paucity of RCTs to guide evidence-based management of persistent post-treatment fatigue in TC survivors.	Cochrane Risk of Bias Tool[17]: Some limitations in reporting of the methods of all the trials; all trials lacked comprehensive reporting of adverse event details. N/A

[16] Two papers were considered as 1 RCT because they reported respective different fatigue outcomes for the same trial population, so data were abstracted together.
[17] For detailed critical appraisal results of included studies, refer to Table 3 in the article.

Author, Year Country	Search date Target population/ Treatment stage Type of cancer/Cancer site	Intervention vs. Comparison	# Ps in intervention group vs. control group	Outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/Effect size	Review limitation Overall conclusion	Quality of review Recommendations
				random-ization").			
Payne, 2012[35] UK	Inception - 2010 Adults 18 years or older with an advanced progressive illness known to have clinically significant fatigue and/or weight loss in the latter stages of illness. Lung/neck, not limited to these/All stages	Eico-sapentaenoic acid (EPA) and any drug therapy for the manage-ment of cancer-related fatigue vs. exercise, inter-ventions by breast care nurses and psychosocial inter-ventions	Total 17342 (116 studies)	Primary/ Not specified Fatigue	Not performed	Exercise interventions can lead to an improvement in fatigue in people with cancer, however, this beneficial effect is still to be proven for those in advanced stages of their illness.	1-specific exercise interventions might best manage fatigue in advanced stages of cancer. 2- Due to the heterogeneity of the included reviews, unable to provide any definitive recommendations for practice. 3- More research, both in terms of primary studies and more robust methodology, is required to ascertain the best interventions to

Author, Year Country	Search date Target population/ Treatment stage Type of cancer/Cancer site	Intervention vs. Comparison	# Ps in intervention group vs. control group	Outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/Effect size	Review limitation Overall conclusion	Quality of review Recommendations
							manage fatigue in advanced illness. There is a need for standardised reporting of these symptoms and the minimum acceptable duration of studies. 4- Researchers could improve the applicability of recommendations by including subgroup analysis.

Table C.5: Characteristics of Included Systematic Reviews - Non-Pharmacological (Psychosocial/Education Intervention)

Author, Year Country	Range of search date Target population/ Treatment stage Type of cancer/Cancer site	Interventions vs. Comparison	Total # of Ps (Ps in intervention group/Ps in control group)	Type of outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/ Effect size	Review limitation Overall conclusion (Quote)	Quality of review Recommend-ations
Psychosocial/Education/CBT							
Larkin, 2014[51] Australia	1990-2012 Males≥18 yrs with prostate cancer at any stage of disease; active treatment or completed within the last 12 months; any previous treatment or comorbidities; fatigue as a result of prostate cancer or its treatment. Prostate	Psychosocial interventions (3 included studies: 2 = CBT; 2 = education; 1= telephone interpersonal counselling) vs. Control (usual care/other non-pharmacological interventions)	461	Fatigue/MFI, FSI, CIS-fat (Primary)	0/NR	NR Physical activity appears to show the greatest benefit; other non-pharmacological interventions like education and CBT have demonstrated benefit and should also be considered as a strategy in treating CRF.	JBI[18]: High (scored≥5). N/A
Goedendorp, 2009[33]	Inception-2008 Males & Females ≥ 16 yrs patients with	Psychosocial interventions vs. Standard care/wait	3324	PFS, EORTC, POMS, MFI, VAS, SCFS, GFS, FSI	0/NR	High heterogeneity across included studies; might have missed relevant	Quality Rating Scale: Moderate.

[18] JBI: Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Randomized and Pseudo-Randomized Studies.

Author, Year Country	Range of search date Target population/ Treatment stage Type of cancer/Cancer site	Interventions vs. Comparison	Total # of Ps (Ps in intervention group/Ps in control group)	Type of outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/ Effect size	Review limitation Overall conclusion (Quote)	Quality of review Recommend-ations
Netherlands	any cancer type receiving active treatment with curative or palliative intention Any	list/control		(As long as fatigue is one of the outcome measures).		studies. There is limited evidence that psychosocial interventions during cancer treatment are effective in reducing fatigue. Fatigue-specific psychosocial interventions seem to be most promising.	N/A
Payne, 2012[35] UK	Inception - 2010 Adults 18 years or older with an advanced progressive illness known to have clinically significant fatigue and/or weight loss in the latter stages of illness. Lung/neck, not limited to these/All stages	Eico-sapentaenoic acid (EPA) and any drug therapy for the management of cancer-related fatigue vs. exercise, interventions by breast care nurses and psychosocial interventions	Total 17342 (116 studies)	Primary/ Not specified Fatigue	Not per-formed	Exercise interventions can lead to an improvement in fatigue in people with cancer, however, this beneficial effect is still to be proven for those in advanced stages of their illness.	1-specific exercise interventions might best manage fatigue in advanced stages of cancer. 2- Due to the heterogeneity of the included reviews, unable to

Author, Year Country	Range of search date Target population/ Treatment stage Type of cancer/Cancer site	Interventions vs. Comparison	Total # of Ps (Ps in intervention group/Ps in control group)	Type of outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/ Effect size	Review limitation Overall conclusion (Quote)	Quality of review Recommend-ations
							provide any definitive recommend-ations for practice. 3- More research, both in terms of primary studies and more robust methodology, is required to ascertain the best interventions to manage fatigue in advanced illness. There is a need for standardised reporting of these symptoms and the minimum acceptable

Author, Year Country	Range of search date Target population/ Treatment stage Type of cancer/Cancer site	Interventions vs. Comparison	Total # of Ps (Ps in intervention group/Ps in control group)	Type of outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/ Effect size	Review limitation Overall conclusion (Quote)	Quality of review Recommend-ations
							duration of studies. 4- Researchers could improve the applicability of recommend-ations by including subgroup analysis.

Table C.6: Characteristics of Included Systematic Reviews Non-Pharmacological (Complementary Therapies)

Author, Year Country	Range of search date Target population/ treatment stage Type of cancer/cancer site	Interventions vs. Comparison	Total # of Ps (Ps in intervention group vs. Ps in control group)	Type of outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/ Effect size	Review limitation Overall conclusion	Quality of review Recommendations
Acupuncture							
Zeng, 2014[47] China & UK	Inception-2013 Cancer survivors who completed post primary treatment + patients undergoing treatment[19] Any	Acupuncture vs. Sham acupuncture	60 vs. 61	Fatigue/ FACT-F, BFI, SF-36, MFI (Primary)	**General CRF score up to 10-week follow-up:** SMD [95% CI], -0.82 [-1.90, .26]; P = 0.14	Methodological flaws in the included trials; only 7 trials (with high risk of bias in methodological quality) included in meta-analysis; significant heterogeneity among combined trials; not all trials reported baseline data. Inconsistent evidence on the effectiveness of acupuncture for CRF.	Cochrane Assessment Tool: mixed results[20]. No recommendation can be made at this time.
		Acupuncture plus an intervention vs. Usual care	232 vs. 82	Fatigue/ FACT-F, BFI, SF-36, MFI (Primary)	**General CRF change scores up to 10-week follow-up:** -2.12 [-3.21, -1.03]; P = 0.0001		
		Acupuncture vs. No treatment/ wait-list control	75 vs. 75	Fatigue/ FACT-F, BFI, SF-36, MFI	**General CRF change scores up to 10-week follow-up:** -		

[19] Inclusion criteria were expanded to include cancer patients undergoing treatment during the searching stage given a limited number of studies found on acupuncture for cancer survivors.
[20] Three trials had a high risk of bias and four trials had a relatively low risk of bias. Major sources of risk of bias related to allocation concealment, blinding study subjects or research personnel, and blinding outcome assessment.

Author, Year Country	Range of search date Target population/ treatment stage Type of cancer/cancer site	Interventions vs. Comparison	Total # of Ps (Ps in intervention group vs. Ps in control group)	Type of outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/ Effect size	Review limitation Overall conclusion	Quality of review Recommendations
				(Primary)	1.46 [-3.56, 0.63]; P = 0.17		
		Acupuncture vs. Other treatment	80 vs. 83	Fatigue/ FACT-F, BFI, SF-36, MFI (Primary)	**General CRF change scores up to 10-week follow-up:** -1.12 [-3.03, 0.78]; P = 0.25		
Posadzki, 2013[30] South Korea/UK	Inception-2012 Patients (≥18 yrs, Males & Females) with any type and duration of cancer Any (most were breast cancer patients)	Aacupuncture /AT, electro-acupuncture/ EA/ AT+EA/ education + AT vs. Any control	548 (NR)	fatigue/ FACT-F, BFI (Primary)	0/NR	Not certain if all relevant trials were located; methodological/ statistical/ clinical heterogeneity; possible publication bias. The effectiveness of AT/EA for CRF is currently not proven.	Too low. No recommendation can be made at this time.
Chinese Herbal Medicine							
	Inception-2013	Chinese	751 (NR)	Fatigue,	0/NR	Most trials were of	Cochrane method:

Author, Year Country	Range of search date Target population/ treatment stage Type of cancer/cancer site	Interventions vs. Comparison	Total # of Ps (Ps in intervention group vs. Ps in control group)	Type of outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/ Effect size	Review limitation Overall conclusion	Quality of review Recommendations
Su, 2014[50] China & Australia	Diagnosed with CRF; any age, gender, tumor type, tumor stage and types of cancer treatment, including palliative care. Any	herbal medicine[21] vs. No treatment/ placebo/ conventional treatment		quality of life/FACT-F, BFI, SF-36, EORTC, AE; FSI; QoL-C; HADS, C30; VAS-F; TOI-F; CFS; BFI-C; KPS (Primary)		poor methodological quality; significant clinical heterogeneity; mostly short term interventions, and little is known about the economic value of CHM for CRF. CHM may be effective and safe in the treatment of CRF.	Mostly poor. Owing to poor and varying methodological quality of these trials and the heterogeneity of CHM intervention, potential promising findings must be interpreted with considerable caution.
Moxibustion							
Lee, 2014[54] South Korea	Inception-2013 Patients with any types/stage/treatment of cancer (including post-	Moxibustion vs. Control (waiting list/no treatment/ placebo	157 vs. 183 (events: 83 vs. 55)	Fatigue/ PFS (Main)	**Effectiveness of moxibustion for treating CRF on response**	All included studies were Chinese trials published in acupuncture journals; no trial compared	Cochrane risk of bias tool, CONSORT, STRICA: Low methodological quality & high risk

[21] Chinese herbal medicine: single herb, Chinese patent medicine, practitioner prescribed herbal formula and herbal products extracted from natural herb.

Author, Year Country	Range of search date Target population/ treatment stage Type of cancer/cancer site	Interventions vs. Comparison	Total # of Ps (Ps in intervention group vs. Ps in control group)	Type of outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/ Effect size	Review limitation Overall conclusion	Quality of review Recommendations
	treatment) with CRF Any	/routine or usual care[22])			**rate:** RR (95% CI), 1.73 (1.29, 2.32); P = 0.0003	moxibustion to a placebo control; most trials had a high risk of bias and methodological flaws. Favorable effects of moxibustion found on RR, but cannot conclude that moxibustion is an effective and safe treatment for CRF given low quality studies.	of reporting bias. No concrete recommendation can be made for the generalized use of moxibustion in patients with CRF.
Unspecified							
Finnegan-John, 2013[32] UK	Inception – 2012 ≥18 yrs Males & Females with cancer undergoing or had cancer treatment	Comp-lementary & alternative medicine (CAM)[23] vs. Control not specified)	1560	fatigue/ FACT-F, BFI, PFS, EORTC, POMS, MFI, MFSI, Trial Outcome	0/NR	Strong emphasis of Jadad scoring on blinding may compromise the perceived methodological quality of included	Jadad score: Most included trials were methodologically weak and at high risk of bias.

[22] Education, physical therapies, psychosocial interventions, or conventional alternative medications.
[23] The article found 20 eligible studies of which 15 were RCTs; forms of CAMs examined included acupuncture, massage, yoga, and relaxation training.

Author, Year Country	Range of search date Target population/ treatment stage Type of cancer/cancer site	Interventions vs. Comparison	Total # of Ps (Ps in intervention group vs. Ps in control group)	Type of outcomes evaluated/ Assessment tools (Outcome)	Meta-Analysis/ Effect size	Review limitation Overall conclusion	Quality of review Recommendations
	Any			Index-Fatigue, VAS for global fatigue, Fatigue subscale of the Glessen Complaints Inventory, Chalder Fatigue Question-naire, Rhoten Fatigue Scale (Primary or secondary)		CAM studies as blinding is almost impossible for CAM trials; Effect sizes could not be calculated. Limited evidence suggests: Hypnosis and ginseng may prevent rises in CRF in people undergoing treatment for cancer; Acupuncture and biofield healing may reduce CRF following cancer treatments. Multivitamins appear ineffective at reducing CRF.	No recommendation made at this time given the inconclusiveness of evidence reviewed.

Appendix D: Summary and Characteristics of Included Randomized Control Trials

Table D.1: Quality Assessment of Included Randomized Control Trials –Pharmacological Intervention

Author, Year	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Free of other bias	Declaration of funding	Statistical analysis methods section	Score
Del Fabbro,2013[62]	+[24]	+	+	+	-[25]	+	+	+	7
Yennurajalingam, 2013[74]	?[26]	?	+	+	+	+	+	+	6
Lesser,2013[65]	+	?	?	?	-	+	+	+	4
Sternberg,2013[71]	+	+	+	?	+	+	+	+	7
Spathis,2014[83]	+	+	+	+	-	+	+	+	7
Hovey,2014[79]	+	+	+	+	+	+	-	+	7
Escalante,2014[77]	?	?	+	+	-	+	+	+	5
Boele,2013[57]	?	+	+	+	-	+	+	+	6
Bruera,2013[58]	+	?	?	?	-	+	+	+	4
del Giglio,2013[63]	?	?	-	-	+	+	+	+	4

[24] + = Low risk of bias
[25] - = High risk of bias
[26] ? = Unclear risk of bias

Table D.2: Quality Assessment of Included Randomized Control Trials- Non-Pharmacological Intervention

Author, Year	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Free of other bias	Declaration of funding	Statistical analysis methods section	Score
Psychosocial/Education									
Montgomery, 2014[82]	+[27]	+	+	+	+	+	+	+	8
Wangnum,2013[72]	+	+	+	+	?[28]	+	-	+	6
Reif,2013[67]	+	+	-[29]	-	-	+	+	+	5
de Raaf,2013[61]	+	+	_	+	_	+	+	+	6
Physical Activity/Exercise									
Chandwani, 2014[76]	?	?	-	+	+	+	+	+	5
Kiecolt-Glaser,2014[81]	+	+	+	+	+	+	+	+	8
Spahn,2013[70]	+	+	-	-	-	+	+	+	5
Andersen,2013[56]	+	+	_	+	+	+	+	+	7
Cantarero-Villanueva,2013[59]	+	+	+	+	+	+	+	+	8
Wenzel,2013[73]	?	?	-	-	+	+	+	+	4
Bourke,2014[75]	?	?	-	-	+	+	+	+	4
Husebo,2014[80]	+	+	_	_	+	+	+	+	6
Cheville,2013[60]	+	+	-	+	+	+	+	+	6
Reis,2013[68]	?	?	?	?	+	-	+	+	3
Complementary Therapies									
Deng,2013[64]	*	+	+	+	+	+	+	+	7
Molassiotis, 2013[66]	+	?	-	+	-	+	+	+	5

[27] + = Low risk of bias
[28] ? = Unclear risk of bias
[29] - = High risk of bias

Author, Year	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Free of other bias	Declaration of funding	Statistical analysis methods section	Score
Smith,2013[69]	+	+	-	+	+	+	+	+	7
FitzHenry,2014[78]	+	?	-	+	+	+	+	+	6

Characteristics of Randomized Control Trials

Table D.3: Characteristics of Included Randomized Control Trials - Pharmacological Intervention

Author, Year Country	Disease site/stage Screen for eligibility	Comparison groups	Sample size (analyzed)	Weeks of response	Assessment tool; cut-off (baseline) Outcome measure (tool)	Effect size expressed as OR/RR/SMD/MD (95% confidence interval) P value	Summary Result
Del Fabbro, 2013[62] USA	All type/ Advanced 581	Intra-muscular testosterone replacement vs. Sesame seed oil placebo	29	D29/4 weeks	FACIT-F, ESASr/NR FACIT-F,ESASr	4±8 vs. −2±12 (mean, SD) 0.11	No effect: 4 weeks of intramuscular testosterone replacement did not significantly improve CRF compared to placebo.
Yennurajalingam, 2013[74] USA	All type/ Advanced 212	Dexametha-sone vs. Placebo (both 4mg twice a day)	43 vs. 41	D8/14 days	ESASr; 4/10 FACIT-F,ESASr	**8.01 ± 7.81 vs. 3.06 ± 7.28 (mean, SD)** **0.005**	**Effect:** Dexamethasone exceeded the effects of placebo in CRF improvement at day 8.
				D15/14 days	ESASr; 4/10 FACIT-F, ESASr	**9 ± 10.3 vs. 3.1 ± 9.59 (mean, SD)** **0.008**	**Effect**: Dexamethasone exceeded the effects of placebo in CRF improvement at day 15.
Lesser, 2013[65] USA	Breast/0-III Not tracked	Coenzyme Q10 vs. Placebo (both 300 mg combined with 300-IU vitamin E divided into 3 daily doses)	139	W24/24 weeks	NR FACIT-F, POMS	FACIT-F scores: 37.6 vs. 37.6 (least squares means); POMS scores: 7.08 vs. 8.24 (least squares means) FACIT-F scores: p = 0.965;	No effect: Coenzyme Q10 did not exceed the effects of placebo in reducing CRF.

Author, Year Country	Disease site/stage Screen for eligibility	Comparison groups	Sample size (analyzed)	Weeks of response	Assessment tool; cut-off (baseline) Outcome measure (tool)	Effect size expressed as OR/RR/SMD/MD (95% confidence interval) P value	Summary Result
						POMS scores: p = 0.257	
Sternberg, 2013[71] Sweden	Prostate/ N/A N/A	Abiraterone acetate (1g daily) + prednisone/ prednisolone (5mg twice daily) vs. Placebo + prednisone/ prednisolone (5mg twice daily)	794 random-ized to abira-terone acetate + prednisone vs. 398 random-ized to placebo + prednisone	W16, 28, 40/56 weeks	BFI; ≥5 BFI	**Fatigue intensity improvement: 1.392 (1.065, 1.818)** (Stratified Cox analysis hazard ratio, 95% CI) **0.0001** – fatigue intensity improvement	**Effect:** Abiraterone acetate and prednisone significantly increased the proportion of patients reporting improvement in fatigue.
				W16, 28, 40/56 weeks	BFI; ≥5 BFI	**Fatigue interference improvement: 1.393 (0.936, 2.071)** (Stratified Cox analysis hazard ratio, CI) **0.0075** - fatigue interference improvement	**Effect:** Abiraterone acetate and prednisone significantly increased the proportion of patients reporting improved fatigue interference.
				W16, 28, 40/56 weeks	BFI; ≥5 BFI	**Time to symptomatic improvement, fatigue intensity:** Median 59 days vs.	**Effect:** Abiraterone acetate and prednisone significantly increased the proportion of patients reporting

Author, Year Country	Disease site/stage Screen for eligibility	Comparison groups	Sample size (analyzed)	Weeks of response	Assessment tool; cut-off (baseline) Outcome measure (tool)	Effect size expressed as OR/RR/SMD/MD (95% confidence interval) P value	Summary Result
						194 days; HR: 1.392 (95% CI: 1.065-1.818) **0.0155** – accelerated fatigue intensity improvement	accelerated improvement in fatigue intensity.
Spathis, 2014[83] UK	Lung/III-IV 928	Modafinil vs. Placebo (both, 100 mg on days 1 to 14; 200 mg on days 15 to 28)	160 (75 vs. 85)	Baseline, D28/28 days	Numeric rating scale (NRS) of fatigue severity; ≥5/10 FACIT-F	No difference between treatments: Adjusted MD, 0.20 (95% CI: -3.56 to 3.97) 0.92	No effect: modafinil had no effect on CRF.
Hovey, 2014[79] Australia	Breast, prostate/ N/A 86	Modafinil (200 mg/day) vs. Placebo	83 (55 vs. 28)	D3-10/15D treat-ment period repeated for 2-4 chemo cycles	MDASI (MD Anderson Symptom Inventory) - Fatigue; ≥4/10 MDASI - Fatigue	Least squares mean: modafinil, 35.9 [32.4, 39.3] vs. placebo, 39.6 [35.1, 44.1]; Difference (modafinil-placebo): −3.7 (95% CI: -8.9, 1.4) 0.15	No effect: modafinil had no statistically significant effect on CRF; observed modest trends towards modafinil-related fatigue improvement.
Escalante, 2014[77]	Breast/ N/A	Methyl-phenidate vs. Placebo	33	W2/4 weeks	BFI; ≥4 BFI	Primary endpoint: No significant difference by the worst level of	No effect: Low-dose methylphenidate did not improve CRF

Author, Year Country	Disease site/stage Screen for eligibility	Comparison groups	Sample size (analyzed)	Weeks of response	Assessment tool; cut-off (baseline) Outcome measure (tool)	Effect size expressed as OR/RR/SMD/MD (95% confidence interval) P value	Summary Result
USA	42	(methyl-phenidate 18mg/day for 2 weeks followed by placebo for 2 weeks, or placebo for 2 weeks followed by methl-phenidate 18 mg/day for 2 weeks)				fatigue (p = 0.54, BASED ON A WILCOXON SIGNED RANK TEST). No significant difference between treatment arms for worst level of fatigue and overall BFI score (McNemar test p = 0.6 and p = 0.5, respectively). See left.	compared to placebo.
Boele, 2013[57] Netherlands	Brain/I-IV 155	Baseline vs. Placebo	36 vs. 26	W6,12/ 12 weeks	NR CIS[30]-Fatigue	Fatigue severity: -3.72[31]* <0.001	No effect: Modafinil did not exceed the effects of placebo with respect to symptom management.
		Baseline vs. Modafinil	36 vs. 29	W6,12/ 12 weeks	NR CIS - Fatigue	Fatigue severity: -2.56* 0.010	No effect: Modafinil did not exceed the effects of placebo with respect to symptom management.

[30] CIS, Checklist Individual Strength
[31] *= z-score [Mean ± SD (Baseline: 41.72 ± 9.22) (Modafinil: 34.99 ± 12.04) (Placebo: 35.14 ± 10.86)]

Author, Year Country	Disease site/stage Screen for eligibility	Comparison groups	Sample size (analyzed)	Weeks of response	Assessment tool; cut-off (baseline) Outcome measure (tool)	Effect size expressed as OR/RR/SMD/MD (95% confidence interval) P value	Summary Result
		Modafinil vs. Placebo	26 vs. 29	W6,12/ 12 weeks	NR CIS - Fatigue	Fatigue severity: -0.75*	No effect: modafinil did not exceed the effects of placebo with respect to symptom management.
Bruera, 2013[58, 32] USA	All types/ Advanced 333	Methyl-phenidate + NTI[33]	37	D15/14 days	ESASr; ≥4/10 FACIT-F	**Day15-Baseline FACIT-F Scores**: Median (IQR), 4.00 (-2.00, 11.0) 0.16	No effect: methyl-phenidate and NTI alone or combined were not superior to placebo in improving CRF. No statistical differences in the FACIT-F fatigue scores across all groups (Methylphenidate + NTI, Methylphenidate + CTI, Placebo + NTI, and Placebo + CTI).
		Methyl-phenidate + CTI[34]	31	D15/14 days	ESASr; ≥4/10 FACIT-F	**Day15-Baseline FACIT-F Scores**: Median (IQR), 7.00 (2.00, 11.00) 0.16	
		Placebo + NTI	38	D15/14 days	ESASr; ≥4/10 FACIT-F	**Day15-Baseline FACIT-F Scores**: Median (IQR), 8.50 (3.00, 17.00) 0.16	

[32] The study included 4 treatments: (1) One 5mg **MP capsule** every 2 hours up to 20 mg/day for 14 days + **NTI phone calls** 4-6 times over 2 weeks; (2) one **placebo** capsule every 2 hours up to 4 capsules/day for 14 days + **NTI phone calls** (as in 1); (3) **MP** treatment (as in 1) + **CTI** phone calls phone calls 4-6 times over 2 weeks; (4) **placebo** treatment (as in 2) + **CTI phone calls** (as in 3)
[33] NTI: Nursing telephone intervention
[34] CTI: Control telephone intervention

Author, Year Country	Disease site/stage Screen for eligibility	Comparison groups	Sample size (analyzed)	Weeks of response	Assessment tool; cut-off (baseline) Outcome measure (tool)	Effect size expressed as OR/RR/SMD/MD (95% confidence interval) P value	Summary Result
		Placebo + CTI	35	D15/14 days	ESASr; ≥4/10 FACIT-F	**Day15-Baseline FACIT-F Scores**: Median (IQR), 5.00 (0, 6.00) 0.16	
		Methyl-phenidate vs. Placebo	68 vs. 73	D15/14 days	ESASr; ≥4/10 FACIT-F	**Day15-Baseline FACIT-F Scores**: Median (IQR), 5.5 (-1.00, 11.00) vs. 6.00 (2.00, 11.00) 0.69	No effect: No significant difference in FACIT-F scores between the methylphenidate and placebo groups.
		NTI vs. CTI	75 vs. 66	D15/14 days	ESASr; ≥4/10 FACIT-F	**Day15-Baseline FACIT-F Scores**: Median (IQR), 6.00 (0, 14.00) vs. 5.50 (1.00, 10.00) 0.27	No effect: No significant difference in FACIT-F scores between the NTI and CTI groups.
		Methyl-phenidate + NPI	37	D15/14 days	ESASr; ≥4/10 ESASr Fatigue	**Day15-Baseline ESASr Fatigue Scores**: Median (IQR), -3.00 (-4.00, -1.00) 0.45	No effect: methylphenidate and NTI alone or combined were not superior to placebo in improving CRF. No statistical differences in the ESASr fatigue scores across all groups
		Methyl-phenidate +	29	D15/14 days	ESASr; ≥4/10	**Day15-Baseline ESASr Fatigue**	

Author, Year Country	Disease site/stage Screen for eligibility	Comparison groups	Sample size (analyzed)	Weeks of response	Assessment tool; cut-off (baseline) Outcome measure (tool)	Effect size expressed as OR/RR/SMD/MD (95% confidence interval) P value	Summary Result
		CTI			ESASr Fatigue	**Scores**: Median (IQR), -1.00 (-3.00, 0) 0.45	(Methylphenidate + NTI, Methylphenidate + CTI, Placebo + NTI, and Placebo + CTI).
		Placebo + NTI	37	D15/14 days	ESASr; ≥4/10 ESASr Fatigue	**Day15-Baseline ESASr Fatigue Scores**: Median (IQR), -2.00 (-5.00, 0) 0.45	
		Placebo + CTI	34	D15/14 days	ESASr; ≥4/10 ESASr Fatigue	**Day15-Baseline ESASr Fatigue Scores**: Median (IQR), -2.00 (-4.00, 0) 0.45	
		Methyl-phenidate vs. Placebo	66 vs. 71	D15/14 days	ESASr; ≥4/10 ESASr Fatigue	**Day15-Baseline ESASr Fatigue Scores**: Median (IQR), -2.00 (-4.00, 0) vs. -2.00 (-5.00, 0) 0.86	No effect: No significant difference in ESASr Fatigue scores between the methylphenidate and placebo groups.
		NTI vs. CTI	74 vs. 63	D15/14 days	ESASr; ≥4/10 ESASr Fatigue	**Day15-Baseline ESASr Fatigue Scores**: Median	No effect: No significant difference in ESASr Fatigue scores between

Author, Year Country	Disease site/stage Screen for eligibility	Comparison groups	Sample size (analyzed)	Weeks of response	Assessment tool; cut-off (baseline) Outcome measure (tool)	Effect size expressed as OR/RR/SMD/MD (95% confidence interval) P value	Summary Result
						(IQR), -2.50 (5.00, 0) vs. -2.00 (-4.00, 0) 0.14	the NTI and CTI groups.
del Giglio, 2013[63] Brazil	All type/ N/A 40	Purified dry extract of Paullinia cupana (PC-18) vs. Placebo	17 vs. 16	Baseline, D21/6 weeks	BFI[35] BFI	**2.503 (1.716, 3.375)** (MD, 95% CI) **0.0002**	**Effect: Fatigue scores improved significantly after PC-18 treatment at Day 21.**
			16 vs. 14	D42/6 weeks	BF BFI	2.790 (2.168) vs. 2.951 (2.873) (mean, SD) 0.8499	No effect: Fatigue did not improve significantly after PC-18 treatment at Day 48.

[35] Fatigue assessment tool (BFI) cut-off "had to show an increase in their BFI scores after 1 week of systemic chemotherapy"

Table D.4: Characteristics of Included Randomized Control Trials Non- Pharmacological (Physical Activity/Exercise Intervention)

Author, Year Country	Disease site/stage Screen for eligibility	Comparison groups	Sample size (analyzed)	Weeks of response	Assessment tool; cut-off Outcome measure	Effect size expressed as Odds Ratios (95% confidence interval) P value	Summary result
Chandwani, 2014[76] USA	Breast/0-III 294	Yoga vs. Wait list control	49 vs. 48	W6/6 weeks	NR BFI	N/A 0.04	**Effect: Significantly greater decrease in fatigue for yoga group than control group at the end of treatment.**
			39 vs. 43	1mo follow-up	NR BFI	N/A 0.09	No effect: No statistically significant difference in fatigue between yoga and control at 1-month follow-up.
		Stretch vs. Wait list control	52 vs. 48	W6/6 weeks	NR BFI	N/A 0.02	**Effect: Significantly greater decrease in fatigue for stretch than control at the end of treatment.**
			41 vs. 42	3 mo follow-up	NR BFI	N/A 0.07	No effect: No statistically significant difference in fatigue between stretch and control at 3-mo follow-up.

Author, Year Country	Disease site/stage Screen for eligibility	Comparison groups	Sample size (analyzed)	Weeks of response	Assessment tool; cut-off Outcome measure	Effect size expressed as Odds Ratios (95% confidence interval) P value	Summary result
Kiecolt-Glaser, 2014[81] USA	Breast/0-III + survivors 458	Yoga classes vs. Wait list control	96 vs. 90	End of treatment (M3)/3 months	NR MSFI-SF [36]	Adjusted mean 6.1 vs. 10.3; Cohen's d = -0.22 0.058	No effect: Immediately post-treatment, fatigue was not lower between yoga and control groups.
				3 months follow-up	NR MSFI-SF	**Adjusted mean 5.4 vs. 12.4; d = -0.36** **0.002**	**Effect: At 3 months post-treatment, fatigue was lower in the yoga group.**
Spahn, 2013[70] Germany	Breast/I-III 335	Multimodal mind-body (MMMB) program vs. Walking intervention alone	30 vs. 25	W10 post-treatment /10 weeks	VAS; >40/100mm MFI, VAS	Post-treatment, group difference in fatigue scores: -0.3 (-1.6, 1.0) (MD, 95%CI) 0.678	No effect: MMMB program had no more beneficial effect on CRF reduction post-treatment than control (walking intervention alone).
				3 month follow-up	VAS; >40/100mm MFI, VAS	Follow-up, group difference in fatigue scores: -0.4 (-1.8, 0.9) (MD, 95%CI) 0.510	No effect: Multimodal mind-body program had no more beneficial effect on CRF reduction at 3-month follow-up than control (walking intervention alone).
	All type/NA	Supervised	213	W6/6	NR	**0.44 (0.17, 0.72) (MD,**	**Effect: Supervised**

[36] MSFI-SF, Multidimensional Fatigue Symptom Inventory - Short Form

Author, Year Country	Disease site/stage Screen for eligibility	Comparison groups	Sample size (analyzed)	Weeks of response	Assessment tool; cut-off Outcome measure	Effect size expressed as Odds Ratios (95% confidence interval) P value	Summary result
Andersen, 2013[56] Denmark	N/A	exercise[37] vs. Wait list control		weeks	FACT-An - fatigue subscale	**CI)** **0.002**	**exercise had a beneficial effect on CRF compared to control (wait list control).**
Cantarero-Villanueva, 2013[59] Spain	Breast/I-III 163	Aquatic exercise vs. Usual control	32 vs. 29	Baseline, W8/8 weeks	Piper Fatigue Scale; NR Piper Fatigue Scale	**Total fatigue score: d = 0.87 (95% CI, 0.48, 1.26)** **<0.001**	**Effect: Aquatic exercise showed a large effect size in total fatigue score immediately after treatment.**
				6 mo follow-up		**Intergroup effect size, d = 1.51 (95% CI, 1.13-1.90)** **<0.001**	**Effect: Aquatic exercise maintained beneficial effect on fatigue scores at 6-month follow-up.**
Wenzel, 2013[73] USA	All type/I-III 5349	Home-based walking intervention vs. Usual care	68 vs. 58	Post-test/5-35 weeks depending on individual cancer treatment protocols	NR PFS, POMS	**PAQFA[38] effect[39] (95% CI), −0.11 (-0.16,0.06)** **<0.001**	**Effect: Home-based walking intervention was more helpful in reducing CRF than usual care.**

[37] Supervised exercise comprised of high-intensity cardiovascular and heavy resistance training, relaxation- and body awareness training and massage, 9h weekly for 6 weeks.
[38] PAQFA: Physical Activity Questionnaire.
[39] PAQFA effect: rate of change in outcome for change in 10 met/hr, adjusted for baseline outcome, age, baseline, and post-test PAQFA.

Author, Year Country	Disease site/stage Screen for eligibility	Comparison groups	Sample size (analyzed)	Weeks of response	Assessment tool; cut-off Outcome measure	Effect size expressed as Odds Ratios (95% confidence interval) P value	Summary result
Bourke, 2014[75] UK	Prostate/ N/A 136	Life style intervention (tapered exercise + dietary advice + behaviour change support) vs. Usual care	85 vs. 68	Week 12/12 weeks	NR FACIT-F	**5.3 (2.7, -7.9) (MD, 95% CI)** **Adjusted p < 0.001**	**Effect: Life style change intervention (with exercise component) had a beneficial effect on CRF reduction at 12 weeks.**
				6 mo follow-up	NR FACIT-F	**3.9 (1.1, 6.8) (MD, 95% CI)** **Adjusted p = 0.007**	**Effect: Life style change intervention (with exercise component) had a beneficial effect on CRF reduction at 6 months follow-up.**
Husebo, 2014[80] Norway	Breast/I-III 93	Scheduled home-based exercise vs. Regular physical activity	54	Baseline/ Depending on individual chemo duration	NR SCFS-6 (Schwartz Cancer Fatigue Scale)	Baseline Fatigue scores, Mean (SD): 10.28 (3.93) vs. 11.36 (3.56) Baseline-end of chemo fatigue score change, p = 0.003; Time x condition, df = 1/58; F = 0.001; p = 0.970	No effect: Fatigue scores increased significantly from baseline to end of chemotherapy for the whole sample. No beneficial effect of exercise on CRF.
				End of chemo-therapy	NR SCFS-6 (Schwartz	End of chemo, Mean (SD): 12.01 (4.38) vs. 13.13 (4.47); Baseline-end of chemo fatigue	

Author, Year Country	Disease site/stage Screen for eligibility	Comparison groups	Sample size (analyzed)	Weeks of response	Assessment tool; cut-off Outcome measure	Effect size expressed as Odds Ratios (95% confidence interval) P value	Summary result
					Cancer Fatigue Scale)	score changes: d = 0.41 Baseline-end of chemo fatigue score change, p = 0.003; Time x condition, df = 1/58; F = 0.001; p = 0.970	
				6 mo follow up	NR SCFS-6 (Schwartz Cancer Fatigue Scale)	Follow-up Fatigue scores, Mean (SD): 10.43 (3.27) vs. 10.42 (3.32) Baseline-follow up fatigue score change, p = 0.181; Time x condition, df = 1/50; F = 0.398; p = 0.463	No effect: There was no significant difference between exercise and control groups in fatigue levels at 6-month follow-up.
Cheville, 2013[60] USA	Lung, colorectal/ IV 93	Incremental walking and home-based strength training vs. Usual care	26 vs. 30	W8/6 weeks	NR FACIT-F	**Intervention vs. Control, Mean change in FACIT-F scores baseline-W8: MD (SD; 95% CI), 4.46 (8.65; 0.81, 8.11) vs. -0.79 (9.11; -4.26, 2.67), p = 0.03**	**Effect: A home-based exercise program improved CRF compared with the usual care group.**

Author, Year Country	Disease site/stage Screen for eligibility	Comparison groups	Sample size (analyzed)	Weeks of response	Assessment tool; cut-off Outcome measure	Effect size expressed as Odds Ratios (95% confidence interval) P value	Summary result
						Intergroup differences in mean FACIT-F scores at W8: **p = 0.002**	
Reis, 2013[68] USA	Breast/I-III N/A	Non-traditional exercise/ home-based Nia program vs. Usual care	29	W6,12/12 weeks	NR FACIT-F	**Between W6-12, FACIT-F total scores increased by almost 17 points in Nia exercise group vs. 4 points in the control group** **0.05**	**Effect: The Nia exercise had a significant beneficial effect on CRF compared to the usual care group.**

Table D.5: Characteristics of Included Randomized Control Trials - Non- Pharmacological (Psychosocial/Education Intervention)

Author, Year Country	Disease site/stage Screen for eligibility	Comparison groups	Sample size (analyzed)	Weeks of response	Assessment tool; cut-off Outcome	Effect size expressed as Odds Ratios (95% confidence interval) P value	Summary result
Montgomery, 2014[82] USA	Breast/0-III 271	CBT + hypnosis (CBTH) vs. Attention control	91 vs. 90	End of RT/ depends on RT	NR FACIT-F; VAS	**z, 6.73; *d*, 0.83 (95% CI: 0.54, 1.11)** **Adjusted p[40] <0.001**	**Effect:** CBTH group had significantly less fatigue than placebo group.
				4 week follow-up	NR FACIT-F; VAS	**z, 6.98; *d*, 0.92 (95% CI: 0.63, 1.21)** **Adjusted p <0.001**	**Effect:** CBTH group had significantly less fatigue than placebo group.
				6 month follow-up	NR FACIT-F; VAS	**z, 7.99; *d*, 1.69 (95% CI: 1.37, 2.01)** **Adjusted <0.001**	**Effect:** CBTH group had significantly less fatigue than placebo group.
Wangnum, 2013[72] Thailand	Lung/III-IV 60	Multi-disciplinary self-care education program vs. Usual care	60	/9 weeks	NR Piper Fatigue Scale	**2.98 1-96 vs, 3.99 1.64 (experiment vs control)** **3.99 ± 1.64 vs. 2.98 ± 1.96 (mean, SD)** **0.036**	**Effect** **Effective in reducing CRF**

[40] A family-wise error correction was applied to maintain an overall α level of 0.05 for each outcome model based; adjusted *p* values were reported on the basis of this single-step multiple comparison correction.

Author, Year Country	Disease site/stage Screen for eligibility	Comparison groups	Sample size (analyzed)	Weeks of response	Assessment tool; cut-off Outcome	Effect size expressed as Odds Ratios (95% confidence interval) P value	Summary result
Reif, 2013[67] Germany	All type/ N/A 327	Patient education vs. Wait list control	234	/6 mo	NCCN rating; >=4/10 FAQ (Fatigue Assessment Questionnaire)	**Partial η2[41]* = 0.248** **F = 76.510, p <0.001**	**Effect: Effective in reducing CRF**
de Raaf, 2013[61] Netherlands	All type/ Advanced cancer Assessment was impossible	Protocolized patient-tailored treatment (PPT) of symptoms vs. Usual care	71 vs. 66	Baseline, 1 month follow-up /10 weeks	NRS; ≥4 BFI, MFI	**MD (SE), -0.84 (0.31); effect size, d = 0.26** **0.007**	**Effect: Significant improvement in fatigue after PPT compared to usual care at month 1**
				2 month follow-up	NRS; ≥4 BFI, MFI	**MD (SE), -1.14 (0.40); effect size, d = 0.35** **0.005**	**Effect: Significant improvement in fatigue after PPT compared to usual care at month 2**

[41] *partial eta-squared (h2)

Table D.6: Characteristics of Included Randomized Control Trials - Non- Pharmacological (Complementary Therapies)

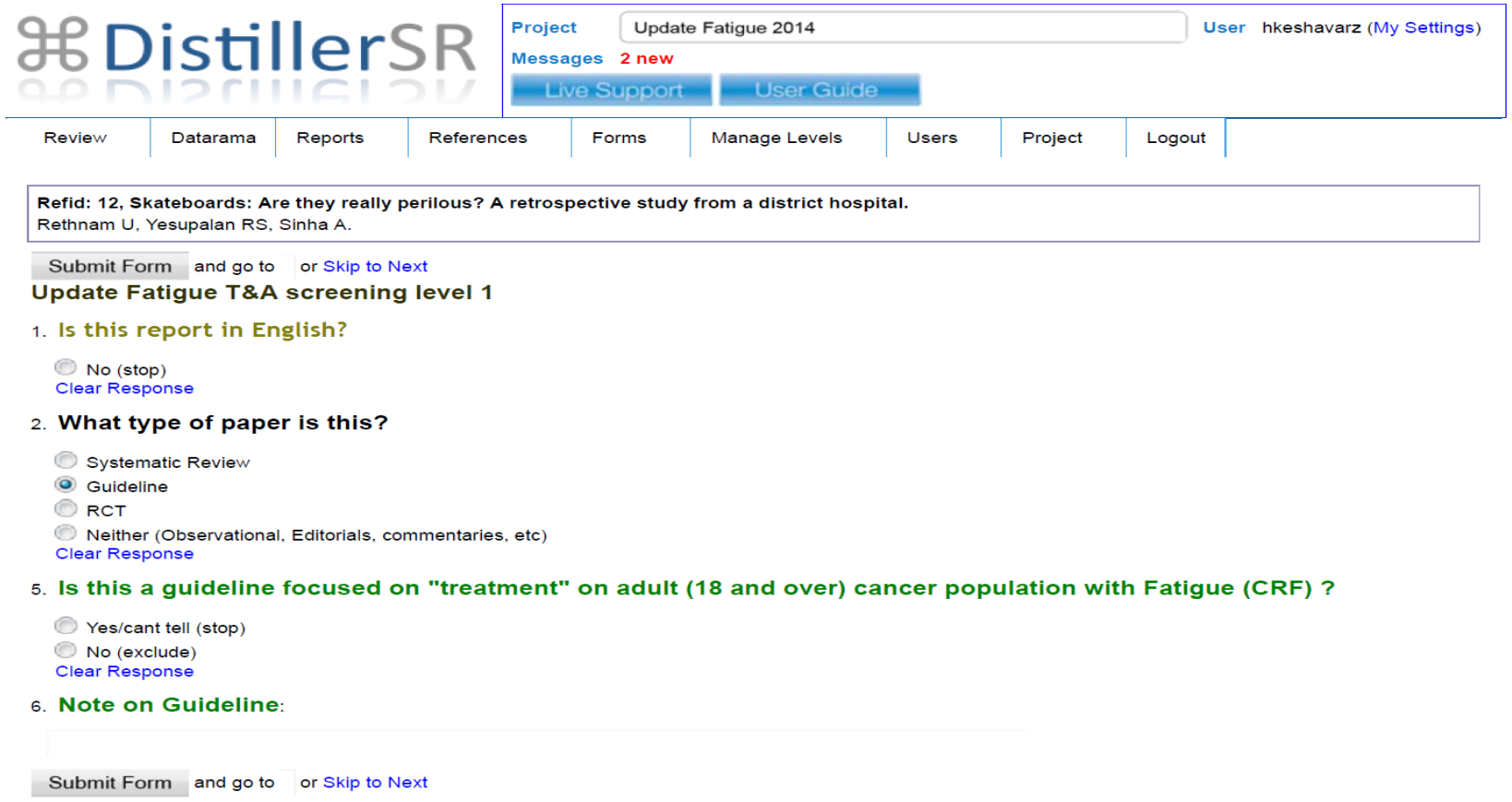
Author, Year Country	Disease site/stage Screen for eligibility	Comparison groups	Sample size (analyzed)	Weeks of response	Assessment tool; cut-off Outcome measure	Effect size expressed as Odds Ratios (95% confidence interval) P value	Summary result
Deng, 2013[64] USA	All type/ N/A 1006	True acupuncture vs. Sham acupuncture	34 vs. 40	Baseline/6 weeks	BFI; ≥4 BFI	Baseline BFI scores, True acupuncture vs. Placebo: Mean (SD), 6.0 (1.36) vs. 6.3 (1.57) Post-treatment difference, p = 0.9	No effect: True acupuncture did not reduce post-chemotherapy chronic fatigue more than did sham acupuncture.
				Post-treatment (mean of D42, 49)	BFI; ≥4 BFI	Post-treatment BFI scores, True acupuncture vs. Placebo: Mean (SD), 4.8 (1.88) vs. 5.1 (2.00) Post-treatment difference, p = 0.9	
				Baseline vs. Post-treatment	BFI; ≥4 BFI	Post-treatment difference in BFI scores: MD (95% CI), 0.04(-0.57, 0.66) Post-treatment difference, p = 0.9	
Molassiotis, 2013[66]	Breast/I-III N/A	Acupunc-turist-delivered main-	56	W10[42]/10 weeks	NR MFI	0.57 (-0.18, 0.04) (MD, 95% CI) 0.13	No effect: Therapist-delivered and self-needling maintenance

[42] Primary outcome was the MFI GF score at 10 weeks (4 weeks after re-randomization)

Author, Year Country	Disease site/stage Screen for eligibility	Comparison groups	Sample size (analyzed)	Weeks of response	Assessment tool; cut-off Outcome measure	Effect size expressed as Odds Ratios (95% confidence interval) P value	Summary result
UK		tenance acupuncture					acupuncture did not improve fatigue beyond the improvements observed after an initial clinic-based course of acupuncture.
		Self-needling main-tenance	46	W10/10 weeks	NR MFI	0.54 (-0.21, 0.13) (MD, 95% CI) 0.13	
		No main-tenance treatment	49	W10/10 weeks	NR MFI	-0.35 (-0.52, 1.21) (MD, 95% CI) 0.13	
Smith, 2013[69] Australia	Breast/ N/A 84	Acupuncture vs. Sham acupuncture vs. Wait list control	9 vs. 10 vs. 10	W2/8 weeks	BFI; ≥4 BFI	**5.3 (4.5, 6.2)** (MD, 95% CI) **0.05**	**Effect: Acupuncture had beneficial effect on CRF than control at week 2.**
				W4/8 weeks	BFI; ≥4 BFI	4.6 (3.6, 5.6) (MD, 95% CI) 0.06	No effect: Acupuncture had no significant effect on fatigue at week 4.
				W6/8 weeks	BFI; ≥4 BFI	4.6 (3.6 to 5.5) (MD, 95% CI) 0.08	No effect: Acupuncture had no significant effect on fatigue at week6.
FitzHenry, 2014[78] USA	Breast/ N/A 70	Healing touch vs. Sham therapy	41	5-7 weeks depending on RT	NR BFI	N/A >0.05	No effect: This pilot study found no beneficial effect of healing touch on fatigue compared to sham therapy.

Appendix E: Screening Forms for Title and Abstract, Full text, Data Extraction, and Quality Assessments

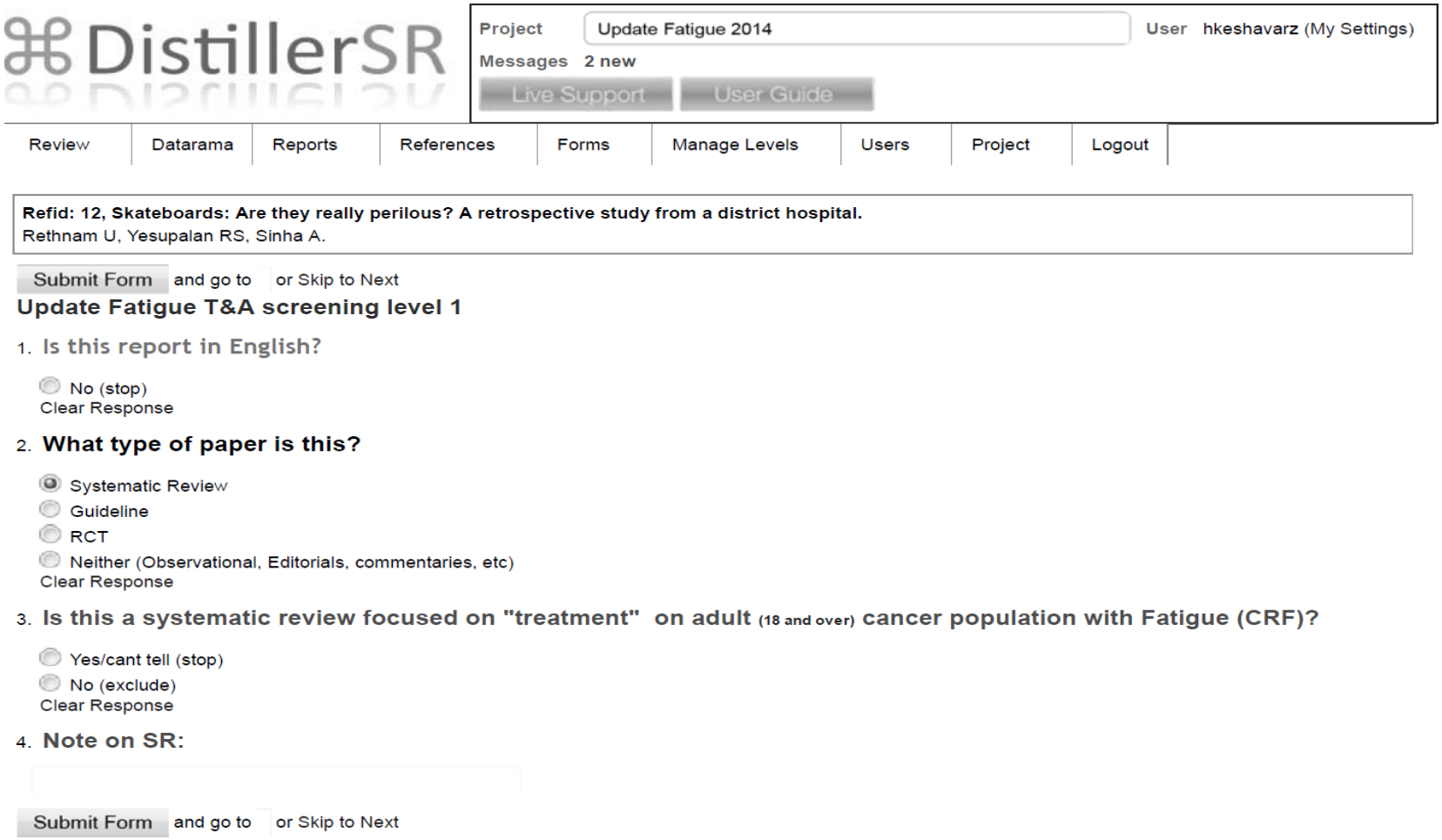
Level 1 Guideline



Level 1 RCT


DistillerSR
Project
Update Fatigue 2014
User
hkeshavarz (My Settings)
Messages
2 new
Live Support
User Guide
Review
Datarama
Reports
References
Forms
Manage Levels
Users
Project
Logout
Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.
Submit Form
and go to
or Skip to Next
Update Fatigue T&A screening level 1
1. Is this report in English?
No (stop)
Clear Response
2. What type of paper is this?
Systematic Review
Guideline
RCT
Neither (Observational, Editorials, commentaries, etc)
Clear Response
7. Is this an RCT/CCT focused on "treatment" on adult (18 and over) cancer population with Fatigue (CRF) ?
yes/cant tell
No (exclude)
Clear Response
8. Note on RCT
Submit Form
and go to
or Skip to Next

Level 1 SR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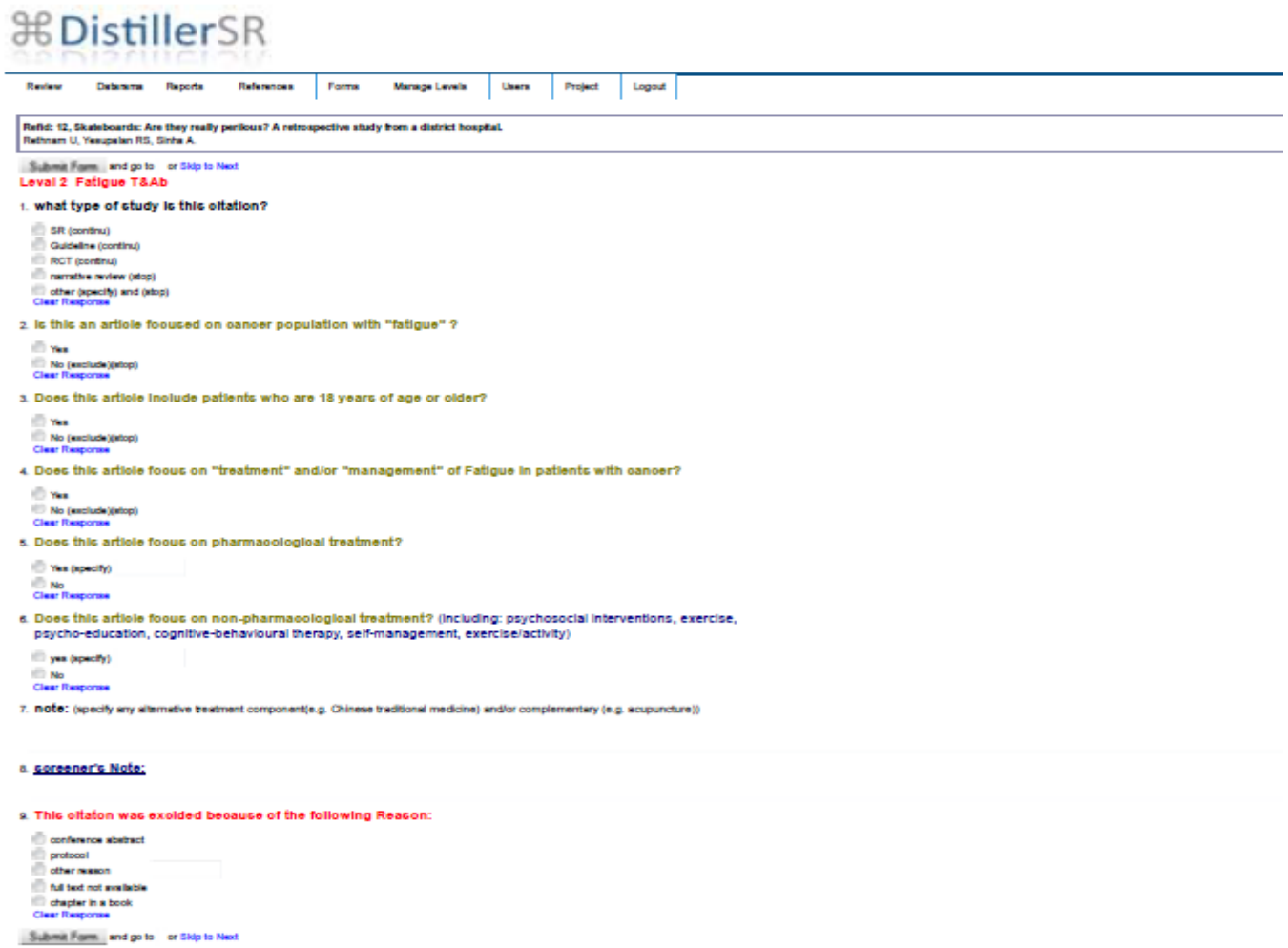
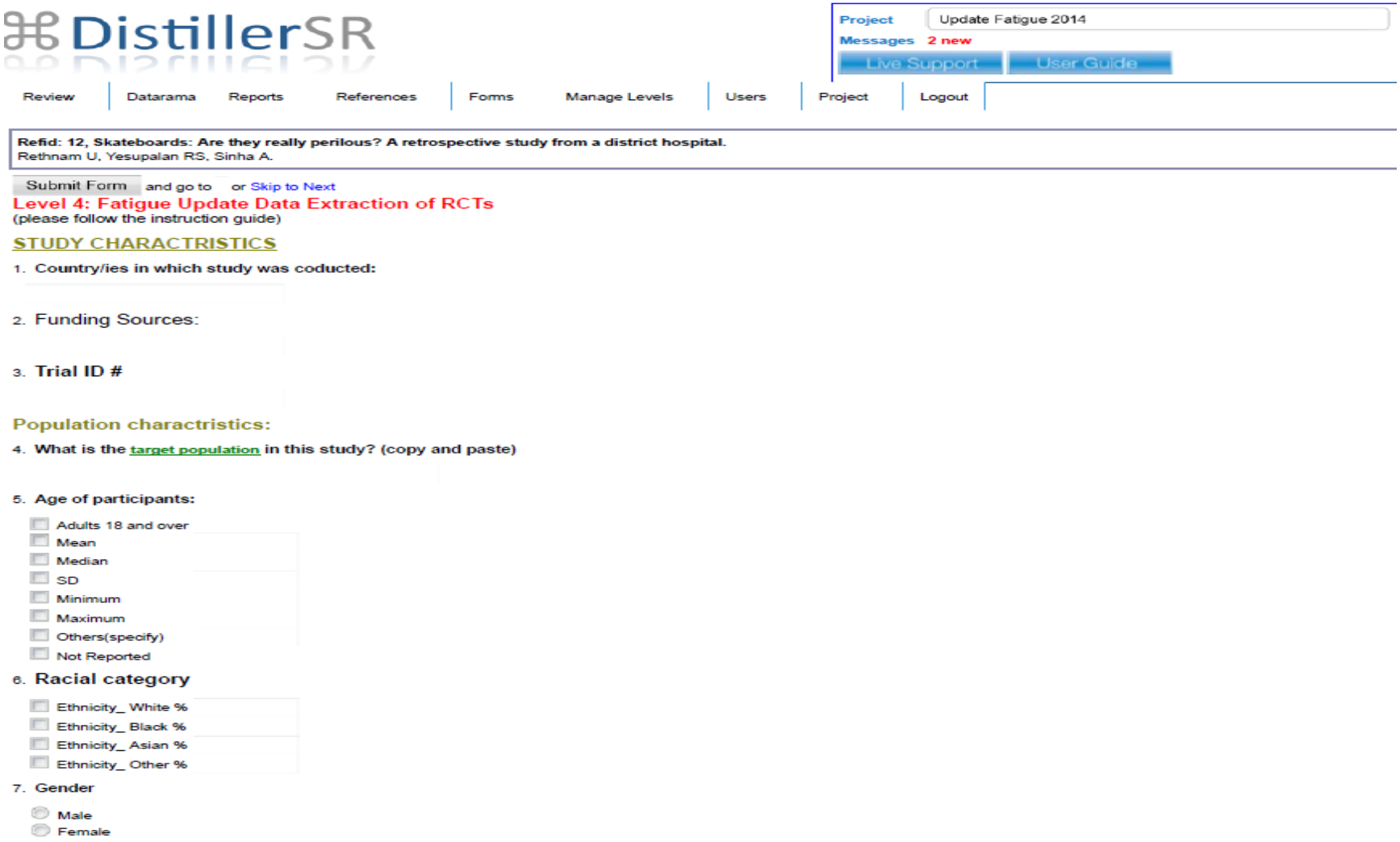
Update Fatigue 2014
User
hkeshavarz (My Settings)
Messages
2 new
Live Support
User Guide
Review
Datarama
Reports
References
Forms
Manage Levels
Users
Project
Logout
Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.
Submit Form
and go to
or Skip to Next
Update Fatigue T&A screening level 1
1. Is this report in English?
No (stop)
Clear Response
2. What type of paper is this?
Systematic Review
Guideline
RCT
Neither (Observational, Editorials, commentaries, etc)
Clear Response
3. Is this a systematic review focused on "treatment" on adult (18 and over) cancer population with Fatigue (CRF)?
Yes/cant tell (stop)
No (exclude)
Clear Response
4. Note on SR:
Submit Form
and go to
or Skip to Next

Level 2 Title and Abstract



Level 3 Data Extraction: RCT



- ◯ Both male & Female
- ◯ Not Reported

Clear Response

8. **% Male**

METHODOLOGY

9. **Cancer site:**

- ☐ 1,
- ☐ 2,
- ☐ 3,
- ☐ All type

10. **Cancer stage:**

- ☐ 1
- ☐ 2
- ☐ 3

11. **Study design**

- ◯ Double blind placebo control
- ◯ Open lable
- ◯ Cross-over double blind placebo control
- ◯ Paralled double blind placebo controlled
- ◯ Single blind
- ◯ parallel trial
- ◯ cross-over trial
- ◯ factorial trial
- ◯ N-of-1 trial
- ◯ cluster trial
- ◯ Other (specified)

Clear Response

12. **Recruitment period: (range-years)**

- ☐ From
- ☐ To
- ☐ duration (months)
- ☐ duration (week)
- ☐ duration (year)

13. **Setting:**

- ◯ Hospital
- ◯ Oncology clinic
- ◯ Outpatient clinic
- ◯ Palliative Care
- ◯ other (specify

Clear Response

14. **Single or multi-center**

- [ ] Single
- [ ] Multi-center(specify)
- [ ] Not Reported
- [ ] # of centers

15. **Duration of treatment** (check one only)

- ( ) Days
- ( ) weeks
- ( ) months
- ( ) years
- ( ) Not Reported

Clear Response

16. **Frequency of treatment** (check 1 only)

- ( ) Time per day
- ( ) Time per week
- ( ) time per month
- ( ) Not reported

Clear Response

17. **Duration of the individual treatment unit** (check 1 only)

- ( ) Weeks
- ( ) Months
- ( ) years
- ( ) Not reported

Clear Response

18. **Lengh of follow up from Randomization:**(specify D,w, M, or Y)

- [ ] Minimum
- [ ] Maximum
- [ ] Median
- [ ] Mean
- [ ] others (specify)

19. **# of Treatment groups/Arm:**

- [ ] Treatment
- [ ] Control

20. **Inclusion criteria**

21. **Exclusion criteria:**

22. **What was the eligibility criteria of Population in this RCT?: Please describ included population in this study. (copy and paste)**

23. **Type of patients' Cancer Treatment:** (check all that apply)

- ☐ Chemotherapy
- ☐ Radiation therapy
- ☐ Hormone therapy
- ☐ Immunotherapy
- ☐ Post treatment/Survivors
- ☐ Post treatment/Disease free
- ☐ Others (specify)

Table: Sample size, Participant Flow throw study:

Number of individual approached to take part in the study?	
Total Patients randomized (raw number)	
Patients randomized (raw number) Treatment group 1	
Patients randomized (raw number) Treatment group 2	
Patients randomized (raw number) Treatment group 3	
Patients randomized (raw number) Control arm	
Lost to follow-up: withdrew consent (raw number)	
31. **Lost to follow-up: withdrew due to adverse effects (please specify)**	
Lost to follow-up: withdrew due to lack of improvement	
Lost to follow-up: withdrew due to loss of contact or migration (raw number)	
Lost to follow-up: withdrew due to Other Reasons (raw number)	

37. **What is the definition of Fatigue in this study? (copy and paste)**

38. **What type of tool measurement assessed/screened for eligibility beofre treatment?**

- [ ] FACRT-F /FACT-F
- [ ] PFS
- [ ] BFI
- [ ] SF-36
- [ ] EORTC
- [ ] Quality of Life Questionnaire fatigue scale
- [ ] POMS
- [ ] MFI
- [ ] Other: used a fatigue measure not categorized above
- [ ] Not Reported

40. **Baseline Fatigue cut off point for diagnosis** (T-score or any other measure e.g. at least 4 of 10 on a 0-10 numerical rating scale)

- [ ] 1
- [ ] Not Reported
- [ ] 2
- [ ] Not Reported

41. **Intervention:**

- [ ] Pharmacological
- [ ] Non-pharmacological
- [ ] Alternative

42. **Type of intervention (list all that apply)**

- [ ] 1,
- [ ] 2,
- [ ] 3,

43. **Type of comparison (list all that apply)**

- [ ] 1,
- [ ] 2,
- [ ] 3,

Outcome Measur:

44. **How many outcomes are measured for fatigue?**

45. **what type of outcome is specific to fatigue?**

- [ ] Primary
- [ ] Secondary
- [ ] Tertiary
- [ ] Main
- [ ] Others (speify)

RESULTS $ Study Outcomes

46. **What type of tool measurement assessed after treatment?**

- [ ] FACRT-F /FACT=F
- [ ] PFS
- [ ] BFI
- [ ] SF-36
- [ ] EORTC
- [ ] Quality of Life Questionnaire fatigue scale
- [ ] POMS
- [ ] MFI
- [ ] Other: used a fatigue measure not categorized above
- [ ] Not Rported

47. **sample size:**

- [ ] Total Sample size
- [ ] # of eligible
- [ ] # of Randomized
- [ ] # of included
- [ ] # completed the study
- [ ] # evaluated

48. **Statistical Methods:** (list statistical tests or cut&paste)

- ( ) Yes
- ( ) No

Clear Response

Table1 Outcome: Treatment/intervention Group (please fill all information that apply only to the treatment/treatment group)

Type of Intervention	Total #	# of events	Binary/Continuous outcome	Effect Measures	Measure of Central Tendency	Effect Size	Low CI	Upp. CI	P-value	Frequency of Treatment	Dose/Duration of treatment
Time1											
Time2											
Time3											

85. **Instruction for table 1 and 2:**
Effect measure can be odds ratio (OR), risk ratio (RR), Hazard ratio (HR), or absolut risk reduction (ARD) or risk decreasd (RD).
Measure of central tendency can be Mean, Median, or Mode.
Unit of variance measure can be standard deviation (SD), standard error (SE), 95% CI. IQR, or Range

Table2 Outcome: Control Group (please fill all information that apply to the control group)

Type of control	Total #	# of events	Binary/Continuous outcome	Effect Measures	Measure of Central Tendency	Effect Size	Low CI	Upp. CI	P-value	Frequency of Treatment	Dose/Duration of treatment
T1											

Time2											
Time3											

122. **Covariate adjustment for:**

- 1.
- 2.
- 3.
- 3.

123. **Outcome assessment related Fatigue** (e.g. % of reduction of score)

124. **Main results:**

- 1.
- 2.
- 3.
- 4.

125. **Summary Main Results**

- Benefits
- No effect
- Inconsistent
- others(specify)

Clear Response

126. **Adverse events or any side effects (specify all that apply)**

- 1
- 2
- 3
- 4

Study Conclusion

127. **Key Conclusion:**

- 1.
- 2.
- 3.
- 4.

128. Data extractor Note:

129. Extracted data verified by:

- HK
- JY
- MW
- other (specify)

Clear Response

Submit Form and go to or Skip to Next

Level 3 Data Extraction: SR

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Level 3: Fatigue Data Extraction of Systematic Reviews
(please follow the instruction guide)

STUDY CHARACTRISTICS

1. **Country in which study was coducted:**

2. **Is it a Cochrane systematic review?**

   - Yes
   - No

   Clear Response

3. **Cancer site:**

   - 1,
   - 2,
   - 3,
   - All type

METHODOLOGY

4. **Search Dates in year (4 digits):**

   - From
   - To

5. **Number of RCTs included in this systematic review:**

   - RCT

- [ ] Number of participants
- [ ] Not Reported

6. **Number of non-RCTs included in this systematic review**

- [ ] Non-RCT
- [ ] Not Reported

7. **What was the eligibility criteria of Population in this systematic review?: Please describe included population in this study/target population. (copy and paste)**

8. **Type of patients' Cancer Treatment:** (check all that apply)

- [ ] Chemotherapy
- [ ] Radiation therapy
- [ ] Hormone therapy
- [ ] Immunotherapy
- [ ] Post treatment/Survivors
- [ ] Post treatment/Disease free
- [ ] Others (specify)

9. **Age of participants:**

- ○ Adults 18 and over
- ○ Other (specify)
- ○ Not Reported

Clear Response

10. **Gender**

- ○ Male
- ○ Female
- ○ Both male & Female
- ○ Not Reported

Clear Response

11. **What is the definition of Fatigue in this study. please copy and paste**

12. **What type of tool measurement assessed beofre treatment?**

- ☐ FACRT-F /FACT-F
- ☐ PFS
- ☐ BFI
- ☐ SF-36
- ☐ EORTC
- ☐ Quality of Life Questionnaire fatigue scale
- ☐ POMS
- ☐ MFI
- ☐ Other: used a fatigue measure not categorized above
- ☐ Not Reported

13. **Baseline Fatigue cut off point for diagnosis (T-score or any other measure)**

- ☐ 1
- ☐ 2
- ☐ Not Reported

14. **Intervention:**

- ☐ Pharmacological
- ☐ Non-pharmacological
- ☐ Alternative

15. **Type of intervention (list all that apply)**

- ☐ 1,
- ☐ 2,
- ☐ 3,
- ☐ 4,
- ☐ 5,
- ☐ 6,
- ☐ 7,
- ☐ 8,

16. **Type of comparison (list all that apply)**

- ☐ 1,
- ☐ 2,
- ☐ 3,

- [ ] 4,
- [ ] Not Reported

Outcome Measur:

17. **How many outcomes are measured for fatigue?**

18. **The main outcome of this study is:**

- [ ] Fatigue
- [ ] Other (specify)

19. **what type of outcome is specific to fatigue?**

- [ ] Primary
- [ ] Secondary
- [ ] Tertiary
- [ ] Main
- [ ] Others (speify)

RESULTS $ Study Outcome

20. **What type of tool measurement assessed after treatment?**

- [ ] FACRT-F /FACT=F
- [ ] PFS
- [ ] BFI
- [ ] SF-36
- [ ] EORTC
- [ ] Quality of Life Questionnaire fatigue scale
- [ ] POMS
- [ ] MFI
- [ ] Other: used a fatigue measure not categorized above
- [ ] Not Rported

21. **Meta-Analysis:**

- ( ) Yes
- ( ) No

Clear Response

22. **How many meta-analysis are specific fatigue outcome in this study?**

- 1
- 2
- 3
- 4

Clear Response

23. **Forest Plot:1**

- Title & page
- No. of studies
- Intervention1
- Total of participants (Int.)
- Total of events (Int.)
- Comparison1
- Total of participants (com.))
- Total of events (com.)
- Measure of effect (RR,OR,SMD)
- Pooled stimation/Effect size (95% CI)
- P-value
- Heterogeneity analysis

24. **Note on forest plot1:**
(please type the title of the forest plot)(please specify the outcome measure clearly)

25. **Forest Plot:2**

- Title & page
- No. of studies
- Intervention2
- Total of participants (Int.)
- Total of events (Int.)
- Comparison2
- Total of participants (com.))
- Total of events (com.)
- Measure of effect (RR,OR,SMD)

- ☐ Pooled stimation/Effect size (95% CI)
- ☐ P-value
- ☐ Heterogeneity analysis

26. **Note on forest plot2:**
(please type the title of the forest plot)(please specify the outcome measure clearly)

27. **Forest Plot:3**

- ☐ Title & page
- ☐ No. of studies
- ☐ Intervention1
- ☐ Total of participants (Int.)
- ☐ Total of events (Int.)
- ☐ Comparison1
- ☐ Total of participants (com.))
- ☐ Total of events (com.)
- ☐ Measure of effect (RR,OR,SMD)
- ☐ Pooled stimation/Effect size (95% CI)
- ☐ P-value
- ☐ Heterogeneity analysis

28. **Note on forest plot 3:**
(please type the title of the forest plot)(please specify the outcome measure clearly)

29. **Forest Plot:4**

- ☐ Title & page
- ☐ No. of studies
- ☐ Intervention2
- ☐ Total of participants (Int.)
- ☐ Total of events (Int.)
- ☐ Comparison2

- [ ] Total of participants (com.))
- [ ] Total of events (com.)
- [ ] Measure of effect (RR,OR,SMD)
- [ ] Pooled stimation/Effect size (95% CI)
- [ ] P-value
- [ ] Heterogeneity analysis

30. **Note on forest plot 4:**
(please type the title of the forest plot)(please specify the outcome measure clearly)

31. **Other treatment effects (e.g. Hedges'd effect size:**

- [ ] Hedges'd
- [ ] Lower Limit CI
- [ ] Upper limit CT
- [ ] Note

32. **Other treatment effects: (specify name and size)**

33. **Main results:**

- [ ] 1,
- [ ] 2,
- [ ] 3,
- [ ] 4,

34. **Summary Main Results**

- ( ) Benefits
- ( ) No effect
- ( ) Inconsistent
- ( ) others(specify)

Clear Response

Quality of Evidence

35. **Quality of Evidence (GRADE)**

- Very Low
- Low
- Moderate
- High
- Insufficient data to assess
- Not Reported

Clear Response

36. **Overview Quality Assessment Questionnaire (OQAQ)**

- Good
- Moderate
- Poor
- Not Reported

Clear Response

37. **Other quality of evidence tool: (speify tool and Rate)**

- Name
- Rate

Study Conclusion

38. **Key Conclusion:**

- 1,
- 2,
- 3,
- 4,

39. **Recommendations:**

- 1,
- 2,
- 3,
- 4,

40. **Data extractor Note:**

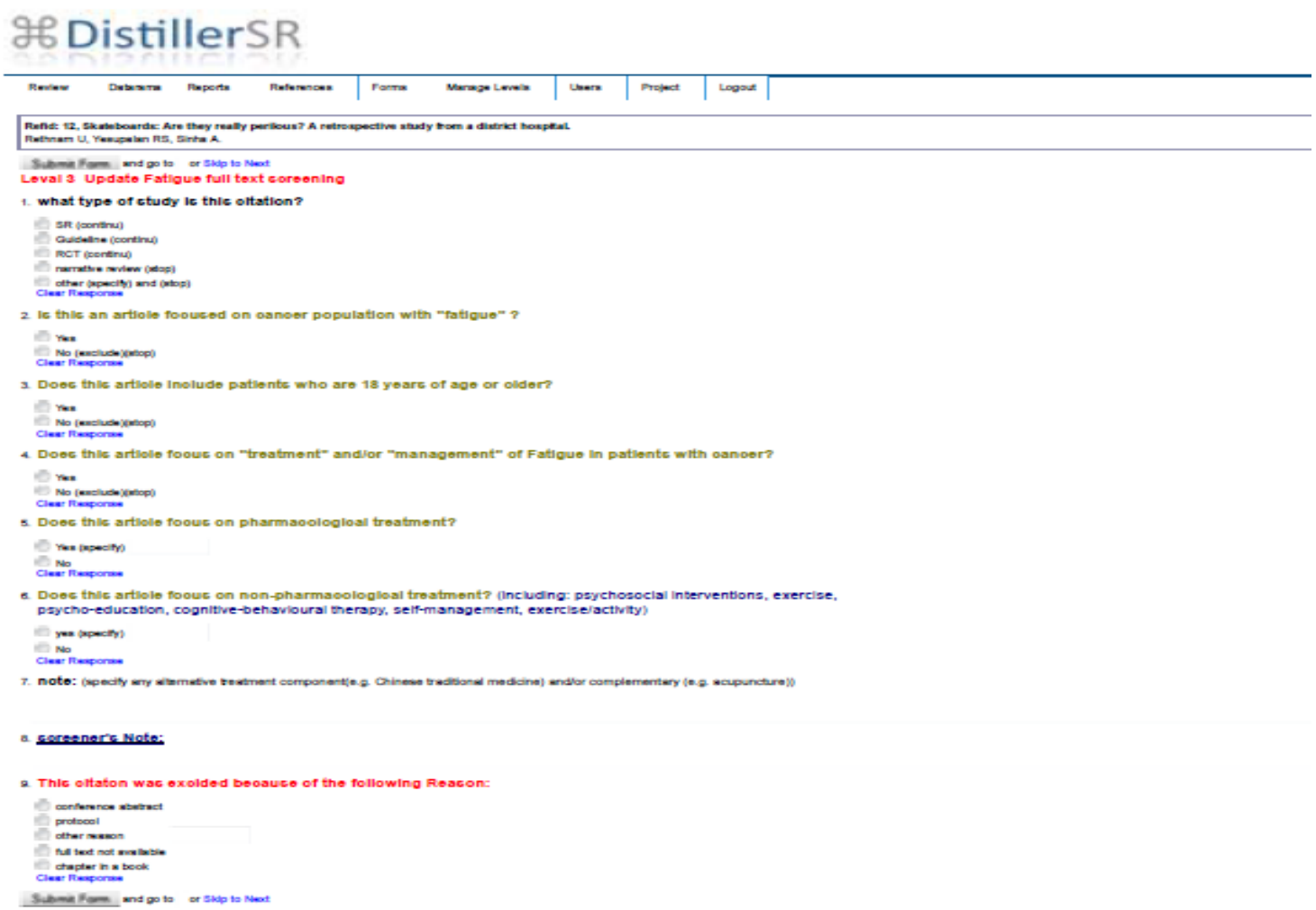
41. **Extracted data verified by:**

- HK
- JY
- RT
- other (specify)

Clear Response

Submit Form and go to or Skip to Next

Level 3 Data Extraction: Full Text



Level 4 Data Extraction: Guideline

8. **What is the target population on this Guideline?** (check all that apply)

9. **What is the definition of Fatigue in this guideline?**

☐ Fatigue

10. **What is the measurement toll/s for Fatigue in this guideline?**

☐ Fatigue

Recommendation #1 for populations with cancer related Fatigue?

11. **Specify Recommendation #1 .** (Please type in the exact wording)

12. **What type of system was used to grade or evaluate the strength of evidence (i.e. GRADE, or some association specific system?**

13. **Grading of the recommendation #1:** (i.e. strong recommendation)

14. **Rating of quality of evidence for Recommendation #1 :** (i.e. evidence at high risk of bias, or level I (indicating RCT design)

15. **For the evidence that is cited to support the recommendation, please list the number and type of studies included:** (i.e. 4 RCTs, and 2 Observational studies)

16. **Does the recommendation specifiy actions/ suggestions for the management of population with cancer related Fatigue?** (Please type in the exact wording)

Recommendation #2 for populations with cancer related Fatigue?

17. **Specify Recommendation #2** (Please type in the exact wording)

18. **What type of system was used to grade or evaluate the strength of evidence (i.e. GRADE, or some association specific system?**

19. **Grading of the recommendation #2:** (i.e. strong recommendation)

20. **Rating of quality of evidence for Recommendation #2 :** (i.e. evidence at high risk of bias, or level I (indicating RCT design)

21. **For the evidence that is cited to support the recommendation, please list the number and type of studies included:** (i.e. 4 RCTs, and 2 Observational studies)

22. **Does the recommendation specifiy actions/ suggestions for the management of population with cancer related Fatigue?** (Please type in the exact wording)

Recommendation #3 for populations with cancer related Fatigue?

23. **Specify Recommendation #3**(Please type in the exact wording)

24. **What type of system was used to grade or evaluate the strength of evidence (i.e. GRADE, or some association specific system?**

25. **Grading of the recommendation #3:** (i.e. strong recommendation)

26. **Rating of quality of evidence for Recommendation #3 :** (i.e. evidence at high risk of bias, or level I (indicating RCT design)

27. **For the evidence that is cited to support the recommendation, please list the number and type of studies included:** (i.e. 4 RCTs, and 2 Observational studies)

28. **Does the recommendation specifiy actions/ suggestions for the management of population with cancer related Fatigue?** (Please type in the exact wording)

29. **Note:**

30. **Data Extractor/Reviewer:**

31. **Second Reviewer:**

Submit Form and go to or Skip to Next

Appendix F: Excluded Studies

Table F.1: Summary of Excluded Studies

Exclusion Criteria	Total
Not Participant with Cancer Related Fatigue	72
Not on management of Cancer Related Fatigue	6
Protocol, Editorial, Conference abstraction, Chapter in a book	59
Not a systematic review	47
Not an RCT	20
Not a guideline	12
Full text no available	1
Summary	2
Educational	1
Synopsis	1
News letter	1
Pilot study	1
Dissertation abstract	1

List of Excluded Studies

1. Mustian KM, Peppone L, Darling TV, Palesh O, Heckler CE, Morrow GR. A 4-week home-based aerobic and resistance exercise program during radiation therapy: a pilot randomized clinical trial. The Journal of Supportive Oncology. 2009;7(5):158-67.
   Excluded: Not Participant with Cancer Related Fatigue.
2. Bardy J, Finnegan-John J, Richardson A, Mackereth P, Ryder WD, Filshie J, Ream E, Molassiotis A. 15 Acupuncture and Self-acupuncture for Managing Cancer-related Fatigue in Patients with Breast Cancer – a Pragmatic Randomised Controlled Trial. European Journal Oncology Nursing. 2012;16:S6.
   Excluded: Not an RCT.
3. Zick SM, Wyatt GK, Murphy SL, Arnedt JT, Sen A, Harris RE. Acupressure for persistent cancer-related fatigue in breast cancer survivors (AcuCrft): a study protocol for a randomized controlled trial. BMC Complementary & Alternative Medicine. 2012;12:132.
   Excluded: Not an RCT.
4. Carayol M, Romieu G, Bleuse JP, Senesse P, Gourgou-Bourgade S, Sari C, Jacot W, Sancho-Garnier H, Janiszewski C, Launay S, Cousson-Gelie F, Ninot G. Adapted physical activity and diet (APAD) during adjuvant breast cancer therapy: Design and implementation of a prospective randomized controlled trial. Contemporary Clinical Trials. 2013;36(2):531-43.
   Excluded: Not an RCT.
5. Basu Ray I. Advancing evidence-based practice: A quarterly compilation of research updates most likely to change clinical practice. Ochsner Journal. 2013;13(3):288-92.
   Excluded: Not a guideline.
6. Fontein DBY, de Glas NA, Duijm M, Bastiaannet E, Portielje JEA, Van de Velde CJH, Liefers GJ. Age and the effect of physical activity on breast cancer survival: A systematic review. Cancer Treatment Review. 2013;39(8):958-65.
   Excluded: Not Participant with Cancer Related Fatigue.
7. Neefjes ECW, Van Der Vorst MJDL, Blauwhoff-Buskermolen S, Verheul HMW. Aiming for a Better Understanding and Management of Cancer-Related Fatigue. Oncologist. 2013;18(10):1135-43.
   Excluded: Not a guideline.
8. Chinapaw MJ, Buffart LM, van Mechelen W, Schep G, Aaronson NK, van Harten WH, Stuiver MM, Kersten MJ, Nollet F, Kaspers GJ, van Dulmen-den Broeder E, Huisman J, Takken T, van Tulder M, Brug J. Alpe d'HuZes cancer rehabilitation (A-CaRe) research: four randomized controlled exercise trials and economic evaluations in cancer patients and survivors. International Journal Behavioral Medicine. 2012;19(2):143-56.
   Excluded: Protocol, Editorial, Conference abstraction, Chapter in a book.

9. Pedro M, Ricardo M, Andre A, De Barros Nelson F. The application of techniques of Reiki, Therapeutic Touch and Healing Touch in cancer: A systematic review. European Journal of Integrative Medicine. 2012;4:132.
Excluded: Not Participant with Cancer Related Fatigue.
10. Barsevick AM, Cleeland CS, Manning DC, O'Mara AM, Reeve BB, Scott JA, Sloan JA, Ascpro. ASCPRO recommendations for the assessment of fatigue as an outcome in clinical trials. Journal of Pain Symptom Management. 2010;39(6):1086-99.
Excluded: Not on management of Cancer Related Fatigue.
11. Cleeland CS, Sloan JA, Group AO. Assessing the Symptoms of Cancer Using Patient-Reported Outcomes (ASCPRO): searching for standards. Journal of Pain Symptom Management. 2010;39(6):1077-85.
Excluded: Not a guideline.
12. Borneman T. Assessment and Management of Cancer-Related Fatigue. Journal of Hospital Palliative Nursing. 2013;15(2):77-88.
Excluded: Not a systematic review.
13. von Gruenigen VE, Huang HQ, Gil KM, Frasure HE, Armstrong DK, Wenzel LB. The association between quality of life domains and overall survival in ovarian cancer patients during adjuvant chemotherapy: a Gynecologic Oncology Group Study. Gynecologic Oncology. 2012;124(3):379-82.
Excluded: Protocol, Editorial, Conference abstraction, Chapter in a book.
14. Fernandez-Lao C, Cantarero-Villanueva I, Diaz-Rodriguez L, Cuesta-Vargas AI, Fernandez-Delas-Penas C, Arroyo-Morales M. Attitudes towards massage modify effects of manual therapy in breast cancer survivors: a randomised clinical trial with crossover design. European Journal of Cancer Care. 2012;21(2):233-41.
Excluded: Protocol, Editorial, Conference abstraction, Chapter in a book.
15. Berger AM, Kuhn BR, Farr LA, Lynch JC, Agrawal S, Chamberlain J, Von Essen SG. Behavioral therapy intervention trial to improve sleep quality and cancer-related fatigue. Psychooncology. 2009;18(6):634-46.
Excluded: Not on management of Cancer Related Fatigue.
16. Errico J, Hughes D. The benefits of physical activity for cancer survivors. Coping With Cancer. 2012;26(5):27.
Excluded: Not a guideline.
17. Keogh JW, MacLeod RD. Body composition, physical fitness, functional performance, quality of life, and fatigue benefits of exercise for prostate cancer patients: a systematic review. Journal of Pain Symptom Management. 2012;43(1):96-110.
Excluded: Not Participant with Cancer Related Fatigue.
18. Heist RS, Wang X, Hodgson L, Otterson GA, Stinchcombe TE, Gandhi L, Villalona-Calero MA, Watson P, Vokes EE, Socinski MA. CALGB 30704 (Alliance): A randomized phase II study to assess the efficacy of pemetrexed or sunitinib or pemetrexed plus sunitinib in the second-line treatment of advanced non-small-cell lung cancer. Journal of Thoracic Oncology. 2014;9(2):214-21.

Excluded: Protocol, Editorial, Conference abstraction, Chapter in a book.
19. Cramer H, Lange S, Klose P, Paul A, Dobos G. Can yoga improve fatigue in breast cancer patients? A systematic review. Acta Oncologica. 2012;51(4):559-60.
Excluded: Protocol, Editorial, Conference abstraction, Chapter in a book.
20. Matzo M, Hill JA. Cancer: physical activity and palliative care: interventions appear to be promising. American Journal of Nursing. 2009;109(9):73.
Excluded: Not a systematic review.
21. De Waele S, Van Belle S. Cancer-related fatigue. Acta Clinica Belgica. 2010;65(6):378-85.
Excluded: Not a systematic review.
22. Johnson RL, Amin AR, Matzo M. Cancer-Related Fatigue. American Journal of Nursing. 2012;112(4):57-60.
Excluded: Protocol, Editorial, Conference abstraction, Chapter in a book.
23. van Weert E, May AM, Korstjens I, Post WJ, van der Schans CP, van den Borne B, Mesters I, Ros WJ, Hoekstra-Weebers JE. Cancer-related fatigue and rehabilitation: a randomized controlled multicenter trial comparing physical training combined with cognitive-behavioral therapy with physical training only and with no intervention. Physical Therapy. 2010;90(10):1413-25.
Excluded: Not Participant with Cancer Related Fatigue.
24. Balachandran DD, Faiz S, Bashoura L, Manzullo E. Cancer-related fatigue and sleep disorders. Sleep Medicine Clinics. 2013;8(2):229-34.
Excluded: Not a systematic review.
25. Bruera E. Cancer-related fatigue: a multidimensional syndrome. The Journal of Supportive Oncology. 2010;8(4):175-6.
Excluded: Not a systematic review.
26. Kirshbaum M. Cancer-related fatigue: a review of nursing interventions. British Journal of Community Nursing. 2010;15(5):214.
Excluded: Not a systematic review.
27. Kangas M, Bovbjerg DH, Montgomery GH. "Cancer-related fatigue: A systematic and meta-analytic review of non-pharmacological therapies for cancer patients": Correction to Kangas, Bovbjerg, and Montgomery (2008). Psychological Bulletin. 2009;135(1):172.
Excluded: Not a systematic review.
28. Horneber M, Fischer I, Dimeo F, Ruffer JU, Weis J. Cancer-related fatigue: Epidemiology, pathogenesis, diagnosis, and treatment. Deutsches Arzteblatt International. 2012;109(9):161-72.
Excluded: Not a systematic review.
29. Vardy J. The challenge - Current trials in exercise and cancer. Asia Pacific Journal of Clinical Oncology. 2009;5:145.
Excluded: Full text not available.
30. Liao C, Li J, Bin Q, Cao Y, Gao F. Chronomodulated chemotherapy versus conventional chemotherapy for advanced colorectal cancer: a meta-analysis of

five randomized controlled trials. International Journal of Colorectal Disease. 2010;25(3):343-50.
Excluded: Not Participant with Cancer Related Fatigue.
31. Baumann FT, Zopf EM, Bloch W. Clinical exercise interventions in prostate cancer patients-a systematic review of randomized controlled trials. Support Care Cancer. 2012;20(2):221-33.
Excluded: Not an RCT.
32. Chan R. Cochrane Review summary for cancer nursing: drug therapy for the management of cancer-related fatigue. Cancer Nursing. 2011;34(3):250-1.
Excluded: Not a systematic review.
33. Galvao DA, Taaffe DR, Spry N, Joseph D, Newton RU. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. Journal of Clinical Oncology. 2010;28(2):340-7.
Excluded: Not Participant with Cancer Related Fatigue.
34. Urlic K, Bennett S. Critically appraised papers. Some limited evidence exists for the benefits of psychosocial interventions in the management of cancer-related fatigue. Australian Occupational Therapy Journal. 2010;57(2):148-9.
Excluded: Synopsis.
35. Bradt J, Goodill SW, Dileo C. Dance/movement therapy for improving psychological and physical outcomes in cancer patients. Cochrane Database of Systematic Reviews. 2011; Volume10 Article ID:CD007103.
Excluded: Not Participant with Cancer Related Fatigue.
36. Hoffman AJ, von Eye A, Gift AG, Given BA, Given CW, Rothert M. The Development and Testing of an Instrument for Perceived Self-efficacy for Fatigue Self-management. Cancer Nursing. 2011;34(3):167-75.
Excluded: Protocol, Editorial, Conference abstraction, Chapter in a book.
37. Lindsey H. Dexamethasone a Potential Treatment for Cancer-Related Fatigue. Oncology Times. 2013;35(23):31-2.
Excluded: News letter.
38. Guest DD, Evans EM, Rogers LQ. Diet components associated with perceived fatigue in breast cancer survivors. European Journal of Cancer Care. 2013;22(1):51-9.
Excluded: Not an RCT.
39. Puetz TW, Herring MP. Differential effects of exercise on cancer-related fatigue during and following treatment: a meta-analysis. American Journal of Preventive Medicine. 2012;43(2):1-24.
Excluded: Not Participant with Cancer Related Fatigue.
40. Eton DT, Cella D. Do erythropoietic-stimulating agents relieve fatigue? A review of reviews. Cancer Treatment and Research. 2011;157:181-94.
Excluded: Not a systematic review.
41. Andersen AH, Vinther A, Poulsen LL, Mellemgaard A. Do patients with lung cancer benefit from physical exercise? Acta Oncologica. 2011;50(2):307-13.

Excluded: Not Participant with Cancer Related Fatigue.
42. Zee PC, Ancoli-Israel S. Does Effective Management of Sleep Disorders Reduce Cancer-Related Fatigue? Drugs. 2009;69:29-41.
Excluded: Not a systematic review.
43. Wright F, Squires A. Does Exercise Help Reduce Cancer-Related Fatigue? Journal of Clinical Outcomes Management. 2014;21(4):155-6.
Excluded: Not a systematic review.
44. Arnold M, Taylor NF. Does exercise reduce cancer-related fatigue in hospitalised oncology patients? A systematic review. Onkologie. 2010;33(11):625-30.
Excluded: Not Participant with Cancer Related Fatigue.
45. Lapid MI, Atherton PJ, Kung S, Cheville AL, McNiven M, Sloan JA, Clark MM, Rummans TA. Does gender influence outcomes from a multidisciplinary intervention for quality of life designed for patients with advanced cancer? Support Care Cancer. 2013;21(9):2485-90.
Excluded: Protocol, Editorial, Conference abstraction, Chapter in a book.
46. McGovern K, Rohm AE, Sadowski K, Wagner BR, Haladay DE. Does gender matter? A systematic review of gender differences in cancer-related fatigue among individuals following exercise interventions... Combined Sections meeting 2011, New Orleans, LA, February 2011. Rehabilitation Oncology. 2011;29(1):27.
Excluded: Not a systematic review.
47. Wood LJ, Nail LM, Winters KA. Does muscle-derived interleukin-6 mediate some of the beneficial effects of exercise on cancer treatment-related fatigue? Oncology Nursing Forum. 2009;36(5):519-24.
Excluded: Not a systematic review.
48. O'Brien L, Loughnan A, Purcell A, Haines T. Education for cancer-related fatigue: could talking about it make people more likely to report it? Support Care Cancer. 2014;22(1):209-15.
Excluded: Protocol, Editorial, Conference abstraction, Chapter in a book.
49. Bennett S, Purcell A, Meredith P, Beller E, Haines T, Fleming J. Educational interventions for the management of cancer-related fatigue in adults [Protocol]. Cochrane Database of Systematic Reviews. 2009(4).
Excluded: Protocol, Editorial, Conference abstraction, Chapter in a book.
50. Bennett S, Purcell A, Meredith P, Beller E, Haines T, Dalaney C. Educational interventions for the management of cancer-related fatigue in adults: a cochrane systematic review... Occupational Therapy Australia, 24th National Conference and Exhibition, 29 June - 1 July 2011. Australia Occupational Therapy Journal. 2011;58:70-1.
Excluded: Not a systematic review.
51. Samuel SR, Maiya GA, Babu AS, Vidyasagar MS. Effect of exercise training on functional capacity & quality of life in head & neck cancer patients receiving chemoradiotherapy. Indian Journal of Medical Research. 2013;137(3):515-20.

Excluded: Protocol, Editorial, Conference abstraction, Chapter in a book.
52. Velthuis MJ, Agasi-Idenburg SC, Aufdemkampe G, Wittink HM. The effect of physical exercise on cancer-related fatigue during cancer treatment: a meta-analysis of randomised controlled trials. Clinical Oncology (Royal College of Radiologists). 2010;22(3):208-21.
Excluded: Not an RCT.
53. Aghabati N, Mohammadi E, Pour Esmaiel Z. The effect of therapeutic touch on pain and fatigue of cancer patients undergoing chemotherapy. Evidence-Based Complementary & Alternative Medicine. 2010;7(3):375-81.
Excluded: Not Participant with Cancer Related Fatigue.
54. Nafees S, Williams N, Din N, Hendry M, Edwards R, Wilkinson C. Effectiveness and cost-effectiveness of patient education materials about physical activity among adult cancer survivors: A systematic review. Psycho-Oncology. 2013;22:14-5.
Excluded: Not Participant with Cancer Related Fatigue.
55. Saarto T, Penttinen HM, Sievanen H, Kellokumpu-Lehtinen PL, Hakamies-Blomqvist L, Nikander R, Huovinen R, Luoto R, Kautiainen H, Jarvenpaa S, Idman I, Utriainen M, Vehmanen L, Jaaskelainen AS, Elme A, Ruohola J, Palva T, Vertio H, Rautalahti M, Fogelholm M, Blomqvist C, Luoma ML. Effectiveness of a 12-month exercise program on physical performance and quality of life of breast cancer survivors. Anticancer Research. 2012;32(9):3875-84.
Excluded: Protocol, Editorial, Conference abstraction, Chapter in a book.
56. Molassiotis A, Brearley S, Saunders M, Craven O, Wardley A, Farrell C, Swindell R, Todd C, Luker K. Effectiveness of a home care nursing program in the symptom management of patients with colorectal and breast cancer receiving oral chemotherapy: a randomized, controlled trial. Journal of Clinical Oncology. 2009;27(36):6191-8.
Excluded: Not Participant with Cancer Related Fatigue.
57. Duijts SF, Faber MM, Oldenburg HS, van Beurden M, Aaronson NK. Effectiveness of behavioral techniques and physical exercise on psychosocial functioning and health-related quality of life in breast cancer patients and survivors-a meta-analysis. Psycho-Oncology. 2011;20(2):115-26.
Excluded: Not Participant with Cancer Related Fatigue.
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Appendix G: External Review Members Results

A draft version of this report was reviewed by 8 health care professionals from across Canada and USA involved in the Cancer Related Fatigue and psychosocial and supportive care of cancer survivors. Respondents were asked to complete a survey about the relevance and quality of the guideline and comment on the draft. The Cancer Journey Cancer Related Fatigue Expert Panel reviewed the results of the external review, addressed the comments and made modifications accordingly. The findings of the external review are summarized in Table G.1.

Table G.1 shows that all respondents found the guideline's objectives, target population were described clearly. All agreed that appropriate systematic methods were used to identify relevant evidence and the adaptations were appropriate. All agreed that the supporting evidence for formulating the fatigue recommendations were clearly described and the majority agreed that the recommendations for fatigue were appropriately stated based on the supporting evidence. All respondents rated the overall quality of the guideline as good or of highest quality.

Table G.1. Summary of External Review Survey Results

Survey Items	Strongly Disagree (1) N(%)	Disagree (2) N(%)	Neutral (3) N(%)	Somewhat Agree (4) N(%)	Strongly Agree (5) N(%)
The overall objective of the fatigue guideline is specifically described.	0 (0%)	0 (0%)	0 (0%)	0 (0%)	8 (100%)
The target population for the fatigue guideline is clearly described.	0 (0%)	0 (0%)	0 (0%)	0 (0%)	8 (100%)
The target users of the fatigue guideline are clearly described.	0 (0%)	0 (0%)	0 (0%)	1 (12.5%)	7 (87.5%)
Systematic search methods for identifying relevant evidence for adaptations were appropriate.	0 (0%)	0 (0%)	0 (0%)	1 (12.5%)	7 (87.5%)
The supporting evidence for formulating the fatigue recommendations are clearly described.	0 (0%)	0 (0%)	0 (0%)	2 (25%)	6 (75%)
The recommendations for fatigue are appropriately stated based on the supporting evidence.	0 (0%)	1 (12.5%)	0 (0%)	5 (62.5%)	2 (25%)
I would recommend this guideline for use in practice.	0 (0%)	1 (12.5%)	0 (0%)	3 (37.5%)	4 (50%)
When applied the fatigue guideline will produce more benefits than harms.	0 (0%)	1 (12.5%)	0 (0%)	2 (25%)	5 (62.5%)
I would make use of this guideline in my professional decisions.	0 (0%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	5 (62.5%)
Survey Items	**Lowest Quality**	**Acceptable Quality**	**Fair Quality**	**Good Quality**	**Highest Quality**
The overall quality of the guideline report on the scale from (1) lowest quality to (5) highest quality.	0 (0%)	0 (0%)	0 (0%)	5 (62.5%)	3 (37.5%)