LIVERPOOL JOHN MOORES UNIVERSITY

LJMU Research Online

Khatib, MN, Shankar, A, Kirubakaran, R, Gaidhane, A, Gaidhane, S, Simkhada, PP and Quazi Syed, Z

Ghrelin for the management of cachexia associated with cancer

http://researchonline.ljmu.ac.uk/id/eprint/3787/

Article

Citation (please note it is advisable to refer to the publisher's version if you intend to cite from this work)

Khatib, MN, Shankar, A, Kirubakaran, R, Gaidhane, A, Gaidhane, S, Simkhada, PP and Quazi Syed, Z (2016) Ghrelin for the management of cachexia associated with cancer. Cochrane Database of Systematic Reviews, 2016 (6). pp. 1-12. ISSN 1469-493X

LJMU has developed **LJMU Research Online** for users to access the research output of the University more effectively. Copyright © and Moral Rights for the papers on this site are retained by the individual authors and/or other copyright owners. Users may download and/or print one copy of any article(s) in LJMU Research Online to facilitate their private study or for non-commercial research. You may not engage in further distribution of the material or use it for any profit-making activities or any commercial gain.

The version presented here may differ from the published version or from the version of the record. Please see the repository URL above for details on accessing the published version and note that access may require a subscription.

For more information please contact researchonline@ljmu.ac.uk

http://researchonline.ljmu.ac.uk/

Cochrane Library

Cochrane Database of Systematic Reviews

Ghrelin for the management of cachexia associated with cancer (Protocol)

Khatib MN, Shankar A, Kirubakaran R, Gaidhane A, Gaidhane S, Simkhada P, Quazi Syed Z

Khatib MN, Shankar A, Kirubakaran R, Gaidhane A, Gaidhane S, Simkhada P, Quazi Syed Z.
Ghrelin for the management of cachexia associated with cancer.
Cochrane Database of Systematic Reviews 2016, Issue 6. Art. No.: CD012229.
DOI: 10.1002/14651858.CD012229.

www.cochranelibrary.com

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
BACKGROUND 1
OBJECTIVES 3
METHODS 3
ACKNOWLEDGEMENTS 6
REFERENCES 7
APPENDICES 10
CONTRIBUTIONS OF AUTHORS 11
DECLARATIONS OF INTEREST 11
SOURCES OF SUPPORT 11

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[Intervention Protocol]

Ghrelin for the management of cachexia associated with cancer

Mahalaqua Nazli Khatib[1], Anuraj Shankar[2], Richard Kirubakaran[3], Abhay Gaidhane[4], Shilpa Gaidhane[5], Padam Simkhada[6], Zahiruddin Quazi Syed[4]

[1]Department of Physiology, Datta Meghe Institute of Medical Sciences, Wardha, India. [2]Department of Nutrition, Harvard University, Boston, Massachusetts, USA. [3]South Asian Cochrane Network & Center, Prof. BV Moses Center for Evidence-Informed Health Care and Health Policy, Christian Medical College, Vellore, India. [4]Department of Community Medicine, Datta Meghe Institute of Medical Sciences, Wardha, India. [5]Department of Medicine, Datta Meghe Institute of Medical Sciences, Wardha, India. [6]Centre for Public Health, Liverpool John Moores University, Liverpool, UK

Contact address: Mahalaqua Nazli Khatib, Department of Physiology, Datta Meghe Institute of Medical Sciences, Sawangi Meghe, Wardha, Maharashtra, 442004, India. nazli.786@rediffmail.com.

Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: New, published in Issue 6, 2016.

Citation: Khatib MN, Shankar A, Kirubakaran R, Gaidhane A, Gaidhane S, Simkhada P, Quazi Syed Z. Ghrelin for the management of cachexia associated with cancer. *Cochrane Database of Systematic Reviews* 2016, Issue 6. Art. No.: CD012229. DOI: 10.1002/14651858.CD012229.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the efficacy and safety of ghrelin on improving food intake, body composition and survival in patients with cachexia associated with cancer.

BACKGROUND

This protocol is partly based on suggested wording from the Pain, Palliative and Supportive Care Review Group (PaPaS CRG).

Description of the condition

Cancer and its co-morbidities, like cancer cachexia, have afflicted humans for centuries and still continue to be a major public health problem. Patients suffering from cancer are amongst the most malnourished of all the patient groups (Ryan 2016). It has been estimated that cachexia affects 60% to 80% of all advanced cancer patients (Baracos 2011) and more than 30% of patients die due to cachexia (von Haehling 2012). Cancer cachexia is commonly associated with decreased life expectancy and poor quality of life (Utech 2012).

Cancer cachexia is defined as "a multifactorial syndrome characterised by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment" (Fearon 2011). Cachexia syndrome can develop progressively, through stages of pre-cachexia to cachexia to refractory cachexia (Fearon 2011). The incidence of cancer cachexia varies according to tumor type (Teunissen 2007; Tisdale 2009; Sun 2015). The prevalence of cachexia is highest in people with pancreatic cancer (88.9%), followed by gastric cancer (76.5% to 87%) and esophageal cancer (52.9%) (Sun 2015; Tisdale 2009). The frequency of weight loss is lowest in patients with breast can-

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

cer, sarcomas, non-Hodgkin's lymphoma and acute nonlymphocytic leukemia (Teunissen 2007; Tisdale 2009). Cachexia can be a presenting symptom in a majority of patients with advanced cancer; mainly those with hepatic, lung, or bone metastasis and primary cancers of the lung, cervix or head and neck (Mendes 2015). Although certain tumor types are more commonly associated with cachexia, even with the same tumor type there are variations in the extent to which patients exhibit cachexia (Tisdale 2009).

During the last few decades extensive research has been carried out to understand the complex pathophysiology of cachexia associated with cancer. Anorexia, anaemia, asthenia, inflammation, altered hormonal homeostasis, energy imbalance, and several cancer-related metabolic changes (like negative protein balance and increased lipolysis) leading to significant weight loss have been attributed to the pathogenesis of cancer cachexia (Mendes 2015; Penna 2010; Stephens 2008). Therapies for cancer, such as chemotherapy, surgery and radiotherapy, also cause anorexia, muscle atrophy and weight loss (Chen 2015; Garcia 2005; Tisdale 2009). Deregulation of control of energy expenditure and hunger/satiety by the hypothalamus promotes cachexia in cancer patients (Mendes 2015). A discrepancy between anabolic and catabolic pathways mediated by chronic inflammation can cause muscle wasting in patients with cancer cachexia (Madeddu 2015a). Depletion of adipose tissue as well as skeletal muscle mass with relative preservation of non-muscle protein compartment can contribute to weight loss in cancer patients (Tisdale 2009). Studies suggest that the tumour cells secrete certain humoral factors which promote central and peripheral-mediated cancer cachexia (Stewart 2006). Cachectic factors (like activin and proteolysis-inducing factor) secreted by the tumour cells decrease the synthesis and increase the breakdown of muscle proteins, and thereby induce sarcopenia (Stewart 2006). Excretion of cytokines and lipid-mobilising factors may contribute to depletion of adipose tissue (Stewart 2006). Tumor cells secrete pro-inflammatory factors that promote cachexia by signaling anorexia, muscle wasting and atrophy of white adipose tissue (WAT). The release of inflammatory cytokines like TNF-α (cachexin or cachectin), interferon gamma, interleukin-6 and angiotensin II can also have a role in cancer cachexia (Tisdale 2009).

As cachexia progresses, wasting of skeletal muscles limits mobility and thereby leads to poor quality of life which in turn pushes cancer patients towards isolation and depression (Stewart 2006; Watanabe 1996; Windsor 1988). Not only patients, but also family members - especially caregivers - and healthcare professionals often suffer from depression as they try to palliate cancer patients' symptoms (Reid 2012). Although cancer cachexia is associated with increased mortality and poor quality of life, treatment options for the condition are limited (Penna 2016). As the condition is associated with complex pathophysiological processes, therapies with potential orexigenic, anabolic and anti-inflammatory effects should be targeted to counter this condition.

Description of the intervention

The approach to treatment for cancer cachexia is multimodal and includes nutritional support, pharmacological treatments, and non-pharmacological therapies like physical training (Madeddu 2015a). Caloric supplementation or appetite stimulants like megestrol acetate, medroxyprogesterone acetate (MPA), cyproheptadine, marijuana, and corticosteroids such as dexamethasone, prednisolone and methylprednisolone have been used for enhancing appetite in cancer patients (Fearon 2011; Tisdale 2009). However, these interventions have limited efficacy. No definitive pharmacological treatment is available to address the relevant components of the syndrome (Esposito 2015).

Ghrelin, a novel orexigenic gut hormone, is primarily secreted by the endocrine X/A-like cells of the stomach mucosa and also by intestinal mucosa, arcuate nucleus of the hypothalamus, pituitary gland, pancreatic islets, and other tissues (Khatib 2015b). Studies have shown that this 28-amino acid peptide hormone is an endogenous ligand for the growth hormone secretagogue receptor and can be a potential therapeutic agent for cachexia-associated cancer (Chen 2015; Garcia 2015; Pietra 2014; Tsubouchi 2014; Zhang 2015). It has shown promising results in randomised clinical trials (Garcia 2007; Garcia 2013; Garcia 2015; Khatib 2014b; Khatib 2014e; Madeddu 2015b). Ghrelin has the potential to increase body weight and body composition through increased appetite, increased growth hormone (GH) secretion and prevention of muscle catabolism, which suggests that ghrelin could be an effective treatment for cancer anorexia (DeBoer 2007; Fujitsuka 2011; Garcia 2005; Garcia 2013; Khatib 2014a; Khatib 2014d; Khatib 2014f; Khatib 2015b; Klok 2007; Neary 2004; Tsubouchi 2014; Wren 2001). Ghrelin is well tolerated with no reported side effects (Akamizu 2010; Khatib 2015a; Neary 2004).

Ghrelin agonists are being developed and tested for the treatment of anorexia/cachexia. Anamorelin, a first-in-class, potent orally-active and highly-specific ghrelin receptor agonist, increases food intake, body weight and lean body mass (Northrup 2013; Pietra 2014). It is well tolerated with no dose-limiting toxicities (Zhang 2015). Anamorelin treatment for 12 weeks had a favourable clinical response profile in patients with cancer anorexia-cachexia syndrome in one study (Garcia 2015). Administration of RC-1291, a ghrelin mimetic, in cachectic cancer patients increased lean body mass in another study (Garcia 2007); it represents a new class of drug for patients with cancer cachexia.

How the intervention might work

Although the mechanisms of action of ghrelin have not been fully elucidated, an increase in appetite and decrease in energy expenditure via hypothalamic effects (Fujitsuka 2014; Garcia 2013; Murphy 1998); promotion of anabolic activity (Chen 2015); decrease in inflammation (Dixit 2004; Tsubouchi 2014); an increase in growth hormone (Garcia 2009; Khatib 2014a; Khatib 2014d;

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Khatib 2014f); control of gastrointestinal motility (Fujino 2003); and direct effects in adipose tissue (Kos 2009) and skeletal muscle (Porporato 2013; Tsubouchi 2014) have been proposed.

Ghrelin and synthetic ghrelin receptor agonists cause weight gain by increasing food intake and by food intake-independent mechanisms (Garcia 2013; Sugiyama 2012; Tschop 2000). Ghrelin promotes weight gain and lean body mass via anti-inflammatory action and effects involving orexigenic neuropeptides (DeBoer 2007; Khatib 2014c; Khatib 2015b). Animals treated with ghrelin exhibit a decreased expression of IL-1 receptor-I transcript in the hypothalamus and brainstem and an increased expression of orexigenic peptides and neuropeptide Y (NPY) in the hypothalamus (DeBoer 2007; Tisdale 2009). Administration of ghrelin prevents muscle atrophy by down-regulating inflammation and activating protein kinase B (a protein kinase that plays a key role in apoptosis, cell proliferation, and cell migration), myogenin (a transcription factor involved in myogenesis and repair) and myoD (a protein that plays a major role in regulating muscle differentiation) (Chen 2015). Both acytylated and unacytylated ghrelin blocks skeletal muscle atrophy in a growth hormone-independent manner (Porporato 2013). In vitro studies have demonstrated that ghrelin may regulate mesenchymal cell development by stimulating myogenesis (Zhang 2007). Cells expressing ghrelin have demonstrated a significant increase in the differentiation of premyocytes into myocytes (Zhang 2007). Ghrelin inhibits the production and prevents the increase of pro-inflammatory cytokines released by the tumour cells (Chen 2015; Dixit 2004; Tsubouchi 2014). Activation of the ghrelin receptor in the central nervous system releases GH which regulates insulin-like growth factor-1 (IGF-1) (Khatib 2014f; Khatib 2014a; Velloso 2008). GH/IGF-1 axis acts directly on bone, muscle and fat tissue and also indirectly by producing anti-cachectic cytokines and muscle-restricted insulin-like growth factor-1 (mIGF-1) (Fuoco 2015). Since GH secretagogue receptors (GHS-R) are expressed in vagal afferent neurons, the gastric vagus nerve is involved in the effect of ghrelin on food intake and GI motility (Date 2002). Gastric ghrelin signaling via vagal afferents suppresses the activity of the sympathetic nerves and increases the discharge of both the gastric and the vagus efferent nerves (Fujitsuka 2009). Ghrelin also promotes fasted motor activity by activating the NPY neurons in the brain (Fujino 2003). Anamorelin increases GH, IGF-1 and body weight with good tolerability and selectivity (Garcia 2009). Oral administration of rikkunshito increases plasma acyl ghrelin levels in humans, mice, rats and dogs (Fujitsuka 2009; Fujitsuka 2011; Takeda 2008). It may be a viable treatment modality for cancer-associated cachexia.

Why it is important to do this review

Despite the high prevalence of cancer cachexia, effective therapies are still limited and no definitive pharmacological treatment is available to address the relevant components of this syndrome (Esposito 2015). There is a strong need for more effective appetite-stimulatory therapies for patients with this condition. Several studies have demonstrated positive and encouraging effects of ghrelin or GH secretagogues (GHS) in patients with cancer cachexia (Esposito 2015; Garcia 2007; Garcia 2013; Molfino 2014; Neary 2004). However, the safety and efficacy of ghrelin for cancer-associated cachexia have not been systematically reviewed. There is a need to synthesise the evidence for patients, practitioners and policy makers to decide whether ghrelin can be incorporated in the management of cachexia associated with cancer and, if data permit, to explore the optimal drug programme for this group of patients. Therefore, systematic evaluation of the role of ghrelin in the treatment of cancer cachexia is warranted.

OBJECTIVES

To assess the efficacy and safety of ghrelin on improving food intake, body composition and survival in patients with cachexia associated with cancer.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) with unblinded or blinded assessment of outcomes. Full journal publication is required, with the exception of extended abstracts of otherwise unpublished clinical trials. We will exclude short abstracts (usually meeting reports), non-randomised studies, studies of experimental pain, case reports, and clinical observations.'

Types of participants

We will include cachexic adults of 18 years and over with a histological or clinical diagnosis of cancer; or meeting any of the international criteria for cancer cachexia (Bozzetti 2009; Fearon 2006; Fearon 2011). Both inpatients and outpatients with any stage of cancer irrespective of gender or race will be considered for inclusion. We will include patients in any healthcare setting (including hospice, hospital, oncology centre or community).

Types of interventions

We will include studies in which the intervention is the administration of ghrelin in any form, at any dose, at any frequency, by any route and for any duration, administered for improving food intake, body composition and survival, compared to placebo

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

or any active comparator (such as appetisers, nutritional supplements, etc.).

The following comparisons will be made in the review:

1. Ghrelin versus placebo;
2. Ghrelin versus no treatment;
3. Ghrelin versus alternative experimental treatment modality (like appetisers, nutritional supplements, etc);
4. Ghrelin in combination with other treatments versus ghrelin treatment alone;
5. Ghrelin treatment versus ghrelin analogues/ghrelin mimetics (anamorelin, ipamorelin, eganamorelin, hexarelin, MK-677, etc.) or ghrelin potentiators/enhancers (rikkunshito).

Types of outcome measures

Primary outcomes

1. Change in food intake as difference between baseline and the end of treatment. We will express this outcome as a dichotomous variable (number of patients who experienced an increase in food intake) or a continuous variable (actual change in food intake).
2. Change in body weight as difference between baseline and at the end of treatment. We will express this outcome as a dichotomous variable (number of patients who experienced change in body weight) or a continuous variable (actual change in body weight).
3. Adverse events as the number of patients who suffered an event described as an adverse event by the authors of the studies.

Secondary outcomes

1. Change in survival measured as increase in survival in days. We will use hazard ratios for how many times more (or less) likely a participant is to suffer the event at a particular point in time if they receive ghrelin rather than the control intervention.
2. Change in body composition (lean body mass, fat mass) as difference between baseline and the end of treatment. We will express this outcome as a dichotomous variable (number of patients who experienced change in body weight) or a continuous variable (actual change in body composition).
3. Plasma ghrelin levels as difference between baseline and the end of treatment. We will express this outcome as a dichotomous variable (number of patients who experienced increase in plasma ghrelin levels) or a continuous variable (actual change in plasma ghrelin levels).
4. Change in the Quality of Life (QoL) using Health-Related Quality of Life (HRQoL) (CDC 2016).

Reporting of these outcome measures will not form part of the criteria for including studies in a review.

Search methods for identification of studies

Electronic searches

We will search the following databases without language restrictions.

- The Cochrane Central Register of Controlled Trials (CENTRAL) (via the *Cochrane Library*).
- MEDLINE (via Ovid).
- EMBASE (via Ovid).

Medical subject headings (MeSH) or equivalent and text-word terms will be used. Full text translations of all relevant non-English articles will be obtained. Searches will be tailored to individual databases. The search strategy for MEDLINE can be found in Appendix 1.

Searching other resources

We will search the metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mrct), National Cancer Institute (http://www.cancer.gov/clinicaltrials), clinicaltrials.gov (www.clinicaltrials.gov), and the WHO International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/) for ongoing trials. We will also search ClinicalStudyResults.org (www.clinicalstudyresults.org) for clinical trials. In addition, reference lists of reviews and retrieved articles will be checked for additional studies, and citation searches will be performed on key articles. Authors will be contacted where necessary for additional information. We will perform handsearching of abstracts from relevant conferences, such as the International Cachexia Conference. Experts in the field will be contacted for unpublished and ongoing trials to identify any additional literature related to the review.

Data collection and analysis

Selection of studies

Two review authors (MNK,SG) will independently screen the articles retrieved from the searches using the Rayyan online screening tool (Elmagarmid 2014) and determine eligibility by reading the abstract of each study identified by the search. Independent review authors will eliminate studies that clearly do not satisfy inclusion criteria, and obtain full copies of the remaining studies. Two review authors (ZQS, AG) will read these studies independently to select relevant studies, and in the event of disagreement, a third author will adjudicate (AS). We will not anonymise the studies in any way before assessment. We will include a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart in the full review which will show the status of identified studies (Moher 2009) as recommended in Part 2, Section 11.2.1

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

of the *Cochrane Handbook* (Higgins 2011). We will include studies in the review irrespective of whether measured outcome data are reported in a 'usable' way.

Data extraction and management

Two review authors (MNK, SG) will independently extract data using a standard form and check for agreement before entry into Review Manager (RevMan 2014). We will include information about all the primary outcomes. We will collate multiple reports of the same study, so that each study rather than each report is the unit of interest in the review. We will collect characteristics of the included studies in sufficient detail to populate a table of 'Characteristics of included studies' in the full review.

Assessment of risk of bias in included studies

This section is taken from the PaPaS template for protocols.
Two authors (MNK, PS) will independently assess risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion. We will complete a 'Risk of bias' table for each included study using the 'Risk of bias' tool in RevMan (RevMan 2014).
We will assess the following for each study.

- Random sequence generation (checking for possible selection bias): We will assess the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). Studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number) will be excluded.
- Allocation concealment (checking for possible selection bias): The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We will assess the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated).
- Blinding of participants and personnel (checking for performance bias): We will assess the methods used to blind study participants and personnel about the receipt of the intervention. We will assess the methods as: low risk of bias (study states that it was blinded and describes the method used to achieve blinding); unclear risk of bias (study states that it was blinded but does not provide an adequate information of how it was done); high risk of bias (no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; or blinding of participants of the study and personnel was attempted, but it is likely that the blinding could have been broken).
- Blinding of outcome assessment (checking for possible detection bias): We will assess the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We will assess the methods as: low risk of bias (study states that it was blinded and describes the method used to achieve blinding, e.g. identical tablets; matched in appearance and smell); unclear risk of bias (study states that it was blinded but does not provide an adequate description of how blinding was achieved).
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data): We will assess the methods used to deal with incomplete data as: low risk (< 10% of participants did not complete the study and/or used 'baseline observation carried forward' analysis); unclear risk of bias (used 'last observation carried forward' analysis); high risk of bias (used 'completer' analysis).
- Size of study (checking for possible biases confounded by small size). We will assess studies as being at low risk of bias (≥ 200 participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (< 50 participants per treatment arm).
- Selective outcome reporting (checking for reporting bias): We will assess studies as being at low risk of bias (the study protocol is available; or the study protocol is not available but the study reported all expected and pre-specified outcomes); high risk of bias (the study reported one or more outcomes of interest incompletely); unclear risk of bias (the study provides insufficient information to permit judgement of 'low risk' or 'high risk').
- Other bias: We will assess the study as: low risk of bias (the study appears to be free of other sources of bias); unclear risk of bias (there may be a risk of bias, but there is insufficient information to judge whether risk of bias exists; or insufficient evidence that a problem under consideration will introduce bias); or high risk of bias (there is at least one important risk of bias).

Measures of treatment effect

We will use a fixed-effect model or random-effects model to estimate the overall direction, size and consistency of an effect. For dichotomous variables, we will compute treatment effects as risk ratios (RR) or odds ratios (OR) with 95% confidence intervals (CI). For continuous data we will use mean differences (MD) with 95% CI when the results are measured in the same way in different studies. We will use standardised mean differences (SMD) when the results obtained are conceptually the same but used different measurement scales. We will record means and standard deviations. The mean change in each group will be obtained by subtracting the final mean from the baseline mean. The change in standard deviation will be obtained from CI, standard errors,

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

t values, P values or F values (whichever is available) using the RevMan calculator. When there is not enough information available to calculate the standard deviations for the changes, they will be imputed. If the required data are not available, then we will use a comparison of final measurements. We will evaluate the direction and size of the effect as well as looking at the consistency of the effect across the selected studies. Clinically meaningful change will be considered taking into account the change in weight and appetite with a measurable entity and time span.

Unit of analysis issues

In parallel-group randomised controlled trials, we will consider the individual patient as the unit of analysis. When incorporating cross-over trials into a meta-analysis, we will follow the approach suggested by Elbourne (Elbourne 2002). We will incorporate these trials by taking measurements from experimental intervention periods and measurements from control intervention periods and analysing these as if the trial were a parallel group trial of intervention versus control. If carry-over is thought to be a problem, we will include only data from the first period. The effect estimate of cross-over trials will be included in a meta-analysis using the generic inverse-variance method.

Dealing with missing data

We will carry out an intention-to-treat analysis. When published data are missing, incomplete or inconsistent with RCT protocols, we will ask for further information from the authors/manufacturers. We will contact authors by email if studies did not report the outcome measures of interest, did not describe randomisation or intention-to-treat analysis or had missing data.

Assessment of heterogeneity

We plan to assess clinical heterogeneity by using the Chi^2 test (P value < 0.10 for statistical significance) and use the I^2 statistic to quantify heterogeneity. Heterogeneity will be regarded as considerable if I^2 is more than 75%; substantial if it is between 50% and 90%; moderate if it is between 30% and 60% and mild if less than 40% (Higgins 2011). If we identify statistical heterogeneity (I^2 greater than, or equal to 50%), we will report it and explore possible causes by prespecified subgroup analysis, and will apply a random-effects model.

Assessment of reporting biases

If there are 10 or more included studies, we plan to conduct a funnel plot test for asymmetry to assess for any evidence of reporting bias. Additionally, possible sources of asymmetry in a funnel plot will be explored.

Data synthesis

We will undertake a meta-analysis only if participants, interventions, comparisons and outcomes are judged to be sufficiently similar to ensure an answer that is clinically meaningful and relevant. For analysis, we plan to use RevMan 2014, the statistical package provided by the Cochrane Collaboration.

If statistical heterogeneity (I^2 greater than, or equal to 50%) is detected, we will attempt to identify the sources of the heterogeneity and will perform subsequent meta-analysis using a random-effects model. If the meta-analysis is inappropriate for any other reason, we will not pool the results of the included studies, but will present a qualitative description of these studies with supporting tables. If there are sufficient and homogeneous data with consistent or comparable outcomes, we plan to perform a meta-analysis using a fixed-effect model.

'Summary of findings' tables

We will include a 'Summary of findings' (SoF) table as set out in the PaPaS author guide (AUREF 2012) and recommended in the *Cochrane Handbook*, chapter 4.6.6 (Higgins 2011). We will present the SoF tables under the following comparisons for all of the primary outcomes:

1. Ghrelin versus placebo;
2. Ghrelin versus an alternative experimental treatment modality; and
3. Ghrelin in combination with other treatments versus ghrelin treatment alone.

Two review authors (ZQS, MNQ) will assess the overall quality of the evidence for each outcome using the GRADE system (GRADEpro GDT 2015) and present the findings in the 'Summary of findings' tables. In particular, we will include key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the main outcomes.

We will decrease the grade if there is:

- A serious (-1) or very serious (-2) limitation to study quality;
- Important inconsistency (-1);
- Some (-1) or major (-2) uncertainty about directness;
- Imprecise or sparse data (-1);
- High probability of reporting bias (-1).

We will justify all decisions to down-grade the quality of studies using footnotes.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses are planned for form, dose, duration and route of administration of ghrelin, and for different types of cancer.

ACKNOWLEDGEMENTS

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

• We acknowledge the support of Dr Prathap Tharyan, Director, South Asian Cochrane Network & Center, Prof. BV Moses Center for Evidence-Informed Health Care and Health Policy, Christian Medical College, Vellore, India.

• Cochrane Review Group funding acknowledgement: The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane PaPaS Group. Disclaimer: The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the NIHR, National Health Service (NHS) or the Department of Health.

• We acknowledge the external peer referees Dr Ollie Minton, consultant and senior lecturer in palliative medicine, Roger Goucke, anaesthesia/palliative Care, Maria J Silveira, palliative care specialist and researcher, and Marília Seelaender, head of the Cancer Metabolism Group, University of São Paulo, for providing valuable input to the protocol.

• We acknowledge the support of Dr Alka Rawekar, Dr Tripti Shrivastava and Mahafroz Khatib during the preparation of the protocol.

REFERENCES

Additional references

Akamizu 2010
Akamizu T, Kangawa K. Ghrelin for cachexia. *Journal of Cachexia, Sarcopenia and Muscle* 2010;**1**(2):169–76. [PUBMED: 21475698]

AUREF 2012
Cochrane Pain, Palliative and Supportive Care Group. PaPaS Author and Referee Guidance. http://papas.cochrane.org/papas-documents (accessed on 16 August 2015).

Baracos 2011
Baracos VE. Pitfalls in defining and quantifying cachexia. *Journal of Cachexia, Sarcopenia and Muscle* 2011;**2**(2):71–3. [PUBMED: 21766051]

Bozzetti 2009
Bozzetti F, Mariani L. Defining and classifying cancer cachexia: a proposal by the SCRINIO Working Group. *JPEN. Journal of Parenteral and Enteral Nutrition* 2009;**33**(4):361–7. [PUBMED: 19109514]

CDC 2016
Centre for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion. Health-Related Quality of Life (HRQOL) | CDC. http://www.cdc.gov/hrqol/ May 2016.

Chen 2015
Chen JA, Splenser A, Guillory B, Luo J, Mendiratta M, Belinova B, et al. Ghrelin prevents tumour- and cisplatin-induced muscle wasting: characterization of multiple mechanisms involved. *Journal of Cachexia, Sarcopenia and Muscle* 2015;**6**(2):132–43. [PUBMED: 26136189]

Date 2002
Date Y, Murakami N, Toshinai K, Matsukura S, Niijima A, Matsuo H, et al. The role of the gastric afferent vagal nerve in ghrelin-induced feeding and growth hormone secretion in rats. *Gastroenterology* 2002;**123**(4):1120–8. [PUBMED: 12360474]

DeBoer 2007
DeBoer MD, Zhu X, Levasseur P, Meguid M, Suzuki S, Inui A, et al. Ghrelin treatment causes increased food intake and retention of lean body mass in a rat model of cancer cachexia. *Endocrinology* 2007;**148**(6):3004–12. [PUBMED: 17347304]

Dixit 2004
Dixit D, Schaffer M, Pyle S, Collins D, Sakthivel K, Palaniappan R, et al. Ghrelin inhibits leptin- and activation-induced proinflammatory cytokine expression by human monocytes and T cells. *The Journal of Clinical Investigation* 2004;**114**(1):57–66. [PUBMED: 15232612]

Elbourne 2002
Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140–9. [PUBMED: 11914310]

Elmagarmid 2014
Elmagarmid A, Fedorowicz Z, Hammady H, Ilyas I, Khabsa M, Ouzzani M. Rayyan: a systematic reviews web app for exploring and filtering searches for eligible studies for Cochrane Reviews [oral presentation]. Cochrane Colloquium. John Wiley & Sons, 2014.

Esposito 2015
Esposito A, Criscitiello C, Gelao L, Pravettoni G, Locatelli M, Minchella I, et al. Mechanisms of anorexia-cachexia syndrome and rational for treatment with selective ghrelin receptor agonist. *Cancer Treatment Reviews* 2015;**41**(9):793–7. [PUBMED: 26386985]

Fearon 2006
Fearon KC, Voss AC, Hustead DS. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. *The American Journal of Clinical Nutrition* 2006;**83**(6):1345–50. [PUBMED: 16762946]

Fearon 2011
Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *The Lancet. Oncology* 2011;**12**(5):489–95. [PUBMED: 21296615]

Fujino 2003
Fujino K, Inui A, Asakawa A, Kihara N, Fujimura M, Fujimiya M. Ghrelin induces fasted motor activity of the

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

gastrointestinal tract in conscious fed rats. *The Journal of Physiology* 2003;**550**(Pt 1):227–40. [PUBMED: 12837928]

Fujitsuka 2009

Fujitsuka N, Asakawa A, Hayashi M, Sameshima M, Amitani H, Kojima S, et al. Selective serotonin reuptake inhibitors modify physiological gastrointestinal motor activities via 5-HT2c receptor and acyl ghrelin. *Biological Psychiatry* 2009;**65**(9):748–59. [PUBMED: 19058784]

Fujitsuka 2011

Fujitsuka N, Asakawa A, Uezono Y, Minami K, Yamaguchi T, Niijima A, et al. Potentiation of ghrelin signaling attenuates cancer anorexia-cachexia and prolongs survival. *Translational Psychiatry* 2011;**1**:e23.

Fujitsuka 2014

Fujitsuka N, Uezono Y. Rikkunshito, a ghrelin potentiator, ameliorates anorexia-cachexia syndrome. *Frontiers in Pharmacology* 2014;**5**:271. [PUBMED: 25540621]

Fuoco 2015

Fuoco D, Kilgour RD, Vigano A. A hypothesis for a possible synergy between ghrelin and exercise in patients with cachexia: biochemical and physiological bases. *Medical Hypotheses* 2015;**85**(6):927–33. [PUBMED: 26404870]

Garcia 2005

Garcia JM, Garcia-Touza M, Hijazi RA, Taffet G, Epner D, Mann D, et al. Active ghrelin levels and active to total ghrelin ratio in cancer-induced cachexia. *The Journal of Clinical Endocrinology and Metabolism* 2005;**90**(5):2920–6. [PUBMED: 15713718]

Garcia 2007

Garcia J, Boccia R, Graham C, et al. A phase II randomized, placebo-controlled, double-blind study of the efficacy and safety of RC-1291 (RC) for the treatment of cancer cachexia. *Journal of Clinical Oncology* 2007 (June 20 Supplement);**25**(18S):9133.

Garcia 2009

Garcia JM, Polvino WJ. Pharmacodynamic hormonal effects of anamorelin, a novel oral ghrelin mimetic and growth hormone secretagogue in healthy volunteers. *Growth Hormone & IGF Research* 2009;**19**(3):267–73. [PUBMED: 19196529]

Garcia 2013

Garcia JM, Friend J, Allen S. Therapeutic potential of anamorelin, a novel, oral ghrelin mimetic, in patients with cancer-related cachexia: a multicenter, randomized, double-blind, crossover, pilot study. *Supportive Care in Cancer* 2013;**21**(1):129–37. [PUBMED: 22699302]

Garcia 2015

Garcia JM, Boccia RV, Graham CD, Yan Y, Duus EM, Allen S, et al. Anamorelin for patients with cancer cachexia: an integrated analysis of two phase 2, randomised, placebo-controlled, double-blind trials. *The Lancet. Oncology* 2015; **16**(1):108–16. [PUBMED: 25524795]

GRADEpro GDT 2015 [Computer program]

Brozek J, Oxman A, Schünemann H. GRADEpro Guideline Development Tool. McMaster University: Evidence Prime, Inc., 2015.

Higgins 2011

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. Available from www.cochrane-handbook.org. Vol. **5.1.0**, The Cochrane Collaboration, 2009 [Updated March 2011].

Khatib 2014a

Khatib MN, Gaidhane S, Gaidhane A, Syed ZQ. Role of ghrelin in regulation of growth hormone secretion by ghrelin-pituitary-GH axis. *International Journal of Medical Science and Public Health* 2014;**3**(4):425–9. [DOI: 10.5455/ijmsph.2014.250120141]

Khatib 2014b

Khatib MN, Simkhada P, Gode D. Cardioprotective effects of ghrelin in heart failure: from gut to heart. *Heart Views* 2014;**15**(3):74–6. [DOI: 10.4103/1995-705X.144792]

Khatib 2014c

Khatib MN, Khatib M, Gaidhane S, Gaidhane A, Quazi SZ. Ghrelin for regulating appetite and energy balance: a systematic review. *National Journal of Physiology, Pharmacy and Pharmacology* 2014;**4**(3):101–5. [DOI: 10.5455/njppp.2014.4.230420141]

Khatib 2014d

Khatib MN, Gode D, Simkhada P, Agho K, Gaidhane S, Saxena D, et al. Somatotropic and cardio-protective effects of ghrelin in experimental models of heart failure: a systematic review. *Annals of Tropical Medicine and Public Health* 2014;**7**(1):30–42. [DOI: 10.4103/1755-6783.145008]

Khatib 2014e

Khatib MN, Gaidhane S, Simkhada P, Gaidhane A, Quazi SZ. Cardiovascular effects of ghrelin in heart failure: a systematic review. *International Journal of Medical Science and Public Health* 2014;**3**(6):756–63. [DOI: 10.5455/ijmsph.2014.060420141]

Khatib 2014f

Khatib MN, Gaidhane S, Gaidhane AM, Khatib M, Simkhada P, Gode D, et al. Ghrelin: ghrelin as a regulatory peptide in growth hormone secretion. *Journal of Clinical and Diagnostic Research* 2014;**8**(8):MC13–7. [PUBMED: 25302229]

Khatib 2015a

Khatib MN, Shankar A, Kirubakaran R, Agho K, Simkhada P, Gaidhane S, et al. Effect of ghrelin on mortality and cardiovascular outcomes in experimental rat and mice models of heart failure: a systematic review and meta-analysis. *PloS One* 2015;**10**(5):e0126697. [PUBMED: 26016489]

Khatib 2015b

Khatib MN, Gaidhane S, Gaidhane AM, Simkhada P, Zahiruddin QS. Ghrelin-O-acyl-transferase (GOAT) as a novel metabolic regulatory enzyme. *Journal of Clinical and Diagnostic Research* 2015;**9**(2):LE01–5. [PUBMED: 25859472]

Klok 2007

Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

in humans: a review. *Obesity Reviews* 2007;**8**(1):21–34. [PUBMED: 17212793]

Kos 2009

Kos K, Harte AL, O'Hare PJ, Kumar S, McTernan PG. Ghrelin and the differential regulation of des-acyl (DSG) and oct-anoyl ghrelin (OTG) in human adipose tissue (AT). *Clinical Endocrinology* 2009;**70**(3):383–9. [PUBMED: 18616714]

Madeddu 2015a

Madeddu C, Mantovani G, Gramignano G, Astara G, Maccio A. Muscle wasting as main evidence of energy impairment in cancer cachexia: future therapeutic approaches. Future Oncology 2015; Vol. [Epub ahead of print]. [PUBMED: 26376740]

Madeddu 2015b

Madeddu C, Mantovani G, Gramignano G, Maccio A. Advances in pharmacologic strategies for cancer cachexia. *Expert Opinion on Pharmacotherapy* 2015;**16**(14):2163–77. [PUBMED: 26330024]

Mendes 2015

Mendes MCS, Pimentel GD, Costa FO, Carvalheira JBC. Molecular and neuroendocrine mechanisms of cancer cachexia. *Journal of Endocrinology* 2015;**226**(3):R29–43.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009;**6**(7):e1000097.

Molfino 2014

Molfino A, Formiconi A, Rossi Fanelli F, Muscaritoli M. Ghrelin: from discovery to cancer cachexia therapy. *Current Opinion in Clinical Nutrition and Metabolic Care* 2014;**17**(5):471–6. [PUBMED: 24905862]

Murphy 1998

Murphy MG, Plunkett LM, Gertz BJ, He W, Wittreich J, Polvino WM, et al. MK-677, an orally active growth hormone secretagogue, reverses diet-induced catabolism. *The Journal of Clinical Endocrinology and Metabolism* 1998;**83**(2):320–5. [PUBMED: 9467534]

Neary 2004

Neary NM, Small CJ, Wren AM, Lee JL, Druce MR, Palmieri C, et al. Ghrelin increases energy intake in cancer patients with impaired appetite: acute, randomized, placebo-controlled trial. *The Journal of Clinical Endocrinology and Metabolism* 2004;**89**(6):2832–6. [PUBMED: 15181065]

Northrup 2013

Northrup R, Kuroda K, Duus EM, Barnes SR, Cheatham L, Wiley T, et al. Effect of ghrelin and anamorelin (ONO-7643), a selective ghrelin receptor agonist, on tumor growth in a lung cancer mouse xenograft model. *Supportive Care in Cancer* 2013;**21**(9):2409–15. [PUBMED: 23579947]

Penna 2010

Penna F, Costamagna D, Fanzani A, Bonelli G, Baccino FM, Costelli P. Muscle wasting and impaired myogenesis in tumor bearing mice are prevented by ERK inhibition. *PloS one* 2010;**5**(10):e13604. [PUBMED: 21048967]

Penna 2016

Penna F, Busquets S, Argiles JM. Experimental cancer cachexia: evolving strategies for getting closer to the human scenario. *Seminars in Cell and Developmental Biology* 2016;**54**:20–7. [DOI: 10.1016/j.semcdb.2015.09.002; PUBMED: 26343953]

Pietra 2014

Pietra C, Takeda Y, Tazawa-Ogata N, Minami M, Yuanfeng X, Duus EM, et al. Anamorelin HCl (ONO-7643), a novel ghrelin receptor agonist, for the treatment of cancer anorexia-cachexia syndrome: preclinical profile. *Journal of Cachexia, Sarcopenia and Muscle* 2014;**5**(4):329–37. [PUBMED: 25267366]

Porporato 2013

Porporato PE, Filigheddu N, Reano S, Ferrara M, Angelino E, Gnocchi VF, et al. Acylated and unacylated ghrelin impair skeletal muscle atrophy in mice. *The Journal of Clinical Investigation* 2013;**123**(2):611–22. [PUBMED: 23281394]

Reid 2012

Reid J, Mills M, Cantwell M, Cardwell CR, Murray LJ, Donnelly M. Thalidomide for managing cancer cachexia. *Cochrane Database of Systematic Reviews* 2012, Issue 4. [DOI: 10.1002/14651858.CD008664.pub2]

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Ryan 2016

Ryan AM, Power DG, Daly L, Cushen SJ, Ni Bhuachalla E, Prado CM. Cancer-associated malnutrition, cachexia and sarcopenia: the skeleton in the hospital closet 40 years later. The Proceedings of the Nutrition Society. 2016:1–13. [PUBMED: 26786393]

Stephens 2008

Stephens NA, Skipworth RJ, Fearon KC. Cachexia, survival and the acute phase response. *Current Opinion in Supportive and Palliative Care* 2008;**2**(4):267–74. [PUBMED: 19060563]

Stewart 2006

Stewart GD, Skipworth RJ, Fearon KC. Cancer cachexia and fatigue. *Clinical Medicine* 2006;**6**(2):140–3. [PUBMED: 16688969]

Sugiyama 2012

Sugiyama M, Yamaki A, Furuya M, Inomata N, Minamitake Y, Ohsuye K, et al. Ghrelin improves body weight loss and skeletal muscle catabolism associated with angiotensin II-induced cachexia in mice. *Regulatory Peptides* 2012;**178**(1-3):21–8. [PUBMED: 22750276]

Sun 2015

Sun L, Quan XQ, Yu S. An epidemiological survey of cachexia in advanced cancer patients and analysis on its

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

diagnostic and treatment status. *Nutrition and Cancer* 2015 Oct;**67**(7):1056–62. [PUBMED: 26317149]

Takeda 2008
Takeda H, Sadakane C, Hattori T, Katsurada T, Ohkawara T, Nagai K, et al. Rikkunshito, an herbal medicine, suppresses cisplatin-induced anorexia in rats via 5-HT2 receptor antagonism. *Gastroenterology* 2008;**134**(7): 2004–13. [PUBMED: 18439428]

Teunissen 2007
Teunissen SC, Wesker W, Kruitwagen C, de Haes HC, Voest EE, de Graeff A. Symptom prevalence in patients with incurable cancer: a systematic review. *Journal of Pain and Symptom Management* 2007;**34**(1):94–104. [PUBMED: 17509812]

Tisdale 2009
Tisdale MJ. Mechanisms of cancer cachexia. *Physiological Reviews* 2009;**89**(2):381–410. [PUBMED: 19342610]

Tschop 2000
Tschop M, Smiley DL, Heiman ML. Ghrelin induces adiposity in rodents. *Nature* 2000;**407**(6806):908–13. [PUBMED: 11057670]

Tsubouchi 2014
Tsubouchi H, Yanagi S, Miura A, Matsumoto N, Kangawa K, Nakazato M. Ghrelin relieves cancer cachexia associated with the development of lung adenocarcinoma in mice. *European Journal of Pharmacology* 2014;**743**:1–10. [PUBMED: 25257464]

Utech 2012
Utech AE, Tadros EM, Hayes TG, Garcia JM. Predicting survival in cancer patients: the role of cachexia and hormonal, nutritional and inflammatory markers. *Journal of Cachexia, Sarcopenia and Muscle* 2012;**3**(4):245–51. [PUBMED: 22648739]

Velloso 2008
Velloso CP. Regulation of muscle mass by growth hormone and IGF-I. *British Journal of Pharmacology* 2008;**154**(3): 557–68. [PUBMED: 18500379]

von Haehling 2012
von Haehling S, Anker SD. Cachexia as major underestimated unmet medical need: facts and numbers. *International Journal of Cardiology* 2012;**161**(3):121–3. [PUBMED: 23084543]

Watanabe 1996
Watanabe S, Bruera E. Anorexia and cachexia, asthenia, and lethargy. *Hematology/Oncology Clinics of North America* 1996;**10**(1):189–206. [PUBMED: 8821567]

Windsor 1988
Windsor JA, Hill GL. Risk factors for postoperative pneumonia. The importance of protein depletion. *Annals of Surgery* 1988;**208**(2):209–14. [PUBMED: 3401064]

Wren 2001
Wren AM, Seal LJ, Cohen MA, Brynes AE, Frost GS, Murphy KG, et al. Ghrelin enhances appetite and increases food intake in humans. *The Journal of Clinical Endocrinology and Metabolism* 2001;**86**(12):5992. [PUBMED: 11739476]

Zhang 2007
Zhang W, Zhao L, Mulholland MW. Ghrelin stimulates myocyte development. *Cellular Physiology and Biochemistry: International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology* 2007;**20**(5):659–64. [PUBMED: 17762192]

Zhang 2015
Zhang H, Garcia JM. Anamorelin hydrochloride for the treatment of cancer-anorexia-cachexia in NSCLC. *Expert Opinion on Pharmacotherapy* 2015;**16**(8):1245–53. [PUBMED: 25945893]

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Appendix. MEDLINE search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:
1 Ghrelin/
2 (ghrelin or ppghrelin or (motilin adj2 peptide) or ghrl or obestatin or ppmtlrp or "appetite regulating hormone" or Anamorelin or Ipamorelin or Eganamorelin or Hexarelin or MK-677 or Rikkunshito).tw.
3 Cachexia/
4 cachexia.tw.
5 cachexic.tw.
6 (weight or underweight or malnutrition or wasting).tw.
7 Weight Loss/
8 or/3-7

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

9 exp Neoplasms/
10 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma* or adenocarcinoma* or choricarcinoma* or leukemia* or leukaemia* or metastat* or sarcoma* or teratoma*).tw.
11 or/9-10
12 1 or 2
13 8 and 11 and 12

CONTRIBUTIONS OF AUTHORS

MNK and ZQS designed and developed the protocol with input from AG, SG, PS, RK and AS. MNK and SG developed the search strategy with the help of the PaPaS Group Information Specialist, and ZQS wrote the Background section. MNK and SG will be responsible for data extraction in the full review. All authors will be responsible for completing the protocol, full review, and updating the review in future.

DECLARATIONS OF INTEREST

MNK: none known.

AS: none known.

RK: none known.

AG: none known.

SG: none known. SG is a specialist physician and manages patients with cancer cachexia.

PS: none known.

ZQS: none known.

Commercial funding of reviews or authors

The authors have not received any funding from any source.

SOURCES OF SUPPORT

Internal sources

- Datta Meghe Institute of Medical Sciences, India.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

External sources

- No sources of support supplied

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.