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Interventions for fatigue in people with chronic kidney disease requiring dialysis (Protocol)

Ju A, Strippoli GFM, Craig JC, Tong A, Saglimbene VM, Unruh ML

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Interventions for fatigue in people with chronic kidney disease requiring dialysis

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A B S T R A C T

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

This review aims to evaluate the effects of any pharmacological and non-pharmacological interventions on fatigue in patients on chronic dialysis.

B A C K G R O U N D

Description of the condition

Fatigue is one of the most common symptoms in patients on dialysis. It is a debilitating symptom that affects patients worldwide, regardless of demographic factors such as ethnicity, gender and socioeconomic status. The prevalence of fatigue ranges from 60% to as high as 97% in adult patients on haemodialysis (HD) (Jhamb 2008) and about 55% to 89% in patients on peritoneal dialysis (PD) (Chang 2001; Yngman-Uhlin 2010).

Although the exact causes are not fully understood, several factors may be associated with fatigue in the dialysis population. For patients on HD, physiological factors such as anaemia have been shown to be associated with fatigue and studies suggest that the use of erythropoietin stimulating agents (ESAs) to treat anaemia improves quality of life, fatigue and energy levels in patients on HD (Johansen 2012; Ross 2003). In patients with cancer, fatigue is associated with cytokines released from therapy (Mücke 2015). Similarly, cytokines may contribute to fatigue in patients on HD as elevated levels of pro-inflammatory cytokines are seen in end-stage kidney disease (ESKD) (Bergstrom 2000, Rao 2007, Artom 2014). Treatment-related factors such as dialysis frequency, modality, and time to recovery have also been shown to affect fatigue (Jhamb 2008). Post-dialysis fatigue is a temporary yet intense fatigue associated with treatment. Patients who received daily HD reported less post-dialysis fatigue than those who had days off between dialysis sessions, suggesting that this symptom may

be related to treatment frequency. Modalities such as nocturnal dialysis may help patients recover from post-dialysis fatigue faster (Himmelfarb 2010). Psychosocial and lifestyle factors correlated with fatigue in HD include depression, physical inactivity, and poor sleep quality (Jhamb 2008).

In the PD population, clinical factors associated with fatigue scores including cholesterol concentration, weekly creatinine clearance and serum intact parathyroid hormone (Chang 2001). Similar to the HD population, self-report sleep quality and disorders have been correlated with fatigue (Jhamb 2013; Unruh 2006; Yngman-Uhlin 2006; Yngman-Uhlin 2010).

Fatigue for patients on dialysis is associated with various outcomes relating to quality of life, cardiovascular disease (CVD) and death (Chiaranai 2016; Jhamb 2008). It can be extremely debilitating and intrusive both emotionally and physically (Chiaranai 2016; Horigan 2013; Yngman-Uhlin 2010). Patients experience a limitation in freedom, a loss of sense of self and a loss of social connectedness (Monaro 2014). Reiterating the pervasiveness of this symptom, fatigue has recently been established by patients and health professionals as a critically important outcome to be reported in all clinical studies in patients on HD (Evangelidis 2017; Tong 2017). Furthermore, fatigue has previously been marked as a predictor for cardiovascular events and death, independent of potential confounding risk factors such as age, diabetes, body mass index, and history of CVD (Jhamb 2008; Jhamb 2013; Koyama 2010).

Description of the intervention

As the causes of fatigue are uncertain and likely to be multifactorial, a range of interventions - both pharmacological and non-pharmacological - will be considered.

How the intervention might work

The exact causal mechanism of improvements seen in various interventions remains unknown. However, both pharmacological and non-pharmacological interventions may improve fatigue. For example, erythropoietin or other interventions to achieve higher haemoglobin targets, and levocarnitine to modify the effects of defective fatty-acid metabolism, have been shown to improve symptoms of fatigue (Foley 2009; Johansen 2012; Ossareh 2003; Schreiber 2005,). Non-pharmacological interventions that focus on psychosocial and lifestyle aspects such as diet, exercise, sleep, foot reflexology and yoga may also help to improve fatigue (Eglence 2013; Yurtkuran 2007). Physical activity may improve fatigue through indirect effects on cytokine levels or by increasing muscle strength (Jhamb 2008). Cognitive behavioural therapy has also demonstrated improvement in sleep and fatigue in this population (Chen 2008). However, the exact causal mechanism of improvements seen in these studies remains unknown. For instance, sleep disturbances result in daytime tiredness as well as increased levels of inflammatory cytokines, which are both associated with fatigue.

Why it is important to do this review

It is widely known that fatigue is one of the most common and debilitating symptoms experienced by patients on dialysis. In the HD population, fatigue has been consistently identified as the most critically important outcome and a high research priority in patients on HD (Evangelidis 2017; Urquhart-Secord 2016). The last decade has seen a growing number of studies on pharmacological and lifestyle interventions to improve fatigue. There have been systematic reviews focusing on one particular type of pharmacological intervention such as levocarnitine (Schreiber 2005). Only one systematic review has been published on non-pharmacological interventions for fatigue, which included 25 studies and only 11 (44%) were randomised controlled trials (RCTs) (Astroth 2013). Furthermore, it is unclear how the efficacy of these interventions compares to pharmacological interventions.

In this review, we will summarise and synthesize all current evidence of benefits and harms for interventions that have been evaluated for their impact on fatigue in patients on dialysis. We will consider all pharmacological and non-pharmacological interventions as the potential causes of fatigue are diverse and likely to be multifactorial. In doing so, this review will shed light on any existing evidence for an intervention that effectively reduces or manages fatigue. Information on the efficacy of different interventions and other factors that facilitate or challenge the improvement of fatigue will allow clinicians to provide effective care for their patients' experience of this debilitating symptom. Furthermore, as fatigue is associated with other outcomes such as CVD, death and broader quality of life, improvement in this symptom may translate into better patient outcomes overall.

OBJECTIVES

This review aims to evaluate the effects of any pharmacological and non-pharmacological interventions on fatigue in patients on chronic dialysis.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth, or other predictable methods) of interventions whereby fatigue was reported as an outcome (either primary or secondary outcome).

Types of participants

Inclusion criteria

Patients of any age with ESKD on any form of dialysis.

Exclusion criteria

None.

Types of interventions

We will consider any intervention affecting levels of fatigue in patients on dialysis. Studies will be included if fatigue is reported as an outcome.

- Pharmacological treatment (including but not limited to): psychostimulants (amphetamines, modafinil, armodafinil, methylphenidate, pemoline), amantadine, corticosteroids (dexamethasone, prednisone, methylprednisolone), donepezil, antidepressants (selective serotonin reuptake inhibitors, paroxetine), anxiolytics, ESAs, human growth hormone, TNF inhibitor, acetylsalicylic acid, megestrol acetate, alfacalcidol and intravenous levocarnitine
- Non pharmacological treatment (including but not limited to): nutrition (lean body mass, albumin, diet), therapeutic exercise (sleep hygiene, yoga, exercise), alternative and complementary medicine (acupressure, Chinese herbal medicine and acupuncture), psychosocial (psychotherapy, psycho-education e.g. cognitive restructuring, coping strategies, stress management), educational (goal-setting, providing information/advice on symptom management/nutrition).

Any mode, frequency, prescription, and duration of therapy, will be considered. The intervention may be administered at any time or day (i.e. dialysis or non-dialysis days), and in clinical or non-clinical settings.

Types of outcome measures

We will use time points of measurements as reported by investigators, as well as assess outcome measures at the end of the treatment.

Primary outcomes

Fatigue and fatigue-related outcomes such as tiredness, exhaustion, weakness and asthenia that have been assessed through any self-report measure (open-ended questionnaires such as fatigue diary, fatigue-specific scales e.g. FACIT-F, Chalder Fatigue Scale, or fatigue subscale as part of a measure assessing a broader construct e.g. SF-36, or visual analogue scale (VAS)). We will consider all patient-reported outcome measures for fatigue given the lack of validation work conducted in the dialysis population.

Secondary outcomes

Quality of life, depression, anxiety, death, vascular access, CVD, hypertension, diabetes.

Search methods for identification of studies

No restrictions based on date of the study/publications, language, or publication will be applied when searching and selecting studies for inclusion. The search will be conducted with the Cochrane Kidney and Transplant Information Specialist using search terms relevant to this review.

Electronic searches

We will search the Cochrane Kidney and Transplant Register of Studies through contact with the Information Specialist using search terms relevant to this review. The Register contains studies identified from the following sources:

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these searches, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the "Specialised Register" section of information about Cochrane Kidney and Transplant. See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.

2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described will be used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts will be screened independently by two authors. Two authors will independently assess retrieved abstracts, and if necessary the full text, of these studies to determine which studies satisfy the inclusion criteria.

Data extraction and management

Data relating to study design (RCT, quasi-RCT), participant characteristics (e.g. age, gender, dialysis vintage, comorbidities), interventions (pharmacological, non-pharmacological) and outcomes (as described above) will be extracted and organised using the software Review Manager 5.4 (RevMan2014). The two authors will independently carry out data extraction using a standard data extraction form. Studies reported in non-English language will be translated before assessment. Where more than one publication of a study exists, the publications will be grouped together and the report with the most complete data will be included in the meta-analyses. Where relevant outcomes are only published in earlier versions these data will be used. Any discrepancy between published versions will be highlighted. Any further information required from the original author will be requested by written correspondence and any relevant information obtained in this manner will be included in the review. Disagreements will be resolved by consensus in consultation with a third author.

Assessment of risk of bias in included studies

The following items will be independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).
- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?

- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (e.g. adverse events, cardiovascular event, death) results will be expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used to assess the effects of treatment (e.g. depression, fatigue), the mean difference (MD) will be used, or the standardised mean difference (SMD) if different scales have been used.

Unit of analysis issues

Cluster-randomised studies

We anticipate that studies using clustered randomisation will have controlled for clustering effects. In case of doubt, we will contact the first authors to ask for individual participant data to calculate an estimate of the intra cluster correlation coefficient (ICC). If this is not possible, we will obtain external estimates of the ICC from a similar study or from a study of a similar population as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). When the ICC is established, we will use it to re-analyse the study data. If ICCs from other sources are used, we will report this and conduct sensitivity analyses to investigate the effect of variations in the ICC.

Cross-over studies

We will include all randomised cross-over studies in the systematic review if they report a paired (comparison within patient) analysis using all periods. If not, we will only use the data from the first period.

Studies with more than two treatment arms

If more than one of the interventions is a fatigue intervention, and there is sufficient information in the study to assess the similarity of the interventions, we will combine similar interventions to allow for a single pair-wise comparison.

Dealing with missing data

Any further information required from the original author will be requested by written correspondence (e.g. emailing the corresponding author) and any relevant information obtained in this manner will be included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population will be carefully performed. Attrition rates, for example drop-outs, losses

to follow-up and withdrawals will be investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) will be critically appraised (Higgins 2011).

Assessment of heterogeneity

We will first assess the heterogeneity by visual inspection of the forest plot. We will quantify statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). A guide to the interpretation of I^2 values will be as follows:

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi^2 test, or a confidence interval for I^2) (Higgins 2011).

Assessment of reporting biases

If possible, funnel plots will be used to assess for the potential existence of small study bias (Higgins 2011).

Data synthesis

Data will be pooled using the random-effects model but the fixed-effect model will also be used to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

We will report the results of our findings separately focusing on fatigue. Data will be pooled using the random-effects model but the fixed-effect model will also be used to ensure robustness of the model chosen and susceptibility to outliers. Adverse effects will be tabulated and assessed with descriptive techniques, as they are likely to be different for the various interventions used. Where possible, the risk differences with 95% CI will be calculated for each adverse effect, either compared to no treatment or to another agent.

Based on available data, we will perform the following subgroup analyses:

- Age: < 18 years versus ≥ 18 years; ≥ 18 years and < 64 years versus ≥ 64 years
- Gender: female versus male
- Risk of bias: high versus low (versus unclear) (allocation concealment, blinding of outcome assessors, incomplete outcome data)

- Indication: studies targeting fatigue versus reporting fatigue
- Intervention type: pharmacological versus non-pharmacological
- Presence of comorbidities: CVD (yes versus no), diabetes (yes versus no), hypertension (yes versus no), depression (clinical diagnosis versus none)
- Fatigue outcome measures used: validation data available versus de novo
- Dialysis type: PD versus HD
- Dialysis vintage: < 5 years versus ≥ 5 years

Sensitivity analysis

We will perform sensitivity analyses in order to explore the influence of the following factors on effect size:

- Repeating the analysis excluding abstract-only publication
- Repeating the analysis excluding industry-funded studies
- Repeating the analysis taking account of risk of bias (allocation concealment)
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results.

'Summary of findings' tables

We will present the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schünemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008; GRADE 2011). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b). We plan to present the following outcomes in the 'Summary of findings' tables.

- Fatigue

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor: [Mental Fatigue] this term only 2. fatigue:ti,ab,kw (Word variations have been searched) 3. "lassitude":ti,ab,kw (Word variations have been searched) 4. tired or tiredness:ti,ab,kw (Word variations have been searched) 5. weary or weariness:ti,ab,kw (Word variations have been searched) 6. exhaustion:ti,ab,kw (Word variations have been searched) 7. {or #1-#6} 8. MeSH descriptor: [Renal Dialysis] explode all trees 9. MeSH descriptor: [Hemofiltration] explode all trees 10. MeSH descriptor: [Kidney Failure, Chronic] this term only 11. "dialysis":ti,ab,kw (Word variations have been searched) 12. hemodialysis or haemodialysis:ti,ab,kw (Word variations have been searched) 13. hemofiltration or haemofiltration:ti,ab,kw (Word variations have been searched) 14. hemodiafiltration or haemodiafiltration:ti,ab,kw (Word variations have been searched) 15. "end-stage kidney" or "end-stage renal" or "endstage kidney" or "endstage renal":ti,ab,kw (Word variations have been searched) 16. eskd or eskf or esrd or esrf:ti,ab,kw (Word variations have been searched) 17. MeSH descriptor: [Peritoneal Dialysis] explode all trees 18. peritoneal dialysis:ti.ab.kw (Word variations have been searched) 19. (CAPD or CCPD or APD): ti,ab,kw (Word variations have been searched) 20. {or #8-#19} 21. {and #7, #20}
MEDLINE	1. Fatigue/ 2. fatigue.tw. 3. lassitude.tw. 4. (tiredness or tired).tw. 5. (weary or weariness).tw. 6. exhaustion.tw 7. weakness.tw 8. or/1-7 9. Renal Replacement Therapy/ 10. Renal Dialysis/ 11. Hemodiafiltration/ 12. Hemodialysis, home/ 13. exp Hemofiltration/ 14. dialysis.tw. 15. (hemodialysis or haemodialysis).tw. 16. (hemofiltration or haemofiltration).tw. 17. (hemodiafiltration or haemodiafiltration).tw. 18. exp Peritoneal Dialysis/ 19. peritoneal dialysis.tw 20. (CAPD or CCPD or APD).tw.

	21. or/9-20
	22. and/8,21

EMBASE	1. fatigue/ or exhaustion/ or lassitude/
	2. fatigue.tw.
	3. lassitude.tw.
	4. (tiredness or tired).tw.
	5. (weary or weariness).tw.
	6. exhaustion.tw.
	7. weakness.tw.
	8. or/1-7
	9. exp renal replacement therapy/
	10. extended daily dialysis/
	11. hemodialysis/
	12. home dialysis/
	13. hemofiltration/
	14. hemodiafiltration/
	15. dialysis.tw.
	16. (hemodialysis or haemodialysis).tw.
	17. (hemofiltration or haemofiltration).tw.
	18. (hemodiafiltration or haemodiafiltration).tw.
	19. renal replacement therapy-dependent renal disease/
	20. Peritoneal Dialysis/
	21. Continuous Ambulatory Peritoneal Dialysis/
	22. peritoneal dialysis.tw.
	23. (CAPD or CCPD or APD).tw.
	24. peritoneal dialysis fluid/
	25. peritoneal dialysis catheter/
	26. or/9-25
	27. and/8,26

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random)
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention

(Continued)

	Unclear: Insufficient information about the sequence generation process to permit judgement
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes)
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear: Randomisation stated but no information on method used is available
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement

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Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear: Insufficient information to permit judgement

(Continued)

Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: AJ, AT, GS, JC, CR, VS, MR, MU

2. Study selection: AJ, VS

3. Extract data from studies: AJ, VS

4. Enter data into RevMan: AJ

5. Carry out the analysis: AJ, VS

6. Interpret the analysis: AJ, VS, GS, JC

7. Draft the final review: AJ

8. Disagreement resolution: AT, GS, JC

DECLARATIONS OF INTEREST

None known.