



in collaboration with:



Avatrombopag and lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing an elective procedure

Produced by

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Authors

Nigel Armstrong, Health Economist, KSR Ltd
Isaac Corro Ramos, Health Economics Researcher, Erasmus School of Health Policy & Management, EUR, the Netherlands
Nasuh Büyükkaramikli, Health Economics Researcher, EUR
Rob Riemsma, Reviews Manager, Kleijnen Systematic Reviews Ltd, UK
Marie Westwood, Systematic Reviewer, KSR Ltd
Stephanie Swift, Systematic Reviewer, KSR Ltd
Thea Drachen, Systematic Reviewer, KSR Ltd
Steve Ryder, Health Economist, KSR Ltd
Dhwani Shah, Health Economist, KSR Ltd
Titas Buksnys, Health Economist, KSR Ltd
Gill Worthy, Statistician, KSR Ltd
Steven Duffy, Information Specialist, KSR Ltd
Maiwenn Al, Health Economics Researcher, EUR
Jos Kleijnen, Director, KSR Ltd, Professor of Systematic Reviews in Health Care, Maastricht University

Correspondence to Nigel Armstrong, Kleijnen Systematic Reviews
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, UK
YO19 6FD

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Kleijnen Systematic Reviews Ltd
Unit 6, Escrick Business Park
Riccall Road
Escrick
York
YO19 6FD

Telephone: +44 (0)1904 727980
Fax: +44 (0)1904 720429
Email: jos@systematic-reviews.com
Website: www.systematic-reviews.com

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1. TITLE OF THE PROJECT

Avatrombopag and lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing an elective procedure.

2. NAME OF TAR TEAM AND 'LEAD'

TAR Team: Kleijnen Systematic Reviews Ltd.

Team lead: Nigel Armstrong, Health Economist

Nigel Armstrong, PhD; Kleijnen Systematic Reviews Ltd; Unit 6, Escrick Business Park; Riccall Road; Escrick; York YO19 6FD; United Kingdom.

Tel. +44 (0)1904 727993

Fax. +44 (0)1904 720429

Email. nigel@systematic-reviews.com

3. PLAIN ENGLISH SUMMARY

Thrombocytopenia is characterised as a reduction in the number of circulating platelets within the blood. Platelets come from megakaryocytes in the bone marrow. They play a critical role in haemostasis, a process which causes bleeding to stop. Thrombocytopenia can generally be classified on the basis of the platelet count in the blood. It is usually defined as a platelet count of less than 150×10^9 per litre of blood.

Thrombocytopenia is a common complication in people with chronic liver disease either as a direct result of the liver pathology or a consequence of interferon-based antiviral therapy. While mild to moderate thrombocytopenia rarely causes bleeding during procedures including liver biopsy or liver transplantation, severe thrombocytopenia increases the risk of excessive bleeding during and after surgery and can have a significant impact on the clinical management of chronic liver disease. It can delay or prevent the start of appropriate therapy leading to increased morbidity and mortality and a reduced quality of care.

The prevalence of thrombocytopenia in people with chronic liver disease varies from 15% to 70% depending on the stage of liver disease and differences in platelet count cut-off used to define thrombocytopenia. Between 2016 and 2017, Hospital Episode Statistics showed 27,927 admissions with liver disease in England.¹

There are currently no licensed treatment options in the UK for treating thrombocytopenia in people with chronic liver disease requiring surgery. Therapies include stimulation of megakaryocyte maturation and platelet production. Treatment for severe thrombocytopenia can include platelet transfusion, splenic artery embolisation and surgical splenectomy.

The purpose of this report is to systematically review the effectiveness and estimate the cost effectiveness of avatrombopag and lusutrombopag versus established clinical management without avatrombopag and lusutrombopag and compared with each other for people with thrombocytopenia associated with chronic liver disease needing an elective procedure.

4. DECISION PROBLEM

4.1 PURPOSE OF THE DECISION TO BE MADE

To systematically review the effectiveness and estimate the cost effectiveness of avatrombopag versus lusutrombopag versus established clinical management without avatrombopag and lusutrombopag (including, but not limited to platelet transfusion) for people with thrombocytopenia associated with chronic liver disease needing an elective procedure.

4.2 DEFINITION OF THE INTERVENTIONS

Avatrombopag (Doptelet, Dova Pharmaceuticals) is a small molecule thrombopoietin receptor agonist which targets the c-Mpl thrombopoietin cell surface receptor on megakaryocytes to stimulate platelet production. Avatrombopag is administered orally. It does not currently have a marketing authorisation in the UK. It is currently being studied in clinical trials compared with placebo in people with thrombocytopenia associated with chronic liver disease requiring an elective procedure.

Lusutrombopag (Mulpeta, Shionogi Inc) is a small molecule thrombopoietin receptor agonist which targets the c-Mpl thrombopoietin cell surface receptor on megakaryocytes to stimulate platelet production. Lusutrombopag is administered orally. It does not currently have a marketing authorisation in the UK. It is currently being studied in clinical trials compared with placebo in adults with thrombocytopenia with a platelet count of $<50 \times 10^9$ per blood litre associated with chronic liver disease requiring elective invasive surgery.

4.3 POPULATION/ SETTING

Adults with thrombocytopenia associated with chronic liver disease needing an elective procedure. Such procedures might be classified by the associated bleeding risk based on the published literature into 3 categories:²

- Low risk (paracentesis, thoracentesis, gastrointestinal endoscopy),
- Moderate risk (liver biopsy, bronchoscopy, ethanol ablation therapy, chemoembolization), and
- High risk (vascular catheterization, transjugular intrahepatic portosystemic shunt, dental procedures, renal biopsy, biliary interventions, nephrostomy tube placement, radiofrequency ablation, laparoscopic interventions).

Information on procedure type and bleeding risk will be used to assess comparability of studies. There might also be variation in the degree of thrombocytopenia, which will also need to be considered in assessing comparability.

4.4 RELEVANT COMPARATORS

The interventions listed above compared with each other where appropriate, and with:

- Established clinical management without avatrombopag and lusutrombopag (including, but not limited to platelet transfusion) i.e. standard care

4.4 KEY FACTORS TO BE ADDRESSED

The review aims to:

- evaluate the clinical effectiveness of each intervention
- evaluate the adverse effect profile of each intervention
- evaluate the incremental cost-effectiveness of each intervention compared to:
 - a. each other and
 - b. established clinical management without avatrombopag or lusotrombopag

5. METHODS FOR SYNTHESIS OF EVIDENCE OF CLINICAL EFFECTIVENESS

Throughout this review, the methods recommended by the Cochrane Collaboration Handbook³ and the Centre for Reviews and Dissemination (CRD), York⁴ will be applied in order to reduce the risk of bias and error.

5.1 INCLUSION CRITERIA

The following is a list of inclusion criteria for the systematic review:

- Population:
Adults with thrombocytopenia associated with chronic liver disease needing an elective procedure.
- Intervention:
 - Avatrombopag
 - Lusutrombopag
- Comparator:
 - Any comparator or none
- Outcomes:
 - Platelet count
 - Response rate
 - number of platelet transfusions
 - number of blood transfusions
 - return to operating theatre
 - need for rescue treatments
 - use of concurrent treatments
 - bleeding score
 - mortality
 - adverse effects of treatment
 - health-related quality of life.
- Study design:

- RCTs
- Observational studies (cohort or case series) of at least 20 participants

5.2 LITERATURE SEARCHES

Literature searches will be conducted to identify relevant information on the clinical effectiveness, safety and cost-effectiveness of avatrombopag and lusutrombopag. The searches will also identify studies on the clinical effectiveness, safety and cost-effectiveness of established clinical management of thrombocytopenia in people with chronic liver disease: platelet transfusion; stimulation of megakaryocyte maturation and platelet production; splenic artery embolisation; and surgical splenectomy. All searching will be undertaken to the highest standard to meet best practice requirements recommended by the Centre for Reviews and Dissemination, and Cochrane.^{3,4}

The search strategies will combine relevant search terms comprising indexed keywords (e.g. Medical Subject Headings, MeSH and Emtree) and free text terms appearing in the title and/or abstract of database records. Search terms will be identified through discussion with the review team, by scanning background literature and 'key articles' already known to the review team, and by browsing database thesauri. Search strategies will be developed specifically for each database and the keywords adapted according to the configuration of each database. Only studies conducted in humans will be sought. Searches will not be limited by language, publication status (unpublished or published) or date of publication. Methodological study design search filters will not be included in the search strategies to ensure the identification of efficacy, safety and cost-effectiveness studies.

The Embase search strategy is presented in Appendix 1.

Searches will be undertaken to identify systematic reviews, health technology assessments, clinical trials and observational studies of the efficacy, safety, and cost effectiveness of avatrombopag and lusutrombopag.

The following databases and resources will be searched from inception:

- MEDLINE (Ovid)
- MEDLINE In-Process Citations, Daily Update and Epub Ahead of Print (Ovid)
- PubMed (NLM)
- Embase (Ovid)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)
- Cochrane Database of Systematic Reviews (CDSR) (Wiley)
- KSR Evidence (<https://ksrevidence.com/>)
- Epistemonikos (<https://www.epistemonikos.org/>)
- Database of Abstracts of Reviews of Effects (DARE) (CRD): up to April 2015
- Health Technology Assessment (HTA) database (CRD): up to April 2016
- NHS Economic Evaluation Database (NHS EED) (CRD): up to April 2015
- PROSPERO (CRD)

- Science Citation Index (SCI) (Web of Science)
- CINAHL (EBSCO)
- LILACS (BIREME)
- Northern Light Life Sciences Conference Abstracts (Ovid)
- Transfusion Evidence Library (www.transfusionevidencelibrary.com)
- RePEc: Research Papers in Economics (repec.org/)

Supplementary searches will be conducted to identify completed and ongoing trials by searching the following clinical trials registers:

- ClinicalTrials.gov (<http://www.clinicaltrials.gov/>)
- WHO International Clinical Trials Registry Platform (ICTRP) (<http://www.who.int/ictrp/en/>)

Grey literature will be identified from searches of the following resources:

- US Food & Drug Administration (FDA) (<https://www.fda.gov/>)
- European Medicines Agency (EMA) (<http://www.ema.europa.eu/ema/>)
- OAlster (<http://oaister.worldcat.org/>)
- OpenGrey (www.opengrey.eu/)
- COPAC (<https://copac.jisc.ac.uk/>)

Relevant organisation websites will also be searched, such as: British Society for Haematology, European Hematology Association, International Society on Thrombosis & Haemostasis, and American Society of Hematology.

Reference checking

The bibliographies of identified research and review articles will be checked for relevant studies.

Handling of citations

Identified references will be downloaded into EndNote bibliographic management software for further assessment and handling. Individual records within the EndNote libraries will be tagged with searching information, such as searcher, date searched, database host, database searched, strategy name and iteration, theme or search question. This enables the information specialist to track the origin of each individual database record, and its progress through the screening and review process.

Quality assurance within the search process

For all searches undertaken by the Kleijnen Systematic Reviews Information team, the main Embase strategy will be independently peer reviewed by a second KSR Information Specialist. Strategy peer review will be informed by items based on the CADTH checklist.^{5, 6}

5.3 METHODS OF STUDY SELECTION, QUALITY ASSESSMENT AND DATA EXTRACTION

Study selection

Titles and abstracts identified through electronic database and other searches will be independently screened by two reviewers. During this initial phase of the screening process

any references which obviously do not meet the inclusion criteria listed previously will be excluded. Full paper copies will be obtained for all of the remaining references. These will then be independently examined in detail by two reviewers in order to determine whether they meet the criteria for inclusion in the review. All papers excluded at this second stage of the screening process will be documented in a table along with the reasons for exclusion. These reasons will be categorised as follows:

- Not relevant population (i.e. not neuropathic pain)
- Not relevant intervention
- Not relevant outcome data (i.e. does not assess at least one of the specified outcomes or does not report relevant data or information so as to allow the calculation of relevant data)
- Not relevant study (i.e. not a RCT, cohort or case series)
- Insufficient study size (< 20 participants)

With respect to both screening stages, any discrepancies between reviewers will be resolved through discussion or the intervention of a third reviewer.

A flow diagram of the numbers of studies included and excluded at each stage will be provided following guidance in the PRISMA statement (www.prisma-statement.org).

Studies will be identified by the name of the first author and year in which the trial was first published.

Quality assessment (assessment of risk of bias within included studies)

The quality of each individual study will be assessed using the following quality assessment tools:

- RCTs – Cochrane Collaboration Quality Assessment Tool for RCTs⁷
- Non-RCTs (observational studies) - Tool for assessing risk of bias in non-randomised studies of interventions⁸

Further details of the individual assessment tools are provided in Appendix 2.

The findings of the quality assessment will be used to ensure that the conclusions and findings of these reviews are based on the best available evidence and that any potential sources of bias in the data are identified. In addition, these will be used in the GRADE assessments of levels of evidence.

Two reviewers will assess each of the studies using the relevant checklist and any discrepancies will be resolved through discussion or the intervention of a third reviewer.

Data extraction

Data extraction sheets will be individually designed and piloted using Microsoft Excel. The extraction process will be performed by two reviewers with one checking the extraction of

the other. Any discrepancies will be resolved through discussion or through the intervention of a third reviewer. Studies will be identified by the main study name/identifier. Where this is not available the surname and year of the first author of the main report/publication will be used. To avoid the duplication of data where studies (or study populations) have multiple publications the most complete report will be used as the main reference, but additional details will be extracted from the other publications as necessary. Details of the general information and data to be extracted for each study, regardless of review topic are reported below:

- Endnote ID
- Study ID or name (if reported or otherwise surname of first author)
- Year of publication
- Other related publications
- Study group (if reported)
- Study country(ies)
- Recruitment dates (if relevant)
- Location/setting
- Study funding (public/pharma/not reported)
- Study aim
- Sample size
- Study design
- Study methods
- Patient characteristics
- Treatment characteristics
- Results (all outcomes reported in section 4.1)
- Study conclusions

5.4 ANALYSIS

Data will be summarised by population i.e. type of peripheral neuropathic pain with local origin, which will include painful diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, radicular pain, post-surgical chronic neuropathic pain, and neuropathic cancer pain (such as, chemotherapy-induced neuropathy, neuropathy secondary to tumour antigens, or caused by direct invasion or compression of neural structures).⁹

If a quantitative analysis is possible the following methods may be employed dependent on the data identified.

Quantitative analysis and meta-analysis methods (Direct 'head-to-head' methods)

Forest plots of effect sizes will be prepared for each of the efficacy and safety outcomes. Dichotomous outcomes (e.g. proportion of patients experiencing each type of AE outcome) will be reported as relative risks (RR) with 95% confidence intervals (CIs). If studies report time-to-event outcomes (e.g. time to OS, CR), these will be reported as hazard ratios (HR)

with 95% CI. If the HR is not reported, but can be calculated from other data which are reported, then the HR will be estimated using the methods of Tierney 2007.¹⁰

Pooled effect sizes and 95% CIs using random effects models will only be presented where there are two or more trials which are considered to be clinically and statistically homogeneous.

The judgment of clinical homogeneity will be based on the baseline characteristics of the trial populations, (i.e. age, gender, severity of pain/pain intensity, duration of pain, number and duration of previous recurrences, previous treatments). Statistical homogeneity will be assessed using the I^2 statistic.¹¹ This measures the degree of inconsistency between the study results which is due to genuine heterogeneity rather than chance. The value of I^2 lies between 0% and 100%. For the purposes of this review, a simplified categorisation of heterogeneity will be used: low (0 to 25%), moderate (26 to 75%), and high (>75%). Studies will only be considered to be sufficiently similar for the purposes of pooling if $I^2 < 75\%$.¹¹

Publication bias will be assessed where there are sufficient numbers of trials (i.e. six trials using funnel plots of the point estimate plotted against the standard error (SE)).¹²

Indirect comparisons

Where the intervention and comparator are not compared in the same RCT (i.e. 'head-to-head' trials A versus B), but instead are separately to a common comparator e.g. placebo, an indirect comparison between them will be performed. Point estimates (with 95% CIs) will be estimated using 'indirect' methods e.g. from A versus C and B versus C, where C is a common control group (e.g. placebo). All methods will be applied with consideration for the basic assumptions of homogeneity, similarity, and consistency as reported in Song 2009.¹³ All indirect comparisons will be consistent with NICE recommendations for the conduct of direct and indirect meta-analysis, which include indirect comparisons using the method of Bucher 1997.¹⁴ The following basic assumptions of homogeneity, similarity, and consistency must in principle be fulfilled.

1. Homogeneity – in a standard meta-analysis of randomised trials it is assumed that different trials are sufficiently (not necessarily completely) homogeneous and that they estimate the same single treatment effect (fixed effect model) or different treatment effects distributed around a typical value (random effects model). In adjusted indirect comparison, the homogeneity assumption for conventional meta-analysis should be fulfilled when multiple trials are involved.
2. Similarity – trials should be similar for moderators of relative treatment effect. Trial similarity should be considered from two perspectives: clinical similarity and methodological similarity. Clinical similarity refers to similarity in patients' characteristics, interventions, settings, length of follow-up, and outcomes measured. Methodological similarity refers to aspects of trials associated with the risk of bias.
3. Consistency – a further assumption of consistency is required to combine results of direct and adjusted indirect comparison using fixed effect or random effects model.

Even when the indirect comparison is valid, the indirect evidence may not be consistent with evidence from head-to-head trials because of clinically meaningful heterogeneity

A more practical issue for indirect comparisons concerns the limitations in availability of the same outcomes in the studies of interventions that are candidates for an indirect comparison. Only studies that provide the same outcome measures can be compared with each other. A narrative discussion concerning the feasibility and appropriateness of indirect comparisons will be provided using the criteria of homogeneity, similarity and consistency.

Indirect meta-analysis will be performed using Microsoft Excel using the Bucher method.¹⁵ RR or HR with 95% CIs will be calculated using for each outcome and available treatment comparison.

Heterogeneity will be investigated using the I^2 statistic for heterogeneity for each of the pairwise comparisons.¹¹ If there are concerns about heterogeneity, or any trials appear to have results which differ from the others, then one or more trials will be removed in a sensitivity analysis.

The appropriateness of a NMA will be considered in light of these issues when discussing the review findings and conclusions. If there is sufficient trial evidence then a NMA will be performed using WinBUGs version 1.4.3 (<http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml>) and applying a Bayesian approach consistent with international recommendations¹⁶. NMA combines direct evidence and indirect evidence for particular pairwise comparisons, thereby synthesising a greater share of the available evidence than traditional meta-analysis. RRs or HRs with 95% credible intervals (CrI) will be calculated for each outcome and available treatment comparison using random effects models. Fixed effect models will also be run, but the results from random effects models will be presented as the primary result apart from for any networks which are small and where the lack of data affects the convergence of the WinBUGs model. If there are any doubts about the suitability of the model then results from the more simple fixed effect model will be presented. Inconsistency (whether the direct and indirect estimates are in agreement) will be checked in those networks which contain both direct and indirect estimates.¹³

- NMA analysis using Bayesian methods
- Summary of results from NMA (to be incorporated into the results table and the Power point presentation, outlining the methods used, included studies, data, final results and interpretation/conclusions. This will include appropriate figures and tables as required.

6. METHODS FOR SYNTHESIS OF EVIDENCE OF COST-EFFECTIVENESS

6.1 IDENTIFYING AND SYSTEMATICALLY REVIEWING PUBLISHED COST-EFFECTIVENESS STUDIES

The literature searches described in section 5.2 will be used to identify cost-effectiveness studies. Identified cost-effectiveness studies will be critically assessed using a published critical appraisal checklist for economic evaluations (e.g. Drummond et al.¹⁷)

Additional searches will be conducted to identify health-related quality of life (HRQoL) and resource use data related to thrombocytopenia. Methodological search filters designed to identify HRQoL and resource use data will be combined with search terms for thrombocytopenia. The search strategy will be developed using the same methods described in section 5.2. Searches will not be limited by language, publication status (unpublished or published) or date of publication.

The Embase search strategies are presented in Appendix 1.

The following databases and resources will be searched from inception:

- MEDLINE (Ovid)
- MEDLINE In-Process Citations, Daily Update and Epub Ahead of Print (Ovid)
- PubMed (NLM)
- Embase (Ovid)
- NHS Economic Evaluation Database (NHS EED) (CRD): up to April 2015
- Health Technology Assessment (HTA) database (CRD): up to April 2016
- Science Citation Index (SCI) (Web of Science)
- CINAHL (EBSCO)
- LILACS (BIREME)
- Northern Light Life Sciences Conference Abstracts (Ovid)
- CEA Registry (www.cearegistry.org)
- ScHARRHUD (<https://www.scharrhud.org/>)
- RePEc: Research Papers in Economics (repec.org/)

Grey literature will be identified from searches of the following resources:

- OAlster (<http://oaister.worldcat.org/>)
- OpenGrey (www.opengrey.eu/)
- COPAC (<https://copac.jisc.ac.uk/>)
- ISPOR (<https://www.ispor.org/>)
- HTAi (<https://htai.org/>)

Transferability of these findings from the literature review to UK will be analysed.¹⁸

6.2 EVALUATION OF COSTS AND COST-EFFECTIVENESS, WHICH MAY INCLUDE DEVELOPMENT OF A DE NOVO ECONOMIC MODEL

The Assessment Group (AG) will conduct a de novo economic evaluation for the decision problem, from the UK NHS perspective.

Until the consultee submission period, the AG will conceptualise the economic model needed for the decision problem. For the conceptualisation of the model, information from the findings of the literature review, and clinical expert opinions will be used.

With the advice of the clinical experts in the AG's network and together with NICE, the availability of additional real life data sources on thrombocytopenia will be explored.

After the review of the consultee submissions, the AG will either:

- Adapt one of the submitted company economic models, or
- Build a de novo economic model

The decision will be made based on 1) the level of resemblance of the submitted models to the AG conceptual model, 2) the quality of the submitted models, 3) the appropriateness of the submitted models for the decision problem, and 4) data availability.

Death, perioperative blood platelet transfusion and other risks of complications involved in the medical operation are expected to be the main events in the model. If data are available, these event risks can be modelled as a function of patient baseline characteristics, time and treatment dependent characteristics.

The following direct cost items related with thrombocytopenia, as identified by Brown Jr 2007 might be considered:¹⁹

- Blood monitoring
- Hospital stay peri-procedure
- Therapy required to raise platelet count
- Complications of therapy (e.g., bleeding, transfusion reactions)
- Inadequate therapy for low platelets

Other potential cost items will be searched from the literature as well. If possible, the economic model will explicitly include the time until hospital discharge. However, if the intervention is considered to have an impact after hospital discharge in terms of patient costs and/or utilities, these impacts will be incorporated as well.

The outcomes of the economic evaluation will be total costs per arm, total QALYs per arm, clinically relevant endpoints that were included in the model per arm, incremental costs/QALYs and the incremental cost-effectiveness ratio (ICER). The model aims to be flexible enough to provide the cost-effectiveness outcomes for all relevant operation-specific (high bleeding vs. low bleeding) and patient-specific (with/without HCV or with/without cancer) subpopulations.

For patient/public involvement, the assessment group will attempt to be in contact with relevant patient groups/clinical groups.

7. HANDLING THE COMPANY SUBMISSIONS

All data submitted by the company/sponsor will be considered if received by the AG no later than a date agreed with NICE once the timelines have been finalised. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with NICE's reference case and in line with the decision problem, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model. If the AG judge that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing a de-novo model.

Any 'commercial in confidence' data taken from a company submission, and specified as confidential in the check list, will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company name e.g. in brackets). Any 'academic in confidence' data will be underlined and highlighted in yellow.

8. COMPETING INTERESTS OF AUTHORS

None.

9. REFERENCES

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APPENDIX 1 EMBASE SEARCH STRATEGIES

Clinical effectiveness, cost-effectiveness and safety search strategy

Embase (Ovid): 1974-2018/week 49

Searched: 4.12.18

- 1 avatrombopag/ (59)
- 2 (avatrombopag or doptelet or AKR 501 or AKR501 or AS 1670542 or AS1670542 or E 5501 or E5501 or oralE 5501 or oralE5501 or YM 477 or YM477 or 570406-98-3).af. (130)
- 3 lusutrombopag/ (30)
- 4 (lusutrombopag or mulpeta or S 888711 or S888711 or 1110766-97-6).af. (30)
- 5 or/1-4 (158)
- 6 exp thrombocytopenia/ (156004)
- 7 (thrombocytopeni\$ or thrombocytopeni\$ or thrombopeni\$ or thrombopeni\$ or macrothrombocytopeni\$ or macrothrombocytopeni\$).ti,ab,ot. (87409)
- 8 ((11q or 11q23) adj3 (disorder\$ or syndrome\$ or delet\$ or jacobsen)).ti,ab,ot. (1012)
- 9 (jacobsen adj3 syndrome\$).ti,ab,ot. (187)
- 10 paris trousseau.ti,ab,ot. (49)
- 11 kasabach merritt.ti,ab,ot. (795)
- 12 (hemangioma or haemangioma).ti,ab,ot. (18168)
- 13 (thrombotic adj2 (microangiopath\$ or micro angiopath\$)).ti,ab,ot. (5123)
- 14 (hemolytic uremic or haemolytic uremic).ti,ab,ot. (7418)
- 15 gasser\$.ti,ab,ot. (1869)
- 16 (HELLP adj2 syndrome\$).ti,ab,ot. (3273)
- 17 ((hemolysis or haemolysis) adj2 liver adj2 platelet\$).ti,ab,ot. (11)
- 18 May Hegglin.ti,ab,ot. (261)
- 19 ((haemolytic or hemolytic) adj2 (anaemi\$ or anemi\$) adj2 (microangiopathic or micro angiopathic)).ti,ab,ot. (2031)
- 20 (microangiopath\$ adj2 thrombotic).ti,ab,ot. (5072)
- 21 moschcowitz.ti,ab,ot. (93)
- 22 werlhof.ti,ab,ot. (54)
- 23 (wiskott or aldrich).ti,ab,ot. (4870)
- 24 (immunodeficiency 2 or immunodeficiency2 or lmd2).ti,ab,ot. (71)
- 25 ((platelet\$ or thrombocyte\$) adj3 (defici\$ or reduc\$ or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc\$ or destroy\$)).ti,ab,ot. (33222)
- 26 or/6-25 (222025)
- 27 chronic liver disease/ or liver disease/ or liver cirrhosis/ or liver fibrosis/ or chronic hepatitis/ (243293)
- 28 ((liver or hepat\$ or intrahepat\$) adj2 (disease\$ or disorder\$ or lesion\$)).ti,ab,ot. (168852)
- 29 (cirrhosis or cirrhoses or cirrhotic).ti,ab,ot. (133495)
- 30 (chronic adj3 nonsuppurative destructive cholangitis).ti,ab,ot. (65)
- 31 ((fibrosis or fibroses or scar\$) adj3 (liver\$ or hepat\$)).ti,ab,ot. (37794)
- 32 ((hepatitis or hepatopath\$) adj3 (chronic or acute or persistent or long stand\$ or long term or recurr\$)).ti,ab,ot. (93155)
- 33 ((liver or hepat\$ or intrahepat\$) adj3 inflam\$).ti,ab,ot. (20529)

- 34 (haemochromatosis or hemochromatosis or bronze\$ diabet\$ or recklinghausen applebaum or siderochromatosis).ti,ab,ot. (9661)
- 35 primary biliary cholangitis.ti,ab,ot. (1004)
- 36 liver cell carcinoma/ (135495)
- 37 ((liver or hepat\$ or intrahepat\$) adj3 carcinoma\$).ti,ab,ot. (121058)
- 38 (hepatocarcinoma or hepatoma\$).ti,ab,ot. (35014)
- 39 or/27-38 (528594)
- 40 26 and 39 (13701)
- 41 thrombopoietin receptor/ (1764)
- 42 ((thrombopoietin\$ or c-Mpl) adj3 (agonist\$ or agent\$ or mimetic\$)).ti,ab,ot. (1216)
- 43 eltrombopag/ (1764)
- 44 (eltrombopag or promacta or revolade or SB 497115 or SB497115 or 496775-61-2).ti,ab,ot,hw,rn,tn. (1815)
- 45 romiplostim/ (1541)
- 46 (romiplostim or nplate or remiplostim or amg 531 or amg531 or 267639-76-9).ti,ab,ot,hw,rn,tn. (1686)
- 47 promegapoeitin.ti,ab,ot,hw,rn,tn,dj. (25)
- 48 thrombocyte transfusion/ (16944)
- 49 ((platelet\$ or thrombocyt\$) adj3 (transfus\$ or infus\$ or administ\$)).ti,ab,ot. (13804)
- 50 splenectomy/ (32045)
- 51 (splenectom\$ or (spleen adj2 (resect\$ or remov\$ or surg\$))).ti,ab,ot. (27101)
- 52 spleen artery/ and exp artificial embolism/ (445)
- 53 ((spleen or splenic or eria lienalis or lienal) adj3 (embolisation or embolization or embolism or embolus or thrombus or embolotherap\$ or therap\$ occlus\$)).ti,ab,ot. (1525)
- 54 megakaryocyte/ and (stimulation/ or cell maturation/) (1072)
- 55 ((megakaryocyte\$ or karyocyte\$) adj3 (stimul\$ or maturat\$ or produc\$)).ti,ab,ot. (1547)
- 56 thrombocytopoiesis/ (4111)
- 57 (thrombopoiesis\$ or thrombocytopoies\$ or megakaryocytopoies\$).ti,ab,ot. (2707)
- 58 ((platelet\$ or thrombocyt\$) adj3 (produc\$ or formation or stimulat\$)).ti,ab,ot. (20907)
- 59 transjugular intrahepatic portosystemic shunt/ (3375)
- 60 (transjugular intrahepatic portosystemic shunt\$ or transjugular intrahepatic porto systemic shunt\$ or transjugular intrahepatic portacaval shunt\$ or transjugular intrahepatic portal systemic shunt\$ or transjugular intrahepatic portasystemic shunt\$ or transjugular intrahepatic shunt\$ or transjugular intrahepatic stent\$ or TIPS).ti,ab,ot. (35508)
- 61 or/41-60 (123028)
- 62 40 and 61 (1542)
- 63 5 or 62 (1634)
- 64 animal/ or animal experiment/ (3666544)
- 65 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot. (4400418)
- 66 64 or 65 (5688920)
- 67 exp human/ or human experiment/ (19102066)
- 68 66 not (66 and 67) (4404390)
- 69 63 not 68 (1597)**

Utilities/HRQoL search strategy

Embase (Ovid): 1974-2018/week 49

Searched: 4.12.18

- 1 quality adjusted life year/ or quality of life index/ (24865)
- 2 Short Form 12/ or Short Form 20/ or Short Form 36/ or Short Form 8/ (29294)
- 3 "International Classification of Functioning, Disability and Health"/ or "ferrans and powers quality of life index"/ or "gastrointestinal quality of life index"/ (2962)
- 4 (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot. (37039)
- 5 (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot. (2046)
- 6 (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,ot. (8103)
- 7 (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab,ot. (1329)
- 8 (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,ot. (411)
- 9 (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab,ot. (808)
- 10 "health related quality of life".ti,ab,ot. (53274)
- 11 (Quality adjusted life or Quality-adjusted-life).ti,ab,ot. (16419)
- 12 "assessment of quality of life".ti,ab,ot. (2605)
- 13 (euroqol or euro qol or eq5d or eq 5d).ti,ab,ot. (16507)
- 14 (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,ot. (28533)
- 15 (hye or hyes).ti,ab,ot. (119)
- 16 health\$ year\$ equivalent\$.ti,ab,ot. (40)
- 17 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab,ot. (2777)
- 18 (quality time or qwb or "quality of well being" or "quality of wellbeing" or "index of wellbeing" or index of well being).ti,ab,ot,hw. (1077)
- 19 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab,ot. (3979)
- 20 (QALY\$ or DALY\$ or HALY\$ or YHL or HYES or YPLL or YHLL or qald\$ or qale\$ or qtime\$ or AQoL\$).ti,ab,ot. (20978)
- 21 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble\$ or "willingness to pay").ti,ab,ot. (9860)
- 22 15d.ti,ab,ot. (2328)
- 23 (HSUV\$ or health state\$ value\$ or health state\$ preference\$ or HSPV\$).ti,ab,ot. (529)
- 24 (utilit\$ adj3 ("quality of life" or valu\$ or scor\$ or measur\$ or health or life or estimat\$ or elicit\$ or disease\$)).ti,ab,ot. (16936)
- 25 (utilities or disutili\$).ti,ab,ot. (10396)
- 26 or/1-25 (163457)
- 27 animal/ or animal experiment/ (3666544)

28 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (6319146)

29 or/27-28 (6319146)

30 exp human/ or human experiment/ (19102066)

31 29 not (29 and 30) (4879418)

32 26 not 31 (160868)

33 letter.pt. (1048748)

34 editorial.pt. (588819)

35 note.pt. (734109)

36 or/33-35 (2371676)

37 32 not 36 (156386)

38 avatrombopag/ (59)

39 (avatrombopag or doptelet or AKR 501 or AKR501 or AS 1670542 or AS1670542 or E 5501 or E5501 or oralE 5501 or oralE5501 or YM 477 or YM477 or 570406-98-3).af. (130)

40 lusutrombopag/ (30)

41 (lusutrombopag or mulpeta or S 888711 or S888711 or 1110766-97-6).af. (30)

42 or/38-41 (158)

43 exp thrombocytopenia/ (156004)

44 (thrombocytopeni\$ or thrombocytopaeni\$ or thrombopeni\$ or thrombopaeni\$ or macrothrombocytopeni\$ or macrothrombocytopaeni\$).ti,ab,ot. (87409)

45 ((11q or 11q23) adj3 (disorder\$ or syndrome\$ or delet\$ or jacobsen)).ti,ab,ot. (1012)

46 (jacobsen adj3 syndrome\$).ti,ab,ot. (187)

47 paris trousseau.ti,ab,ot. (49)

48 kasabach merritt.ti,ab,ot. (795)

49 (hemangioma or haemangioma).ti,ab,ot. (18168)

50 (thrombotic adj2 (microangiopath\$ or micro angiopath\$)).ti,ab,ot. (5123)

51 (hemolytic uremic or haemolytic uremic).ti,ab,ot. (7418)

52 gasser\$.ti,ab,ot. (1869)

53 (HELLP adj2 syndrome\$).ti,ab,ot. (3273)

54 ((hemolysis or haemolysis) adj2 liver adj2 platelet\$).ti,ab,ot. (11)

55 May Hegglin.ti,ab,ot. (261)

56 ((haemolytic or hemolytic) adj2 (anaemi\$ or anemi\$) adj2 (microangiopathic or micro angiopathic)).ti,ab,ot. (2031)

57 (microangiopath\$ adj2 thrombotic).ti,ab,ot. (5072)

58 moschowitz.ti,ab,ot. (93)

59 werlhof.ti,ab,ot. (54)

60 (wiskott or aldrich).ti,ab,ot. (4870)

61 (immunodeficiency 2 or immunodeficiency2 or lmd2).ti,ab,ot. (71)

62 ((platelet\$ or thrombocyte\$) adj3 (defici\$ or reduc\$ or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc\$ or destroy\$)).ti,ab,ot. (33222)

63 or/43-62 (222025)

64 37 and 63 (846)

HRQoL free-text terms based on: Figure 4: Common free-text terms for electronic database searching for HSUVs in Papaioannou D, Brazier JE, Paisley S. NICE DSU Technical Support

Document 9: the identification, review and synthesis of health state utility values from the literature (Internet), 2011 (accessed: 18.8.11) Available from: <http://www.nicedsu.org.uk>

Resource use/Costs search strategy

Embase (Ovid): 1974-2018/week 49

Searched: 4.12.18

- 1 exp employment/ (82093)
- 2 exp work/ (320102)
- 3 "cost of illness"/ (17921)
- 4 "length of stay"/ (157487)
- 5 ((employment or employed or employee\$ or unemployment or unemployed) adj3 (economic\$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab,ot. (2532)
- 6 (productivity adj3 (economic\$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab,ot. (3747)
- 7 ((long standing or longstanding or long term or longterm or permanent or employee\$) adj2 (absence\$ or absent\$ or ill\$ or sick\$ or disab\$)).ti,ab,ot. (13158)
- 8 llsi.ti,ab,ot. (16)
- 9 (cost\$ adj2 (illness or disease\$ or sickness\$)).ti,ab,ot. (6590)
- 10 (burden\$ adj2 (disease\$ or illness or sickness\$)).ti,ab,ot. (32689)
- 11 ((social or societ\$ or work\$ or employe\$ or business\$ or communit\$ or famil\$ or carer\$ or caregiver\$) adj3 (burden\$ or consequenc\$ or impact\$ or problem\$ or productivity or sickness or impairment\$)).ti,ab,ot. (110610)
- 12 ((allowance or status or long-term or pension\$ or benefit\$) adj2 disab\$).ti,ab,ot. (17715)
- 13 ((unable or inability or incapacit\$ or incapab\$) adj3 work).ti,ab,ot. (2429)
- 14 budget\$ impact\$.ti,ab,ot. (3350)
- 15 budget\$ implicat\$.ti,ab,ot. (85)
- 16 resource\$ use\$.ti,ab,ot. (13438)
- 17 resource\$ utili\$.ti,ab,ot. (16036)
- 18 resource\$ usage.ti,ab,ot. (494)
- 19 (length adj2 stay\$).ti,ab,ot. (88075)
- 20 (hospital\$ adj2 stay\$).ti,ab,ot. (128398)
- 21 (duration adj2 stay\$).ti,ab,ot. (4897)
- 22 extended stay\$.ti,ab,ot. (266)
- 23 prolonged stay\$.ti,ab,ot. (1297)
- 24 ((hospitali?ation or hospitali?ed) adj3 (economic\$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab,ot. (9806)
- 25 economic consequenc\$.ti,ab,ot. (4203)
- 26 or/1-25 (823701)
- 27 exp thrombocytopenia/ (156004)
- 28 (thrombocytopeni\$ or thrombocytopaeni\$ or thrombopeni\$ or thrombopaeni\$ or macrothrombocytopeni\$ or macrothrombocytopaeni\$).ti,ab,ot. (87409)
- 29 ((11q or 11q23) adj3 (disorder\$ or syndrome\$ or delet\$ or jacobsen)).ti,ab,ot. (1012)
- 30 (jacobsen adj3 syndrome\$).ti,ab,ot. (187)
- 31 paris trousseau.ti,ab,ot. (49)

- 32 kasabach merritt.ti,ab,ot. (795)
- 33 (hemangioma or haemangioma).ti,ab,ot. (18168)
- 34 (thrombotic adj2 (microangiopath\$ or micro angiopath\$)).ti,ab,ot. (5123)
- 35 (hemolytic uremic or haemolytic uremic).ti,ab,ot. (7418)
- 36 gasser\$.ti,ab,ot. (1869)
- 37 (HELLP adj2 syndrome\$).ti,ab,ot. (3273)
- 38 ((hemolysis or haemolysis) adj2 liver adj2 platelet\$).ti,ab,ot. (11)
- 39 May Hegglin.ti,ab,ot. (261)
- 40 ((haemolytic or hemolytic) adj2 (anaemi\$ or anemi\$) adj2 (microangiopathic or micro angiopathic)).ti,ab,ot. (2031)
- 41 (microangiopath\$ adj2 thrombotic).ti,ab,ot. (5072)
- 42 moschcowitz.ti,ab,ot. (93)
- 43 werlhof.ti,ab,ot. (54)
- 44 (wiskott or aldrich).ti,ab,ot. (4870)
- 45 (immunodeficiency 2 or immunodeficiency2 or lmd2).ti,ab,ot. (71)
- 46 ((platelet\$ or thrombocyte\$) adj3 (defici\$ or reduc\$ or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc\$ or destroy\$)).ti,ab,ot. (33222)
- 47 or/27-46 (222025)
- 48 animal/ or animal experiment/ (3666544)
- 49 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot. (4400418)
- 50 48 or 49 (5688920)
- 51 exp human/ or human experiment/ (19102066)
- 52 50 not (50 and 51) (4404390)
- 53 26 and 47 (3891)
- 54 53 not 52 (3854)**

APPENDIX 2 QUALITY AND RISK OF BIAS ASSESSMENT TOOLS

COCHRANE COLLABORATION 2011 CHECKLIST FOR RCTS

The following criteria from the Cochrane Collaboration 2011 checklist will be used to assess the quality of randomised controlled trials (RCTs). Each study will be assessed as “yes”(i.e. low risk of bias), “no” (i.e. high risk of bias), or “unclear” (i.e. unclear risk of bias):

Domain	Judgement	Criteria	Supporting text
Selection bias			
Random sequence generation	Low risk of bias	<p>The investigators describe a random component in the sequence generation process such as:</p> <ul style="list-style-type: none"> • Referring to a random number table • Using a computer random number generator • Coin tossing • Shuffling cards or envelopes • Throwing dice • Drawing of lots • Minimisation* <p>*Minimisation may be implemented without a random element, and this is considered to be equivalent to being random</p>	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups
	High risk of bias	<p>The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example:</p> <ul style="list-style-type: none"> • Sequence generated by odd or even date of birth • Sequence generated by some rule based on date (or day) of admission • Sequence generated by some rule based on hospital or clinic record number <p>Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorisation of participants, for example:</p> <ul style="list-style-type: none"> • Allocation by judgement of the clinician • Allocation by preference of the participant • Allocation based on the results of a laboratory test or a series of tests • Allocation by availability of the intervention 	

Domain	Judgement	Criteria	Supporting text
	Unclear risk of bias	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'	
Allocation concealment	Low risk of bias	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: <ul style="list-style-type: none"> • Central allocation (including telephone, web-based and pharmacy-controlled randomisation) • Sequentially numbered drug containers of identical appearance • Sequentially numbered, opaque, sealed envelopes 	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment
	High risk of bias	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: <ul style="list-style-type: none"> • 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 risk of bias	Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.	
Performance bias			
Blinding of participants and personnel <i>Assessments should be made for each main outcome</i>	Low risk of bias	Any one of the following: <ul style="list-style-type: none"> • 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 	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective
	High risk of bias	Any one of the following: <ul style="list-style-type: none"> • No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding 	

Domain	Judgement	Criteria	Supporting text
<i>(or class of outcomes).</i>		<ul style="list-style-type: none"> 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 risk of bias	Any one of the following: <ul style="list-style-type: none"> Insufficient information to permit judgement of 'Low risk' or 'High risk' The study did not address this outcome 	
Detection bias			
Blinding of outcome assessment <i>Assessments should be made for each main outcome (or class of outcomes).</i>	Low risk of bias	Any one of the following: <ul style="list-style-type: none"> 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 	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective
	High risk of bias	Any one of the following: <ul style="list-style-type: none"> 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 are likely to be influenced by lack of blinding 	
	Unclear risk of bias	Any one of the following: <ul style="list-style-type: none"> Insufficient information to permit judgement of 'Low risk' or 'High risk' The study did not address this outcome 	
Attrition bias			
Incomplete outcome data <i>Assessments should be made for each main outcome</i>	Low risk of bias	Any one of the following: <ul style="list-style-type: none"> 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 	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized

Domain	Judgement	Criteria	Supporting text
<i>(or class of outcomes).</i>		<ul style="list-style-type: none"> 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 	participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors
	High risk of bias	Any one of the following: <ul style="list-style-type: none"> 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 standardised 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 risk of bias	Any one of the following: <ul style="list-style-type: none"> Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided) The study did not address this outcome 	
Reporting bias			
Selective reporting.	Low risk of bias	Any of the following: <ul style="list-style-type: none"> 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) 	State how the possibility of selective outcome reporting was examined by the review authors, and what was found
	High risk of bias	Any one of the following: <ul style="list-style-type: none"> 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. subscales) that were not pre-specified 	

Domain	Judgement	Criteria	Supporting text
		<ul style="list-style-type: none"> 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 risk of bias	Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category	
Other bias			
Other sources of bias.	Low risk of bias	The study appears to be free of other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry
	High risk of bias	There is at least one important risk of bias. For example, the study: <ul style="list-style-type: none"> Had a potential source of bias related to the specific study design used or Has been claimed to have been fraudulent or Had some other problem 	
	Unclear risk of bias	There may be a risk of bias, but there is either: <ul style="list-style-type: none"> Insufficient information to assess whether an important risk of bias exists or Insufficient rationale or evidence that an identified problem will introduce bias 	

ROBINS-I CHECKLIST FOR NON-RCTS

The following table will be completed for each non-RCT included in the systematic review of clinical effectiveness, HRQoL and safety. Based on the detail reported in column 2 (relevant to the signalling question in column 1), each criterion will be awarded a response with the overall risk of bias assessed for each domain and across the study as a whole.

NI no information; NA not applicable; PY probably yes; Y yes; PN probably no; N No

Signalling questions	Description	Response options
BIAS DUE TO CONFOUNDING		
1.1 Is there potential for confounding of the effect of intervention in this study? If N/PN to 1.1: the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered		Y / PY / <u>PN</u> / N
If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:		
1.2. Was the analysis based on splitting participants' follow up time according to intervention received? If N/PN, answer questions relating to baseline confounding (1.4 to 1.6) If Y/PY, go to question 1.3.		NA / Y / PY / PN / N / NI
1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? If N/PN, answer questions relating to baseline confounding (1.4 to 1.6) If Y/PY, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)		NA / Y / PY / PN / N / NI
Questions relating to baseline confounding only:		

1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?		NA / Y / PY / PN / N / NI
1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?		NA / Y / PY / PN / N / NI
1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?		NA / Y / PY / PN / N / NI
Questions relating to baseline and time-varying confounding:		
1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?		NA / Y / PY / PN / N / NI
1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?		NA / Y / PY / PN / N / NI
RISK OF BIAS JUDGEMENT	LOW / MODERATE / SERIOUS / CRITICAL / NI	
BIAS IN SELECTION OF PARTICIPANTS INTO THE STUDY		
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?		Y / PY / PN / N / NI
If N/PN to 2.1: go to 2.4		
2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?		NA / Y / PY / PN / N / NI
2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?		NA / Y / PY / PN / N / NI
2.4. Do start of follow-up and start of intervention coincide for most participants?		Y / PY / PN / N / NI
2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?		NA / Y / PY / PN / N / NI

RISK OF BIAS JUDGEMENT	LOW / MODERATE / SERIOUS / CRITICAL / NI	
BIAS IN CLASSIFICATION OF INTERVENTIONS		
3.1 Were intervention groups clearly defined?		Y / PY / PN / N / NI
3.2 Was the information used to define intervention groups recorded at the start of the intervention?		Y / PY / PN / N / NI
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?		Y / PY / PN / N / NI
RISK OF BIAS JUDGEMENT	LOW / MODERATE / SERIOUS / CRITICAL / NI	
BIAS DUE TO DEVIATIONS FROM INTENDED INTERVENTIONS		
If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2		
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?		Y / PY / PN / N / NI
4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?		NA / Y / PY / PN / N / NI
If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6		
4.3. Were important co-interventions balanced across intervention groups?		Y / PY / PN / N / NI
4.4. Was the intervention implemented successfully for most participants?		Y / PY / PN / N / NI
4.5. Did study participants adhere to the assigned intervention regimen?		Y / PY / PN / N / NI
4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?		NA / Y / PY / PN / N / NI
RISK OF BIAS JUDGEMENT	LOW / MODERATE / SERIOUS / CRITICAL / NI	

BIAS DUE TO MISSING DATA		
5.1 Were outcome data available for all, or nearly all, participants?		Y / PY / PN / N / NI
5.2 Were participants excluded due to missing data on intervention status?		
5.3 Were participants excluded due to missing data on other variables needed for the analysis?		Y / PY / PN / N / NI
5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?		
5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?		Y / PY / PN / N / NI
RISK OF BIAS JUDGEMENT	LOW / MODERATE / SERIOUS / CRITICAL / NI	
BIAS IN MEASUREMENT OF OUTCOMES		
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?		Y / PY / PN / N / NI
6.2 Were outcome assessors aware of the intervention received by study participants?		Y / PY / PN / N / NI
6.3 Were the methods of outcome assessment comparable across intervention groups?		Y / PY / PN / N / NI
6.4 Were any systematic errors in measurement of the outcome related to intervention received?		Y / PY / PN / N / NI
RISK OF BIAS JUDGEMENT	LOW / MODERATE / SERIOUS / CRITICAL / NI	
BIAS IN SELECTION OF THE REPORTED RESULT		
Is the reported effect estimate likely to be selected, on the basis of the results, from...		
7.1. ... multiple outcome <i>measurements</i> within the outcome domain?		Y / PY / PN / N / NI

7.2 ... multiple <i>analyses</i> of the intervention-outcome relationship?		Y / PY / PN / N / NI
7.3 ... different <i>subgroups</i> ?		Y / PY / PN / N / NI
RISK OF BIAS JUDGEMENT	LOW / MODERATE / SERIOUS / CRITICAL / NI	
OVERALL RISK OF BIAS JUDGEMENT	LOW / MODERATE / SERIOUS / CRITICAL / NI	

APPENDIX 3 DATA EXTRACTION FIELDS

- Endnote ID
- Study ID or name
- Year of publication
- Other related publications
- Study group (if reported)
- Study country(ies)
- Recruitment dates (if relevant)
- Location/setting
- Study funding (public/pharma/not reported)
- Study aim
- Sample size
- Study design
- Study methods
- Patient characteristics
- Treatment characteristics
- Study conclusions
- Results:
 - Outcome measure name
 - Timing of measure (in weeks)
 - Sample size per treatment arm
 - Statistic per treatment arm
 - Continuous or ranking data: Mean, median, 95% confidence interval, lower and upper quartile, range
 - Dichotomous data: number with event (n), number at risk (N)