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Disease-modifying treatments for primary autoimmune haemolytic anaemia (Protocol)

Liu APY, Cheuk DKL

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# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Header</td>
<td>1</td>
</tr>
<tr>
<td>Abstract</td>
<td>1</td>
</tr>
<tr>
<td>Background</td>
<td>1</td>
</tr>
<tr>
<td>Objectives</td>
<td>3</td>
</tr>
<tr>
<td>Methods</td>
<td>3</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>6</td>
</tr>
<tr>
<td>References</td>
<td>6</td>
</tr>
<tr>
<td>Appendices</td>
<td>7</td>
</tr>
<tr>
<td>Contributions of Authors</td>
<td>9</td>
</tr>
<tr>
<td>Declarations of Interest</td>
<td>9</td>
</tr>
<tr>
<td>Sources of Support</td>
<td>9</td>
</tr>
</tbody>
</table>
Disease-modifying treatments for primary autoimmune haemolytic anaemia

Anthony Pak-yin Liu¹, Daniel KL Cheuk¹

¹Department of Pediatrics and Adolescent Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong, China

Contact address: Anthony Pak-yin Liu, Department of Pediatrics and Adolescent Medicine, The University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong, China. apyliu@hku.hk.

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ABSTRACT

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

To determine the effects of various disease-modifying treatment modalities in people with autoimmune haemolytic anaemia.

BACKGROUND

Description of the condition

Autoimmune haemolytic anaemia (AIHA) is a condition characterised by the presence of autoantibodies which bind to surface of the patient’s own red blood cells (RBCs) leading to premature destruction (Gehrs 2002). Such destruction of RBCs (haemolysis) can occur within the circulation (intravascular haemolysis) or within the spleen (extravascular haemolysis). Incidence of AIHA ranges from 0.8 to 3 new cases per 100,000 individuals per year, and the estimated prevalence is 17 per 100,000 individuals, more commonly occurring in individuals after 50 years of age (Aladjidi 2011; Eaton 2007; Gehrs 2002; Klein 2010; Sokol 1992). AIHA may run an acute or chronic course; severity of the condition can range from fully compensated disease to life-threatening anaemia, and can be classified by the temperature reactivity of RBC autoantibodies, as well as by the underlying aetiology. Warm AIHA is the most common type; it is associated with autoantibodies, often immunoglobulin G (IgG), being most reactive at 37°C and can be secondary to rheumatological disorders and lymphoproliferative conditions. Haemolysis is usually extravascular and takes place in the spleen, with a disease course that is typically chronic and relapsing. Cold AIHA, on the other hand, is a result of autoantibodies, usually immunoglobulin M (IgM), with the highest affinity at 0°C to 4°C and can be associated with underlying lymphoproliferative conditions and infections (e.g. mycoplasma, Epstein-Barr virus). IgM causes complement fixation and results in intravascular haemolysis, which tends to be abrupt but self-limiting. Paroxysmal cold haemoglobinuria is a rare subtype of cold AIHA caused by IgG that preferentially binds at a lower temperature, mostly in children following infections. Infrequently, mixed-type AIHA may occur in an individual where a combination of warm and cold autoantibodies exist. Drug-induced immune haemolytic anaemia (DIIHA) is a distinct entity that may be associated with both warm and cold AIHA (Johnson 2007). This review will focus on the treatment for primary, or idiopathic AIHA, where no underlying systemic disease can be identified.

Diagnosis of primary AIHA depends on the demonstration of haemolysis, serologic evidence of autoantibody against patients’
own RBCs and exclusion of secondary causes (identifiable in 20% to 80% of cases) (Gehrs 2002). The direct antiglobulin test (DAT) is commonly used to demonstrate the presence of autoantibody-coated patient RBCs, although it is important to bear in mind alternative causes for a positive DAT including the use of intravenous immunoglobulin, drug-induced autoantibodies, haemolytic transfusion reaction, thalassaemia, sickle cell disease, and multiple myeloma (Clark 1992). Haemolysis on the other hand, is suggested clinically when yellowish discolouration of the skin (jaundice), together with pallor is detected with or without the presence of enlargement of the spleen (splenomegaly).

In terms of laboratory evaluation, complete blood count with peripheral smear, serum bilirubin, lactate dehydrogenase (LDH), haptoglobin, methaemalbumin and urine haemoglobin are useful in determining the presence and type of haemolysis (presence of schistocytes, low haptoglobin, raised methaemalbumin and urine haemoglobin in intravascular haemolysis; presence of spherocytes, raised unconjugated bilirubin in extravascular haemolysis). In warm AIHA, anti-IgG anti-sera is typically detected in DAT while in cold AIHA, anti-C3d anti-sera is usually present due to IgM-mediated haemolysis. Individuals with AIHA may require immunomodulatory therapies and a proportion of them, especially those with severe anaemia and mixed serological type, may require multiple agents to achieve treatment response (Barcellini 2014). They also experience morbidities and mortality due to the use of immunomodulatory therapies including splenectomy. Between a quarter and half of all individuals who achieve remission might develop disease relapse (Barcellini 2014). Non-responders or those who relapse may be dependent on regular transfusions to alleviate the symptoms of anaemia.

**How the intervention might work**

Immunosuppressive or immunomodulatory therapy interferes with the immune destruction of RBCs

1. Glucocorticoids inhibit Fc receptor-mediated removal of sensitised RBCs, and in the longer term reduce production of autoantibodies (Zanella 2014).

2. Splenectomy removes a major site of RBC destruction and autoantibody production (Zanella 2014).

3. Rituximab is an anti-CD20 monoclonal antibody given as four weekly intravenous infusions. The antibody targets and depletes host B cells, which are responsible for the generation of autoantibodies (Zecca 2003). Side effects include infusion reactions, immunosuppression and hepatitis B reactivation.

4. Alemtuzumab is an anti-CD52 monoclonal antibody targeting CD52, which is an antigen expressed by mature lymphocytes. Lymphodepletion with alemtuzumab would effectively devoid the host’s capability of autoantibody generation (Cheung 2006). Side effects include infusion reactions and immunosuppression.

5. Cyclophosphamide is an alkylating agent with potent myelosuppressive effect. Lymphocytes are highly sensitive to the drug and depletion would disrupt the autoimmune involved (Moyo 2002). Nausea, vomiting, alopecia, myelosuppression, haemorrhagic cystitis, and gonadal toxicity are potential adverse effects with the drug.

6. Danazol is a semi-synthetic androgen with immunomodulatory effect via decreasing IgG production and cell-bound IgG and complement (Pignon 1993). Side effects include its androgenic effects and derangement in liver function.

**Description of the intervention**

Treatment depends on the severity of haemolysis. Supportive treatment including folic acid supplementation, red cell transfusion and avoidance of cold exposure in individuals with cold AIHA are not within the scope of the current review (Gehrs 2002). In AIHA with identifiable secondary causes, treatment should be targeted towards the underlying condition.

Specific treatment for idiopathic AIHA includes immunosuppressive or immunomodulatory therapy. Traditionally, glucocorticoids (prednisolone 1 mg to 1.5 mg/kg/day for one to three weeks then tapered) are the first-line therapy for patients with AIHA with up to three quarters of patients demonstrating improvement within three weeks. Relapse is nevertheless common (15% to 40%) after tapering of glucocorticoids in the first six months to one year, and thus the majority of patients responding to glucocorticoids would have to be continued with a lower maintenance dose (Aladjidi 2011; Sankaran 2016; Zanella 2014). Adverse effects from prolonged glucocorticoid use include Cushingoid changes, hypertension, hyperglycaemia, peptic ulcers, and reduced bone mineral density. Splenectomy has been considered the second-line therapy for patients failing glucocorticoid therapy. Response rates after splenectomy ranged from 60% to 75%, but carry the risk of thrombosis as well as infection due to encapsulated bacteria and parasites including malaria (Davidson 2001; Katkhouda 1998). In patients with refractory disease, a number of interventions have been tested with various degree of success. These include immunosuppressive agents including cyclophosphamide, danazol, cyclosporine, and mycophenolate mofetil (Hershko 1990; Howard 2002; Moyo 2002; Pignon 1993), as well as monoclonal antibodies including anti-CD20 (rituximab) and anti-CD52 (alemtuzumab) (Zecca 2003; Cheung 2006). With a response rate of 80% to 90%, rituximab is increasingly being used in AIHA patients failing glucocorticoids. Each medication possesses its own side effects which are detailed in the next section. (Cheung 2006; Hershko 1990; Howard 2002; Moyo 2002; Pignon 1993, Zecca 2003), Interventions targeted at removing circulating autoantibodies include intravenous immunoglobulin and plasma exchange (Flores 1993; Smith 2003). Accessibility to the above measures may be limited in resource-poor countries.
7. Cyclosporine is a calcineurin inhibitor that suppresses T helper cell activities, decreasing autoantibodies synthesis (Hershko 1990). Patients should be monitored for hair growth, gum hypertrophy, renal impairment, hypertension and rarely, neurological complications.

8. Mycophenolate mofetil reversibly inhibits inosine monophosphate dehydrogenase and in turn inhibits purine synthesis required in the proliferation of B and T cells (Howard 2002). Adverse effects are gastrointestinal disturbances and myelosuppression.

9. Use of intravenous immunoglobulin in AIHA is based on its effectiveness in immune thrombocytopenia, but its efficacy with AIHA is more controversial. The mechanism of action is hypothesised to be through competitive inhibition of autoantibody adsorption to patient blood cells, as well as by decreasing uptake of autoantibody-coated blood cells by the reticuloendothelial system through blockage of macrophage Fc receptors (Flores 1993). Infusion reactions, fever, arthralgia, haemolysis, and aseptic meningitis are possible complications.

10. Plasma exchange is usually reserved for patients with fulminant AIHA. The process effectively removes host circulating immunoglobulins and complements that are responsible for the immune destruction of RBCs (Smith 2003). Side effects are attributed to the insertion of the apheresis catheter, and the process of apheresis which may cause haemodynamic disturbances, hypocalcaemia and coagulopathy.

Why it is important to do this review
Various immunosuppressive medications and other specific treatment modalities are available for the management of idiopathic AIHA. As an uncommon condition, it remains uncertain whether high-quality evidence exists to support any treatment regimen and what the most effective regimen is, in particular for relapsing or refractory disease. This systematic review will provide an evidence base for the selection of immunomodulatory treatment that most likely benefits people with idiopathic AIHA.

OBJECTIVES
To determine the effects of various disease-modifying treatment modalities in people with autoimmune haemolytic anaemia.

METHODS

Criteria for considering studies for this review

Types of studies
We will only include randomised controlled trials (RCTs).

Types of participants
We will include people of both genders and all ages suffering from idiopathic AIHA. Individuals with newly diagnosed, relapsing or refractory disease; warm or cold AIHA will be included. Studies on patients with secondary AIHA will be excluded.

Types of interventions
We will include trials evaluating specific, immunosuppressive or immunomodulatory treatments for AIHA, including but not limited to: corticosteroids, intravenous immunoglobulin (IVIG), rituximab, alemtuzumab, azathioprine, cyclosporine, mycophenolate mofetil (MMF), plasma exchange and splenectomy. We will exclude trials of supportive treatment such as folic acid supplement and transfusion alone. The control interventions can be another specific treatment or placebo treatment or supportive treatment alone, or no treatment. We will also include trials comparing different dosing regimens of the same treatment. Each intervention will be reported separately against each separate comparator. Comparisons could be:
1. one drug versus no treatment;
2. one drug versus placebo;
3. one drug versus another drug;
4. more than one drug (combination treatment) versus no treatment;
5. more than one drug (combination treatment) versus placebo;
6. more than one drug (combination treatment) versus one drug;
7. more than one drug (combination treatment) versus another combination of drugs.

Types of outcome measures
We will not use the outcomes listed below as criteria for study inclusion.

Primary outcomes
1. Frequency of complete haematological response (defined as normalisation of haemoglobin concentration, reticulocyte (immature red blood cells (RBCs)) count, and indirect (or unconjugated) bilirubin level) at months two, six and 12.
2. Frequency of adverse events at two, six and 12 months.
Secondary outcomes

1. Frequency of partial haematological response (defined as improvement in haemoglobin concentration) at two, six and 12 months.
2. RBC transfusion requirement after treatment (measured as units of RBCs transfused per month or millilitres (mL) per kg body weight) at two, six and 12 months.
3. Frequency of direct anti-globulin test (DAT) positivity after treatment at two, six and 12 months.
4. Overall survival at six and 12 months.
5. Relapse-free survival at six and 12 months.
6. Frequency of relapse at six and 12 months.
7. Quality of life (QOL) as measured by validated instruments at 12 months.

Data collection and analysis

Selection of studies

Both review authors will independently examine identified studies and abstracts and select studies meeting the inclusion criteria. Discrepancies will be resolved by discussion. We will report the flow of studies as per the PRISMA statement in a flow chart (Moher 2009), which includes data on the number of records identified through database searching, number of additional records identified through other sources, number of records after duplicates removed, number of records screened, number of records excluded, number of full-text articles examined for eligibility, number of full-text articles excluded with reasons, and numbers of studies included in qualitative and quantitative syntheses (Higgins 2011a).

Data extraction and management

Both review authors will independently extract data using a standardised data collection form (Higgins 2011a). We will extract data on study design and methods including study dates, location, setting, type of study (parallel group or cross-over or other designs), stratified randomisation variables, random sequence generation, allocation concealment, and blinding methods. We will extract data on participant inclusion and exclusion criteria, number of participants in each intervention and control group, and for each group, their demographics (age, sex, ethnicity), baseline laboratory parameters (haemoglobin level, reticulocyte count, bilirubin level, direct anti-globulin test (DAT) positivity), baseline transfusion requirements, associated conditions and comorbidities, and previous intervention received (drug and regimen). We will extract data on details of intervention for each group, and dropouts of each group and follow-up duration. We will extract outcomes measured in each study that match with our pre-specified outcomes. We will also extract data on funding source and declaration of interests. Data will be entered into Review Manager software (RevMan 5.3 (ReMan 2014) by one review author (APYL) and checked by the other review author (DKLC).

Assessment of risk of bias in included studies

Overall strength and quality of evidence will be assessed by GRADE approach as recommended by the Cochrane Handbook for Systematic Reviews of Interventions. Both review authors will independently assess the risk of bias of included studies with the Cochrane 'Risk of bias' tool (Higgins 2011b). The following domains will be assessed: random sequence generation, allocation concealment, blinding of participants, study personnel and outcome assessors, incomplete outcome data, selective reporting, and other sources of bias. For each domain for each study, the risk of bias will be graded as “high”, “unclear” or “low” according to the criteria stated in the Cochrane Handbook for Systematic Reviews.

Search methods for identification of studies

Electronic searches

We will search MEDLINE (Ovid) (1946 to 2015) (Appendix 1), EMBASE (Ovid) (1974 to 2015) (Appendix 2), LILACS (Latin American and Caribbean Health Sciences Literature) (1982 to 2015) (Appendix 3), Cochrane Library (CENTRAL) (latest issue) (Appendix 4), and China Journal Net (1994 to 2015) (Appendix 5). The search strategies for the different electronic databases using a combination of controlled vocabulary and text word terms are shown in the appendices (Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5).

Searching other resources

We will also search conference proceedings of the following scientific meetings using the search terms “haemolytic anaemia” or “hemolytic anemia”:

1. WHO International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/)
2. United States Clinical Trials Registry (https://clinicaltrials.gov/)
3. European Union Clinical Trial Register (http://www.clinicaltrialregister.eu/)

We will also search conference proceedings of the following scientific meetings using the search terms “haemolytic anaemia” or “hemolytic anemia” and “trials”:


We will search reference lists of relevant articles identified in all the searches. We will also contact authors of included studies to enquire about additional studies. We will not apply any language restriction in our searches.
of Interventions. Discrepancies between the review authors will be resolved by discussion.

Measures of treatment effect
We will estimate risk ratio (RR) with 95% confidence intervals (CI) for dichotomous outcomes. We will use hazard ratio (HR) with 95% CI for time-to-event outcomes and mean difference (MD) with 95% CIs for continuous outcomes. For continuous outcomes using different scales (e.g. quality of life (QoL) data), we will use standardised mean difference (SMD) with 95% CI (Deeks 2011).

Unit of analysis issues
We will use appropriate unit of analysis for cluster-randomised trials and cross-over trials according to the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2011), if these types of trials are found and included.

Dealing with missing data
We will contact the study authors in an attempt to acquire any missing information. We will include all participants with intention-to-treat (ITT) analyses. For longitudinal outcome data, we will use the last observation carried forward (LOCF) method for imputing missed data (Higgins 2011c). In the complete absence of continuous outcome data (including transfusion requirement or QoL), we will not impute the data and only available data will be analysed, while the risk of bias due to incomplete outcome data and reporting will be assessed. For missing data on binary outcomes (including response, relapse, DAT positivity, or adverse events), we will assume no response, no relapse, no DAT positivity or no adverse events. Meta-analysis of time-to-event data requires availability of individual patient data from the original investigators (Higgins 2011a). If they are not available, we will use statistical methods according to Tierney 2007.

Assessment of heterogeneity
We will use the I² statistic to evaluate the degree of heterogeneity of treatment effects. We will follow the guide on interpretation of the I² statistic suggested by the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2011) as follows:
1. 0% to 40%: may not be important;
2. 30% to 60%: may represent moderate heterogeneity;
3. 50% to 90%: may represent substantial heterogeneity;
4. 75% to 100%: considerable heterogeneity.
We will also use the Chi² test of homogeneity to assess the strength of evidence regarding heterogeneity. If significant heterogeneity is present (P < 0.1), we will examine the possible reasons for heterogeneity. Heterogeneity can be due to the participants and outcomes. When the participants, definition of outcomes in each study, or the timing of each measurement of outcome in each study is very different, we may consider the studies (even with same intervention and comparator) too heterogeneous for pooling of data.

Assessment of reporting biases
We will assess publication bias using a funnel plot (estimated differences in treatment effects against their standard errors) in case 10 or more studies are identified for a given outcome (Sterne 2011). We will try to obtain clinical trial protocols to assess for reporting bias.

Data synthesis
With the assumption that the different studies would likely be estimating different, yet related, intervention effects, we will use the random-effects model for meta-analysis to obtain the mean effect across studies, unless the studies are so heterogeneous that pooling data for meta-analysis is considered entirely inappropriate (Deeks 2011). If multi-arm studies are included, we will analyse multiple intervention groups in an appropriate way that avoids arbitrary omission of relevant groups or double counting of participants. We will perform all analyses using the most updated version of Review Manager (RevMan 5.3) (RevMan 2014). We will produce 'Summary of findings' tables according to the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2011). Separate 'Summary of findings' tables will be provided for each comparison (separate intervention versus separate comparator). The pre-defined outcomes to be included are: frequency of complete haematological response (defined as normalisation of haemoglobin concentration, reticulocyte count, and indirect bilirubin level) at months two, six and 12 months, frequency of adverse events at two, six and 12 months, overall survival at six and 12 months, relapse-free survival at six and 12 months, RBC transfusion requirement after treatment (measured as units of red cells transfused per month or mL per kg body weight) at two, six and 12 months, and QoL as measured by validated instruments at 12 months. These tables will summarise the results for the pre-defined outcomes of all comparisons and provide grading of the quality of evidence for each outcome according to the GRADE system (GRADEpro 2008; Schünemann 2011). If different tools for measurement of QoL are used, standardised mean difference will be used.

Subgroup analysis and investigation of heterogeneity
We will perform subgroup analyses (Deeks 2011) for the following subgroups as they may have different prognosis and response to treatment (different size of treatment effect).
1. Different age groups (children <18 years or adults >=18 years).
2. With or without associated conditions (such as thrombocytopenia or neutropenia, or other autoimmune phenomena)
3. Different degrees of anaemia (transfusion dependent or transfusion independent)
4. Newly diagnosed versus refractory disease

We will also assess subgroup differences by examining the I² statistic and performing a Chi² test for homogeneity across subgroup results. In case heterogeneity is present, we will investigate the probable reasons for heterogeneity by examining the distribution of important participant factors between trials (age, associated conditions, degrees of anaemia, and previous interventions) and trial factors (randomisation concealment, blinding, dropouts, intervention regimens).

Sensitivity analysis
We will perform sensitivity analysis to assess the impact of excluding studies with high risk of bias (Deeks 2011). We will also perform sensitivity analysis to assess the impact of excluding studies with significant amount (> 30%) of missing outcome data.

Acknowledgements
We are also grateful to the Cochrane Haematological Malignancies Group for their editorial support.

References

Additional references

Aladjidi 2011

Barcellini 2014

Cheung 2006

Clark 1992
Clark JA, Tanley PC, Wallas CH. Evaluation of patients with positive direct antiglobulin tests and nonreactive eluates discovered during pretransfusion testing. Immunohematology 1992;8:9–12.

Davidson 2001

Deeks 2011
Howard 2002

Johnston 2007

Katkhouda 1998

Klein 2010

Lefebvre 2011

Moher 2009

Moyo 2002

Pignon 1993
APPENDICES

Appendix 1. MEDLINE search strategy
1. exp ANEMIA, HEMOLYTIC, AUTOIMMUNE/
2. autoimmune hemolytic anemia.mp.
3. autoimmune haemolytic anaemia.mp.
4. (haemolyt$ or hemolyt$).tw.
5. Evans.tw.
6. AIHA.tw.
7. ((agglutinin* or antibod*) adj2 cold* adj2 diseas*).tw,kf,ot.
8. or/1-7
9. randomized controlled trial.pt.
10. controlled clinical trial.pt.
11. randomi?ed.ab.
12. placebo.ab.
13. drug therapy.fs.
14. randomly.ab.
15. trial.tw.
16. groups.ab.
17. or/9-16
18. human.sh.
19. 17 and 18
20. 19 and 8

Appendix 2. Embase search strategy
1. exp ANEMIA, HEMOLYTIC, AUTOIMMUNE/
2. autoimmune hemolytic anemia.mp.
3. autoimmune haemolytic anaemia.mp.
4. (haemolyt$ or hemolyt$).tw.
5. Evans.tw.
6. AIHA.tw.
7. ((agglutinin* or antibod*) adj2 cold* adj2 diseas*).tw.
8. or/1-7
9. (randomi$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
10. RETRACTED ARTICLE/
11. or/9-10
13. (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/
14. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/
15. 11 not (12 or 13 or 14)
16. 8 and 15
Appendix 3. LILACS search strategy

$db: ("LILACS") AND type_of_study: ("clinical_trials") AND ((autoimmune hemolytic anemia) OR (autoimmune haemolytic anaemia) OR hemoly* OR haemoly* OR Evans OR AIHA)

Appendix 4. CENTRAL search strategy

#1 MeSH descriptor: [Anemia, Hemolytic, Autoimmune] explode all trees
#2 autoimmune hemolytic anemia
#3 autoimmune haemolytic anaemia
#4 (haemolytic* or hemolytic*)
#5 ((agglutinin* or antibod*) near/2 cold near/2 diseas*)
#6 AIHA
#7 Evans:ti,ab,kw
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7 in Trials

Appendix 5. China Journal Net search strategy

1. SU (subject) = 浆血性貧血 (haemolytic anaemia)
2. TI (title) = 浆血性貧血 (haemolytic anaemia)
3. KY (keyword) = 浆血性貧血 (haemolytic anaemia)
4. AB (abstract) = 浆血性貧血 (haemolytic anaemia)
5. (1 OR 2 OR 3 OR 4)
6. AB (abstract) = 随機 (random)
7. (5 AND 6)

Contributions of Authors

APY Liu: conceiving of the review, protocol development, searching for trials, selection of studies, quality assessment of trials, data extraction, data entry, data analyses, data interpretation, development of final review, disagreement resolution, review updates, corresponding author.

DKL Cheuk: conceiving of the review, protocol development, searching for trials, selection of studies, quality assessment of trials, data extraction, data entry, data analyses, data interpretation, development of final review, disagreement resolution, review updates.

Declarations of Interest

APY Liu: none known.

DKL Cheuk: none known.
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