

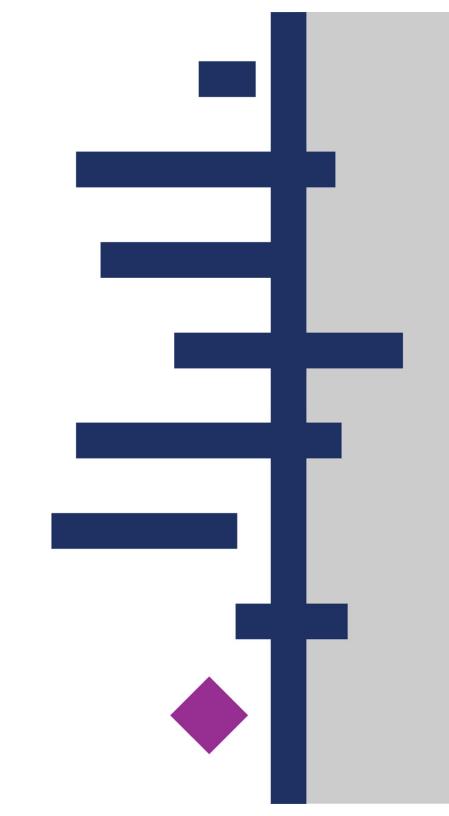
Common errors and best practice when writing a review protocol

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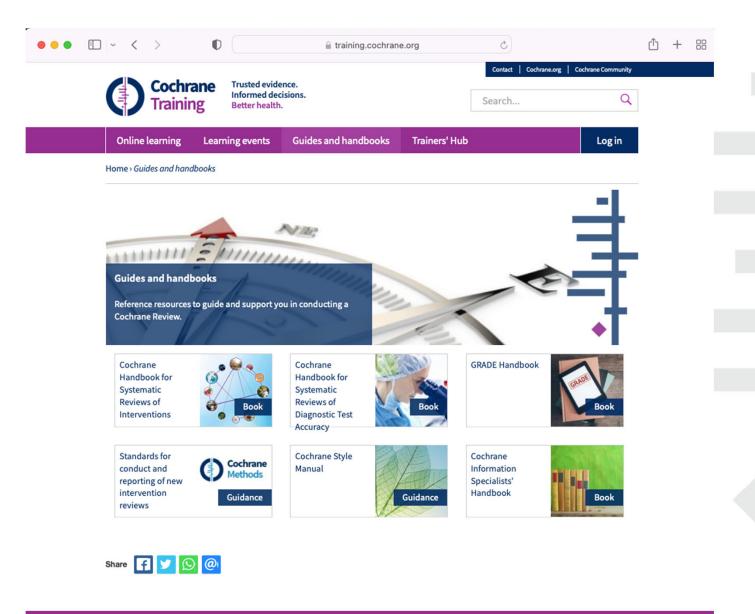
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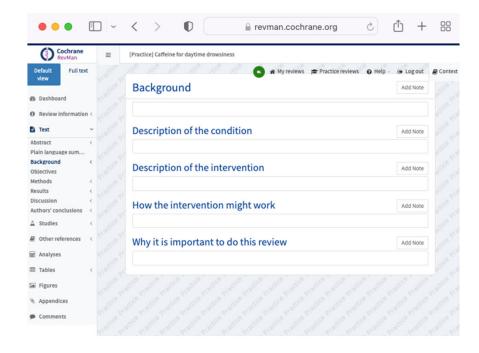
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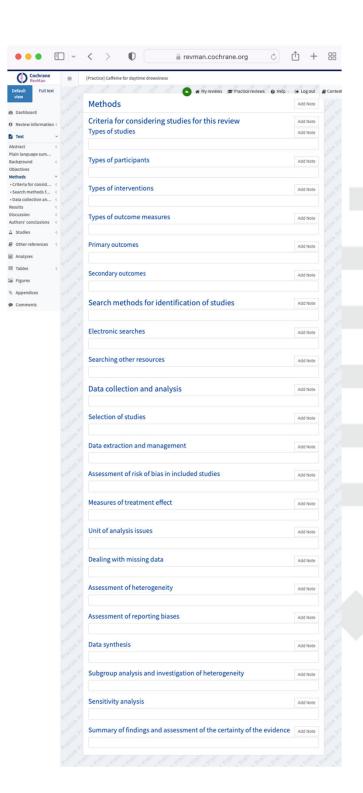


Community

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Background

 Background essential to (succinctly!) justify all subsequent sections of the review.





Background

Ensure the review is clearly and appropriately justified in the section 'why is it important to do this review'.

Why it is important to do this review

In 2009, four Cochrane Reviews were published of the licensed treatments for Alzheimer's disease in people with Down syndrome (Mohan 2009; 2009b; Mohan 2009c; Mohan 2009d). At that time, only one review identified a trial that met its inclusion criteria, namely a small randomised to donepezil. The reviews concluded that nothing was then known about the effectiveness of licensed treatments for Alzheimer's disease in this properties.

Since then, we are aware that a number of RCTs have been completed and published in this area, and an up-to-date review of this area is now feasible

Good to conduct scoping review first to ensure it's feasible

Why it is important to do this review

In 2009, four Cochrane Reviews were published of the licensed treatments for Alzheimer's disease in people with Down syndrome (Mohan 2009a; Mohan 2009b; Mohan 2009c; Mohan 2009d). At that time, only one review identified a trial that met its inclusion criteria, namely a small randomised trial of donepezil. The reviews concluded that nothing was then known about the effectiveness of licensed treatments for Alzheimer's disease in this population.

Since then, we are aware that a number of RCTs have been completed and published in this area, and an up-to-date review of this area is now more feasible.

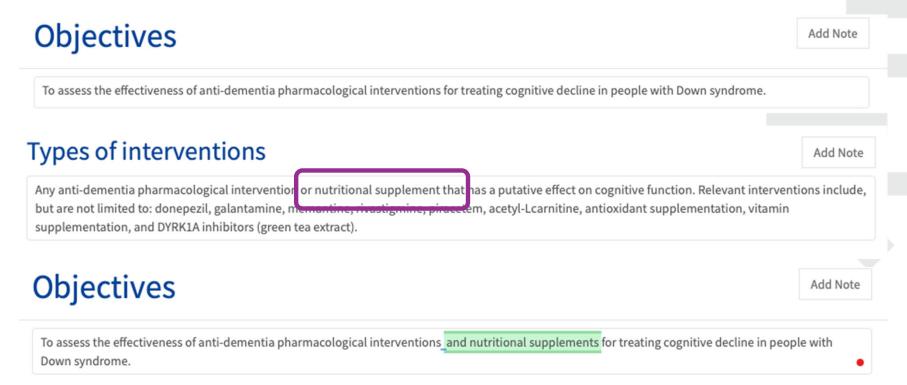
An up-to-date review of this kind is important, not least because people with learning disabilities (including Down syndrome) are often on a large amount of medication, despite limited evidence of its effectiveness and evidence of considerable harmful side effects (RCGP 2012).





Objectives

- "To assess the effects of [intervention or comparison] for [health problem] for/in [types of people, disease or problem and setting if specified]".
- Ensure there is a clear and consistent link between objectives and PICO





Setting the eligibility criteria

Set pre-defined, unambiguous eligibility criteria

✓ Good to define comparators as well as interventions

Types of studies

Randomised controlled trials (RCTs) comparing one relevant anti-dementia pharmacological intervention or nutritional supplement with another, or with placebo or no treatment.

Types of participants

Add Note

Add Note

Adults (aged 18 years and older) with Down syndrome. Where we identify relevant studies that include participants younger than 18 years of age or participants that do not have Down syndrome, we will contact the study authors to request the subgroup data for participants with Down syndrome, aged 18 years and older only.

X What if this subset of relevant data cannot be obtained?

Types of interventions

Add Note

Any anti-dementia pharmacological intervention or nutritional supplement that has a putative effect on cognitive function. Relevant interventions include, but are not limited to: donepezil, galantamine, memantine, rivastigmine, piracetem, acetyl-Lcarnitine, antioxidant supplementation, vitamin
supplementation, and DYRK1A inhibitors (green tea extract).

X Any restrictions on delivery, dose, duration, intensity?



Types of studies

Add Note

Randomised controlled trials (RCTs) comparing one relevant anti-dementia pharmacological intervention or nutritional supplement with another, or with placebo or no treatment.

Types of participants

Add Note

Adults (aged 18 years and older) with Down syndrome. Where we identify relevant studies that include participants younger than 18 years of age or participants that do not have Down syndrome, we will contact the study authors to request the subgroup data for participants with Down syndrome, aged 18 years and older only. If the authors were unable or unwilling to provide this data, the study was excluded from the review. Information from one such study is presented (Eisenburg 1984).

Types of interventions

Add Note

Any anti-dementia pharmacological intervention or nutritional supplement that has a putative effect on cognitive function. Relevant interventions include, but are not limited to: donepezil, galantamine, memantine, rivastigmine, piracetem, acetyl-Lcarnitine, antioxidant supplementation, vitamin supplementation, and DYRK1A inhibitors (green tea extract). Interventions and comparators are eligible regardless of delivery, dose, duration or intensity.



Selecting outcomes

- Minimum number of outcomes selected
- Outcomes should be a mixture of benefit and harm
- Choose outcomes that are relevant to stakeholders such as consumers, health professionals and policy makers
- Define outcome measures/timing of measurement
- Clarify how multiple measures will be handled



Selecting outcomes

Number of outcomes kept to a minimum

Primary outcomes

- 1. Improvement in:
 - a. cognitive abilities,
 - b. global functioning,
 - c. behavioural problems,
 - d. daily living skills, including kitchen skills, laundry skills, self-care skills, etc
- 2. Adverse events, including headache, nausea, and dizziness.*

Add Note

Add Note

Outcomes chosen that are relevant to key stakeholders

Secondary outcomes

- 1. Carer stress (as measured by interviews or self reports).*
- Institutional/home care, including social care placement breakdown (as measured by administrative data).*
- 3. Death (as measured by administrative data).*
- 4. Treatment adherence (as measured by administrative data and self report).

X How are outcomes defined/measured

➤ What are the follow-up time points of interest?



Primary outcomes

Add Note

- 1. Improvement in:
 - a. cognitive abilities, as measured by standardised scales, for example, the Dementia Scale for Down Syndrome (DSDS; Jozsvai 2009), the Cambridge Cognitive Examination (CAMCOG; Schmand 2000), or the Severe Impairment Battery (SIB; Panisset 1994; Saxon 1993);*
 - b. global functioning, as measured by standardised scales, for example, the DSDS (Jozsvai 2009), or the International Classification of Functioning, Disability and Health (ICF) Scales (WHO 2001);
 - c. <u>behavioural</u> problems, as measured by standardised scales, for example, the American Association on Mental Deficiency: Adaptive Behaviour Scale (AAMD: ABS; Nihira 1974), or the Neuropsychiatric Inventory (NPI; Cummings 1994);*
 - d. daily living skills, including kitchen skills, laundry skills, self-care skills, etc. (as measured by carer report).
- 2. Adverse events, including headache, nausea, and dizziness.*

Secondary outcomes

Add Note

- 1. Carer stress (as measured by interviews or self reports).*
- 2. Institutional/home care, including social care placement breakdown (as measured by administrative data).*
- 3. Death (as measured by administrative data).*
- 4. Treatment adherence (as measured by administrative data and self report).

We intend to make comparisons at the following specific follow-up periods:

- 1. short term (less than three months);
- 2. medium term (three to 12 months); and
- 3. long term (over one year).



Outcomes as eligibility criteria

 Clarify <u>and justify</u> in advance if outcomes are to be used as criteria for including studies

Common Errors

- **X** "The evidence base is large, and this will help to reduce the number of studies included in the full review"
- **X** "Only high quality studies will assess the outcomes of interest, and this will help to ensure only high quality studies are included in the review"

Best Practice

- The same intervention may be studied in the same population for different purposes (e.g. botox) and this will ensure only the relevant studies are included
- ✓ The primary objective of this review is to assess the adverse effects of this intervention (e.g., aspirin) used for several conditions



Planning the search

- Searches for studies should be as extensive as possible, to include published and unpublished data
- Plan to rerun or update searches for all relevant databases within 12 months before publication of the review or review update
- Seek advice from experienced Information Specialist.



Selection and Extraction

✓ Use (at least)
two people
working
independently

Selection of studies

Add Note

Titles and abstracts of all records located during the search process will be screened by 2 review authors to determine whether they meet the inclusion criteria for this review. Full text articles will retrieved for records that appeared to meet the inclusion criteria.

X Need to also define in advance the process for resolving disagreements

Selection of studies

Add Note

Titles and abstracts of all records located during the search process will be independently screened by 2 review authors (NL and JH) to determine whether they meet the inclusion criteria for this review. Full text articles will retrieved for records that appeared to meet the inclusion criteria and be independently screened by 2 review authors (NL and JH). In the event of a disagreement between authors, the full review team will discuss the decision until it is resolved

- Include studies in the review irrespective of whether measured outcome data are reported in a 'usable' way
- "Pilot" the data extraction form



Risk of Bias version 1

- ✓ Cite the correct version of the tool (Higgins 2011)
- ✓ Use (at least) two people working independently

Assessment of risk of bias in included studies

Add Note

Two review authors (NL and JH) will assess each included study for risk of bias, using the Cochrane 'Risk of bias' tool (Higgins 2011). Review authors will judge each of the seven domains (below) assessed by the tool to be at either 'low risk of bias', 'high risk of bias', or 'unclear risk of bias':

- 1. sequence generation (was the method used to generate the allocation sequence adequate?);
- 2. allocation concealment (was the method of concealing the allocation sequence sufficient, both prior to, and during the recruitment process?);
- 3. blinding of participants and personnel (was knowledge of the allocated intervention adequately concealed from all participants and relevant personnel during the study?);
- 4. blinding of outcome assessors (was knowledge of the allocated intervention adequately concealed from all outcome assessors during the study?)
- 5. incomplete outcome data (did study authors address issues related to incomplete outcome data adequately?);
- 6. selective outcome reporting (are reports of the study free of suggestion of selective outcome reporting?); and
- 7. other sources of bias (was the study apparently free of other problems that could put it at a high risk of bias, for example, source of study funding?).
- 8. Baseline Characteristics (did participants differ at baseline in key characteristics?)



We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale).

X Avoid 'adding on' domains

X Need to also consider assessing key domains separately for different key outcomes





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Risk of Bias 2

Cite the correct version of the tool (Higgins 2022)

Risk of Bias 2 (RoB 2) tool

 Process for proposing changes to methods or tools used in Cochrane

- Methods Support Unit
- Contact Methods Support or Methods Groups
- Clinical study reports and other regulatory documents
- Data-based predictive distributions for betweenstudy heterogeneity
- · Repeated meta-analyses
- Risk of Bias 2 (RoB 2) tool
- ROBINS-I tool
- QUADAS-C tool
- Reviews using spilt body trials

The Risk of Bias 2 (RoB 2) tool is an update to the original risk of bias tool that launched in 2008. The relevant chapter in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 8, titled 'Assessing risk of bias in a randomized trial 'E'. The Methodological Expectations for Cochrane Intervention Reviews (MECIR) Manual includes standards for assessing risk of bias in included studies; C52-60 'E'. Up-to-date information from the developers on RoB 2 is available via the Risk of Bias tools website: www.riskofbias.info 'E'.

Key Cochrane resources for using RoB 2 in Cochrane Reviews are:

An Introduction to Risk of Bias 2N

The Introduction to RoB 2 is a one-page leaflet with links to short videos that should be watched at different stages of your review, 1) before you start, 2) when writing your Cochrane Review protocol, 3) managing your RoB 2 assessments, and 4) when writing your full Cochrane Review.

Risk of Bias 2 Cochrane Review Starter Pack

The Starter Pack includes all the key resources you'll need, including guidance, training, tools, RoB 2 protocol considerations, RoB 2 considerations for reporting the full review, and support.

Risk of Bias 2 FAQs

Frequently Asked Questions from authors and editors.

Risk of Bias 2 Webinars

The RoB 2 webinar series covers an introduction of RoB 2, detailed sessions on the five RoB 2 domains, reaching overall RoB judgements, RoB 2 bias in other types of studies (crossover and cluster trials) and editorial considerations.

Editorial checklists for RoB 2

Methods Support Unit web clinic

A monthly web clinic for Cochrane authors, editors and staff

Stay connected with our Methods Network newsletter





Measures of treatment effect

Ensure the planned effect measures match <u>all</u> the outcomes of interest

Measures of treatment effect

Add Note

Dichotomous data

For dichotomous outcome data (e.g. adverse events), we will calculate effect sizes as risk ratio (RR) with 95% CIs. For studies with no events in a treatment arm, a fixed value of 0.5 was added to each 'zero event' cell of the contingency table to allow the calculation of an RR.

Continuous data



When study authors use the same measures to assess the same outcome, we will calculate Mean Differences (MD) with 95% CI. When study authors use different measures to assess the same outcome, we will convert continuous outcome data (e.g. cognitive abilities or behavioural problems) into standardised mean differences (SMDs) and presented these with 95% CIs.

X No consideration of time-to-event data?

Time-to-event data

We will convert time-to-event data (e.g. time to institutionalisation) into hazard ratios (HR) with 95% CIs.



Unit of Analyses

- Consider <u>all</u> potential Unit of Analysis issues
 - Cluster RCTs

- Cross over trials
- Multiple treatment groups
- Within body design

Unit of analysis issues

The unit of analysis in this review was the individual.

Cluster-randomised trials

➤ No consideration of different types of UoA issues

If study authors failed to control for a clustering effect, we will request IPD in order to calculate an estimate of the intracluster correlation coefficient (ICC). If IPD are not available, we will obtain an external estimate of the ICC from similar studies or available resources. If an appropriate ICC cannot be found from any available resources, we will seek statistical advice to obtain an estimate of the ICC and use this to reanalyse the trial data to obtain approximately correct analyses. This reanalysed trial data will then be entered into the RevMan software using the generic inverse variance method to analyse effect sizes and CIs (Higgins 2011).

Cross-over trials

We will include relevant eligible cross-over trials in the review, but we will only use data gathered during the first period of the study, up to the point of the first cross-over. This should avoid any problems associated with any carry-over effect from the first period to the second period of the study.

Studies with multiple treatment groups

If a study compares two or more eligible interventions groups to one eligible control group, we will split the sample size for the shared comparator group evenly. If this strategy poses a problem for investigation of heterogeneity, we will compare each group separately as part of the subgroup analyses (see Subgroup analysis and investigation of heterogeneity).



Missing Data

Dealing with missing data

Add Note

We contacted authors and asked them to supply data missing from included s

X No consideration of different types of Missing Data issues

- Consider <u>all</u> potential Missing Data issues
 - Missing participants
 - Missing summary data
 - Missing standard deviations
 - Missing study design information



Assessment of heterogeneity

 Consider clinical, methodological and statistical heterogeneity, to ensure decision to pool data is appropriate.

Assessment of heterogeneity

Add Note

We will examine statistical heterogeneity using the Q statistic and its P value (less than 0.10 suggesting statistical significance), the I² statistic along with the 95% CI for heterogeneity variance, and by visual inspection of the forest plots. Due to the potential unreliability of the I² statistic, we also presented the magnitude of the heterogeneity.

Where possible, we pooled data from studies that were sufficiently similar to minimise heterogeneity.

- Clear Plan to only pool data if sufficiently homogeneous
- X No mention of clinical or methodological heterogeneity

We will examine clinical heterogeneity by inspecting variability in the participants, interventions and outcomes described in each included study within each comparison made. We will examine methodological heterogeneity by inspecting variability in the study design and risk of bias of each included study within each comparison made.



Assessment of Reporting Bias

Assessment of reporting biases

Add Note

The possibility that publication bias affected the review as a whole will be assessed using a funnel plot to identify small study effects, where at least 10 studies are available for meta-analysis.

✓ Clear Plan for funnel plot use

Reaching an overall judgement about risk of bias due to missing results should also consider;

- comparison of protocols with published reports to detect selective nonreporting of results
- consideration of qualitative signals that suggest not all studies were identified
- use of funnel plots to identify small-study effects, for which non-reporting bias is one cause

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Data Synthesis

Clear plan to undertake a metaanalysis only if participants, interventions, comparisons and outcomes are judged to be sufficiently similar

Data synthesis

Add Note

We will perform a meta-analysis on outcome data where we find at least two studies suitable for inclusion that studied the same intervention. We will use a fixed effect model, unless the I2 measure of heterogeneity exceeds 40%, in which case we will use a random effects model.

When a meta-analysis is not possible due to an insufficient number of studies, we will provide a narrative description of the study results.

- X Need to choose fixed or random in advance
- X No clear plan for how this narrative synthesis will be conducted

Data synthesis

Add Note

We will perform a meta-analysis on outcome data where we find at least two studies suitable for inclusion that studied the same intervention. We will use a fixed effect model, unless the I2 measure of heterogeneity exceeds 40%, in which case we will use a random effects model. We will account for the expected heterogeneity amongst included studies by using a random-effects meta-analysis (DerSimonian 1986) in RevMan (Review Manager 2014). The random-effects model was used to incorporate the assumption that the different studies estimate different, yet related, intervention effects (Higgins 2011).

When a meta-analysis is not possible due to an insufficient number of studies, we will provide a narrative description of the study results, using the recommendations of the Synthesis Without Meta-analysis (SWiM) guidance (Campbell 2020)

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Subgroup Analyses

Subgroup analysis and investigation of heterogeneity

Add Note

Subgroup analyses will examine the differential effects of:

- 1. The different types of pharmacological intervention
- 2. Baseline cognitive functioning
- 3. Interventions by stage of dementia; and
- 4. Interventions by the age of the participant
- ➤ Different subgroups should be clearly defined
- ➤ If subgroups are to be compared, use a formal statistical test to compare them.

✓ Potential effect modifiers are

justifiable and kept to a minimum

Subgroup analysis and investigation of heterogeneity

Add Note

Subgroup analyses will examine the differential effects of:

- 1. the different types of pharmacological intervention (e.g. cholinesterase inhibitors versus NMDA receptor antagonists);
- 2. <u>baseline</u> cognitive functioning (mild-to-moderate intellectual disability at baseline versus moderate-to-severe intellectual disability at baseline versus diagnosis of dementia at baseline);
- 3. interventions by stage of dementia (e.g. mild versus moderate versus severe); and
- 4. interventions by the age of the participant (e.g. young adults (18 to 30 years) versus mature adults (31 to 50 years) versus older adults (50 years plus)

We will compare subgroups using the formal test for subgroup differences in RevMan Web.



Sensitivity Analyses

- Use sensitivity analyses to assess the robustness of results, e.g.;
 - Impact of notable assumptions,
 - Impact of imputed data,
 - Impact of borderline decisions
 - Impact of including studies at high risk of bias

Sensitivity analysis

Clear outline of the purpose of sensitivity analyses

We will assess whether the findings of this review are robust to the decisions made in the process of obtaining them through the use of sensitivity analysis. We will perform sensitivity analyses by conducting the following reanalyses:

- 1. excluding studies with issues regarding their study quality, excluding those with high risk of bias, or high attrition and dropout rate;
- 2. without imputing data for the missing participants; and
- 3. excluding studies focusing on patients aged 60 and over

➤ If age is a potential effect modifier, should be explored via subgroup analyses.



Subgroup vs Sensitivity

Subgroup Analyses	Sensitivity Analyses
Used to investigate if findings of a review would change if a different decision was made during review process	Used to investigate heterogeneous results, or to answer specific questions about particular type of patient, intervention, or study type
Method: Repeat of the analysis in which	Method: splitting all the participant data
alternative decisions or ranges of values	into subgroups, often in order to make
are substituted for decisions that were	comparisons between them
arbitrary or unclear.	
Estimates are produced for each subgroup.	Estimates are not produced for the group of studies removed from the analysis
Formal statistical comparisons are made across the subgroups	Informal comparisons are made between different results



Summary of findings tables

- Prespecify comparisons as well as outcomes
- One table per comparison (not per outcome)
- Seven (maximum) clinically important outcomes
 - Consistent with review Objectives/PICO
 - Balanced overview showing both 'benefit' and 'harm'
- Each outcome should only be presented once in the table. Plan in advance
 - Which timepoint is prioritised for presentation
 - Which methods of measurement is prioritised for presentation





X Comparisons should also be prespecified

Summary of findings and assessment of the certainty of the evidence

Add Note

We will created 'Summary of findings' tables for the following outcomes;

- 1. Cognitive improvement
- 2. Health related quality of life
- 3. Adverse events
- 4. Treatment adherence

➤ No hierarchy for which methods of measurement/timepoint is to be prioritised

We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro software (GRADEpro GDT) We will use the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data for the prespecified outcomes. We will justify all decisions to downgrade or upgrade the quality of studies using footnotes.

➤ Upgrading evidence is not relevant to review of RCTs



Summary of findings and assessment of the certainty of the evidence

Add Note

We will create 'Summary of findings' tables for the following outcomes;

- 1. Cognitive improvement
- 2. Health related quality of life
- 3. Adverse events
- 4. Treatment adherence

We will aim to prioritise long term follow up data (>12 months) for presentation, and only present short term follow up data (<12 months) where no long term follow up data is available. When an outcome is measured in different ways, we will aim to priorotise dichotomous measures of outcomes for presentation, and only present continuous where no dichotomous measures are available.

We will create 'Summary of findings' tables for the following comparisons, as they are emost relevant to decicion makers;

- Cholinesterase inhibitors versus placebo
- NMDA Receptor Antagonists versus placebo
- 3. Nutritional supplements versus placebo

We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro software (GRADEpro GDT) We will use the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data for the prespecified outcomes. We will justify all decisions to downgrade or upgrade the quality of studies using footnotes.



GRADE assessment

Carefully review Chapter 5 the the GRADE handbook.

GRADE Handbook

https://gdt.gradepro.or g/app/handbook/handb ook.html





General Issues

- Author Team must include clinical and methodological expertise for the review, as well as the perspectives of stakeholders.
- Remember to write in future tense.
- Avoid copy and pasting directly from templates.
- Prepare for Conflict of Interests if review authors are involved in potential included studies, include a clear plan to exempt them from;
 - Risk of Bias assessment
 - GRADE Judgements
- If in doubt, ask for help, sooner rather than later!



Fail to plan, plan to fail!





Any Questions?

(nlivingstone@cochrane.org)

