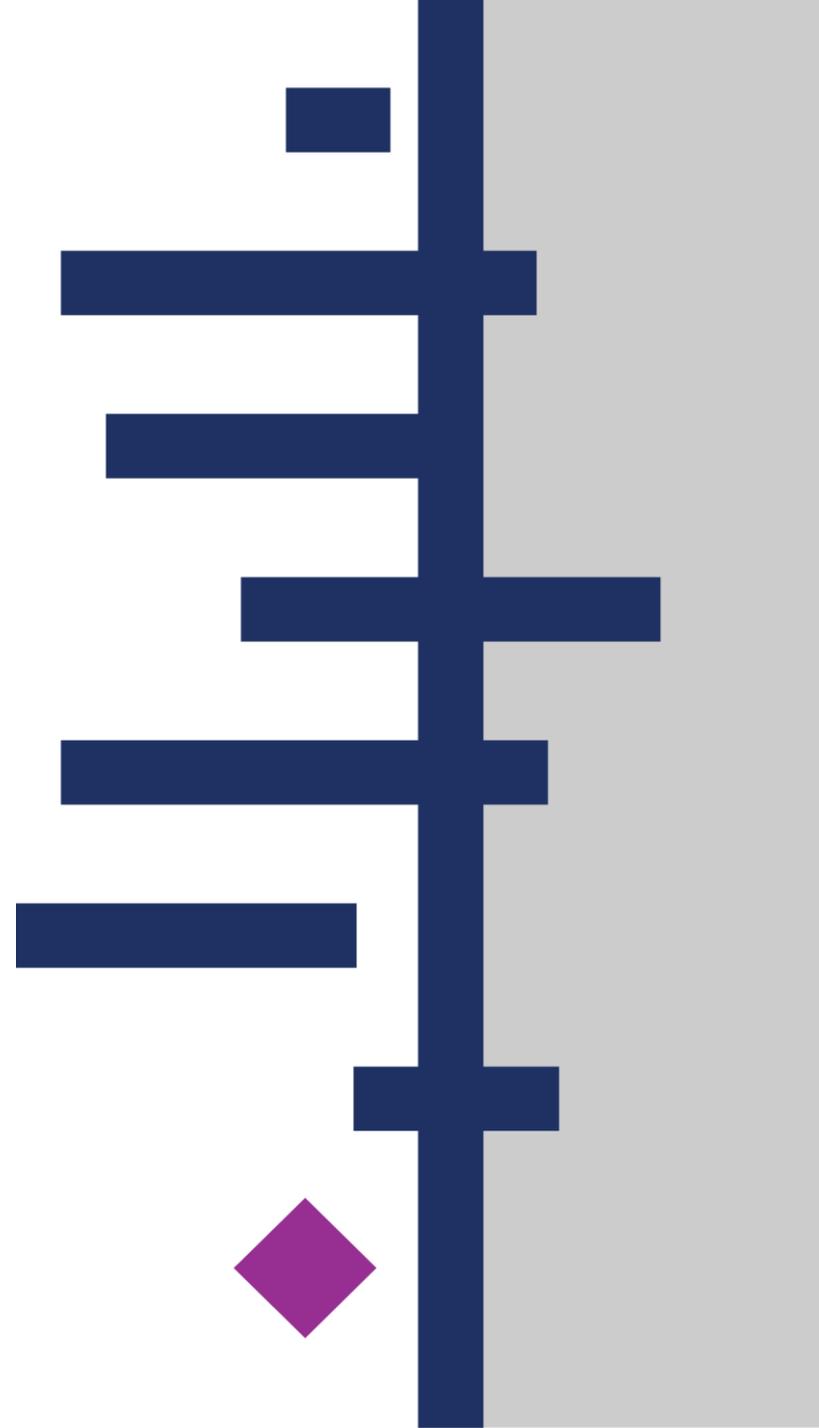# Cochrane

Common errors and best practice when writing a review protocol

Trusted evidence.
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Cochrane Handbook for Systematic Reviews of Interventions

THE COCHRANE COLLABORATION®

Version 5.1.0

[updated March 2011]

Editors: Julian PT Higgins and Sally Green

Handbook information
Part 1: Cochrane reviews
Part 2: General methods for Cochrane reviews
Part 3: Special topics
Additional material

http://handbook.cochrane.org/

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http://editorial-unit.cochrane.org/mecir

Methodological Expectations of Cochrane Intervention Reviews (MECIR)

Methodological standards for the conduct of new Cochrane Intervention Reviews
Version 2.3, 02 December 2013

Jackie Chandler, Rachel Churchill, Julian Higgins, Toby Lasserson and David Tovey

Preface

Cochrane Reviews are seen as exemplifying best practice in the quality of both their conduct and reporting. To maintain this position we need to improve and maintain the quality of our output as standards and expectations for systematic reviews increase generally; we also need to ensure consistency across all Cochrane Review Groups (CRGs) and all reviews. To this end we have undertaken within The Cochrane Collaboration to define Methodological Expectations for Cochrane Intervention Reviews (MECIR).

The documents associated with the MECIR project form a major step forward aimed at ensuring that both researchers and editorial teams have a shared understanding of the expectations of conduct and reporting for reviews in the *Cochrane Database of Systematic Reviews* (CDSR).

The standards below summarize attributes of the conduct of reviews of interventions described in the *Cochrane Handbook* that we have established should be either mandatory or highly desirable for new Cochrane Reviews. The judgments are accompanied by a rationale and reference to the appropriate section of the *Cochrane Handbook*.

We have described the process for determining the expectations for conducting Cochrane Reviews of interventions, including the methods used to develop the initial list and the management of all feedback received during the consultation process (see: www.editorial-unit.cochrane.org/mecir).

Finally, I want to pay tribute to my colleagues who have contributed to this work so far. Julian Higgins and Rachel Churchill have led this initiative with great expertise, perseverance and energy. An important feature of this project, at all levels, has been to reflect the importance of CRG teams and methodologists working alongside one another. Rachel and Julian have been supported by Jackie Chandler and Toby Lasserson, both of whom have made major contributions. In addition, scores of people from within the Collaboration either contributed to the working groups, without which we would have had no 'long-list' of proposed expectations to build on, or the consultation that succeeded the working groups. I hope that the Collaboration recognises the efforts of all the individuals involved and the true sense of collaboration that the work has engendered.

David Tovey, Editor in Chief of *The Cochrane Library*

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Background

- Clear Link between Background and the Methods section. In particular;

  - ➤ Review Objectives
  - ➤ Eligibility Criteria
  - ➤ Outcomes of Interest
  - ➤ Subgroup Analyses
  - ➤ Summary of Findings Tables

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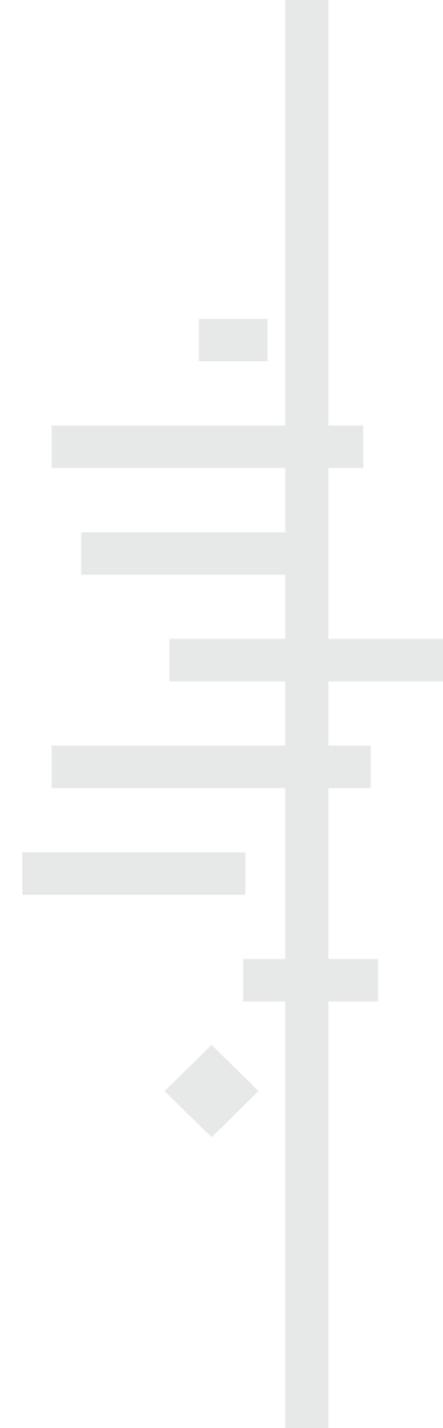
Objectives

- Define in advance the objectives of the review, including participants, interventions, comparators and outcomes (PICO)

- Ensure there is a clear link between objectives and PICO

- Consider any important potential adverse effects of the intervention(s) and ensure that they are addressed
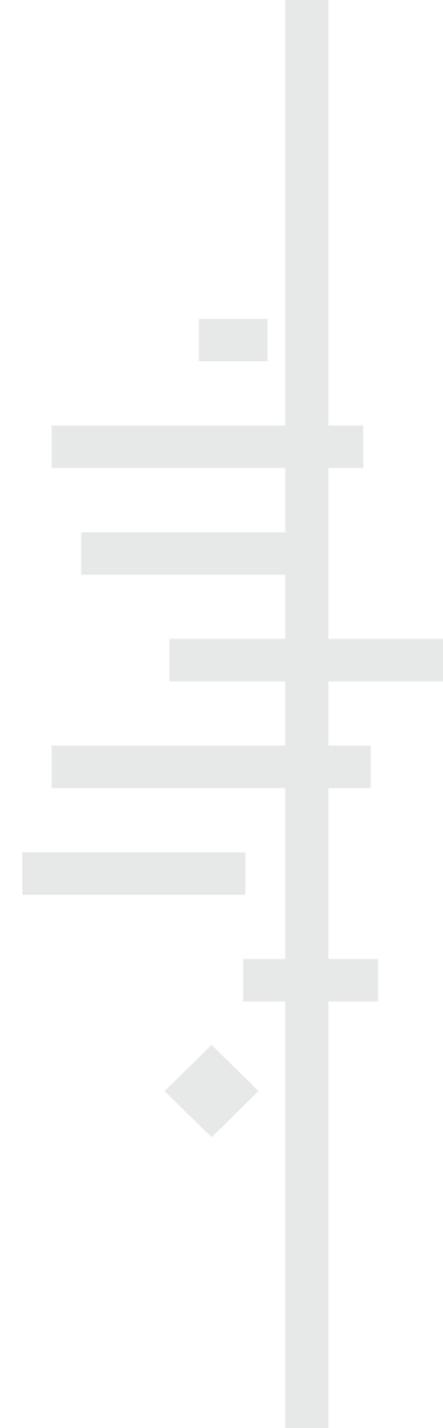
Objectives

To assess the effectiveness of pharmacological interventions for reducing the severity of dementia in people with Down syndrome.

Methods

Criteria for considering studies for this review

Types of studies

Randomised controlled trials. We will include studies comparing relevant anti-dementia pharmacological treatments or supplements with either placebo treatment or no treatment. We will also include relevant studies which compare relevant anti-dementia pharmacological treatments to one another.

Types of participants

Adults (aged 18 years and older) with Down syndrome, but no formal diagnosis of dementia. Where relevant studies of mixed age samples are identified, the full review team will discuss the inclusion of the study until there is a group consensus on its eligibility is reached. Where relevant studies of mixed participant samples are identified, study authors will be contacted to request the subgroup data for Down syndrome participants only.

Types of interventions

Any pharmacological intervention or nutritional supplement which has putative effect on cognitive function. Relevant interventions include donepezil, galantamine, memantine, rivastigmine, piracetem, acetyl-Lcarnitine, antioxidant supplementation, and vitamin supplementation.

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Objectives

To assess the effectiveness of pharmacological interventions or nutritional supplements for reducing the severity of ~~dementia~~cognitive decline in people with Down syndrome.

Methods

Criteria for considering studies for this review

Types of studies

Randomised controlled trials. We will include studies comparing relevant anti-dementia pharmacological treatments or supplements with either placebo treatment or no treatment. We will also include relevant studies which compare relevant anti-dementia pharmacological treatments to one another.
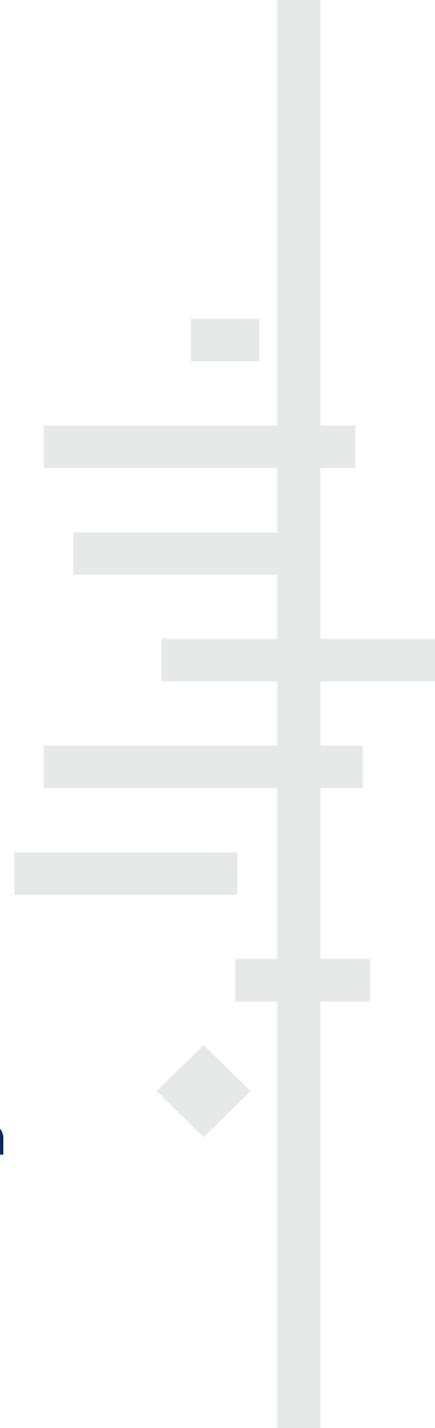
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Types of interventions

Any pharmacological intervention or nutritional supplement which has putative effect on cognitive function. Relevant interventions include donepezil, galantamine, memantine, rivastigmine, piracetem, acetyl-Lcarnitine, antioxidant supplementation, and vitamin supplementation.

Setting the eligibility criteria

- Set pre-defined, unambiguous eligibility criteria

- Define in advance;

  ➢ How studies that include only a subset of relevant participants will be handled

  ➢ Specification of eligible comparator interventions

  ➢ Any restrictions on interventions and comparators, (delivery, dose, duration, intensity)

  ➢ Eligible features of a study's design rather than design labels

Methods

Criteria for considering studies for this review

Types of studies

Randomised controlled trials. We will include studies comparing relevant anti-dementia pharmacological treatments or supplements with either placebo treatment or no treatment. We will also include relevant studies which compare relevant anti-dementia pharmacological treatments to one another.

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Adults (aged 18 years and older) with Down syndrome, but no formal diagnosis of dementia. Where relevant studies of mixed age samples are identified, the full review team will discuss the inclusion of the study until there is a group consensus on its eligibility is reached. Where relevant studies of mixed participant samples are identified, study authors will be contacted to request the subgroup data for Down syndrome participants only.

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⊟ Criteria for considering studies for this review

⊟ *Types of studies*

Randomised controlled trials. We will include studies comparing relevant anti-dementia pharmacological treatments or supplements with either placebo treatment or no treatment. We will also include relevant studies which compare relevant anti-dementia pharmacological treatments to one another.

⊟ *Types of participants*

Adults (aged 18 years and older) with Down syndrome, but no formal diagnosis of dementia. Where relevant studies of mixed age samples are identified, the full review team will discuss the inclusion of the study until there is a group consensus on its eligibility is reached. Where relevant studies of mixed participant samples are identified, study authors will be contacted to request the subgroup data for Down syndrome participants only. If authors are unable or unwilling to provide this data, the study will not be included in the meta-analysis.

⊟ *Types of interventions*

Any pharmacological intervention or nutritional supplement which has putative effect on cognitive function. Relevant interventions include, but are not limited to donepezil, galantamine, memantine, rivastigmine, piracetem, acetyl-Lcarnitine, antioxidant supplementation, and vitamin supplementation. Interventions and comparators are elgibile regardless of delivery, dose, duration, or intensity.

Selecting outcomes

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

- Minimum number of outcomes selected

- 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

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Primary outcomes

We will include studies reporting the following outcomes

1. Improvement in:
   a. cognitive abilities*
   b. global functioning,
   c. behavioural problems*
   d. day to day skills

2. Adverse effects*

Secondary outcomes

1. Carer stress *
2. Institutional/home care, including social care placement breakdown .*
3. Death*
4. Treatment adherence

We will present outcomes indicated by an asterisk (*) in a 'Summary of findings' table. Where data are insufficient, we may provide a narrative account of the outcomes.

⊟ Primary outcomes

~~We will include studies reporting the following outcomes~~

1. Improvement in:
    a. cognitive abilities, as measured by standardised scales, for example, the Dementia Scale for Down Syndrome [DSDS]*
    b. global functioning, as measured by standardised scales, for example, the Dementia Scale for Down Syndrome [DSDS]
    c. behavioural problems, as measured by standardised scales, for example, the American Association of Mental Retardation: Adaptive Behaviour Scale [AAMR: ABS] or the Neuropsychiatric Inventory (NPI).*
    d. day to day skills (as measured by carer report).

2. Adverse effects, including headache, nausea, and dizziness.*

⊟ Secondary outcomes

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)

Where feasible, we will make comparisons at the following specific follow-up periods:

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

~~We will present outcomes indicated by an asterisk (*) in a 'Summary of findings' table. Where data are insufficient, we may provide a narrative account of the outcomes.~~

Outcomes as eligibility criteria

Common Errors	Best Practice
"The evidence base is large, and this will help to reduce the number of studies included in the full review"	The same intervention may be studied in the same population for different purposes (e.g. HRT) and this will ensure only the relevant studies are included
"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"	The primary objective of this review is to assess the adverse effects of this intervention (e.g., aspirin) used for several conditions
"Numerical data for the outcomes of interest could not be obtained (e.g., reported in graphs only). Therefore the study was excluded from this review"	

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
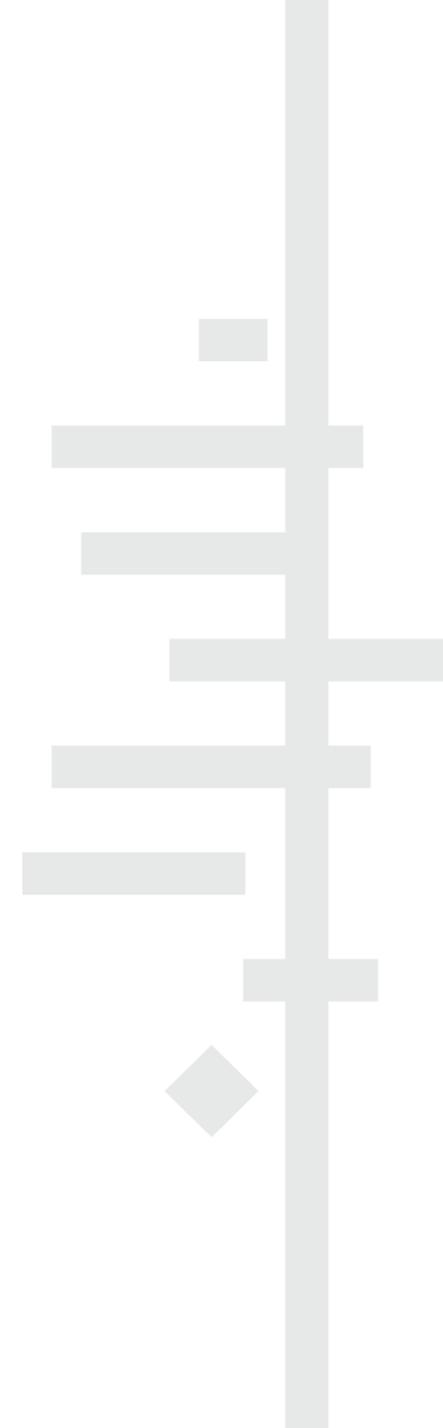
![Cochrane]

Electronic searches

We will search the following databases.

1. Cochrane Central Register of Controlled Trials (CENTRAL), part of the *Cochrane Library*.
2. ALOIS: Specialised Register of the Cochrane Dementia and Cognitive Improvement Group;
3. Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations.
4. EMBASE (Ovid).
5. PsycINFO (Ovid).
6. CINAHL (EBSCOhost).
7. Science Citation Index (Web of Science).
8. Social Sciences Citation Index (Web of Science).
9. Conference Proceedings Citation Index - Science (CPCI-S).
10. Conference Proceedings Citation Index - Social Science & Humanities (CPCI-SSH).
11. Cochrane Database of Systematic Reviews, part of the *Cochrane Library*.
12. Database of Abstracts of Reviews of Effects (DARE), part of the *Cochrane Library*.
13. ClinicalTrials.gov (clinicaltrials.gov/).
14. International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/).

Searching other resources

We will contact relevant authors, key scholars, and the manufacturers of all relevant drugs (see Appendix 1) to ask about reports of unpublished or ongoing trials.

We will also contact Down syndrome voluntary organisations for any further information. E.g. http://www.t21rs.org/ or http://www.fondationlejeune.org/en/.

We will scan the bibliographies of relevant reviews, and included and excluded studies for additional references of interest.

Poll Question #1

If a CRGs "Specialized Register" includes a search of 'ClinicalTrials.gov', I do not need to search this database separately.
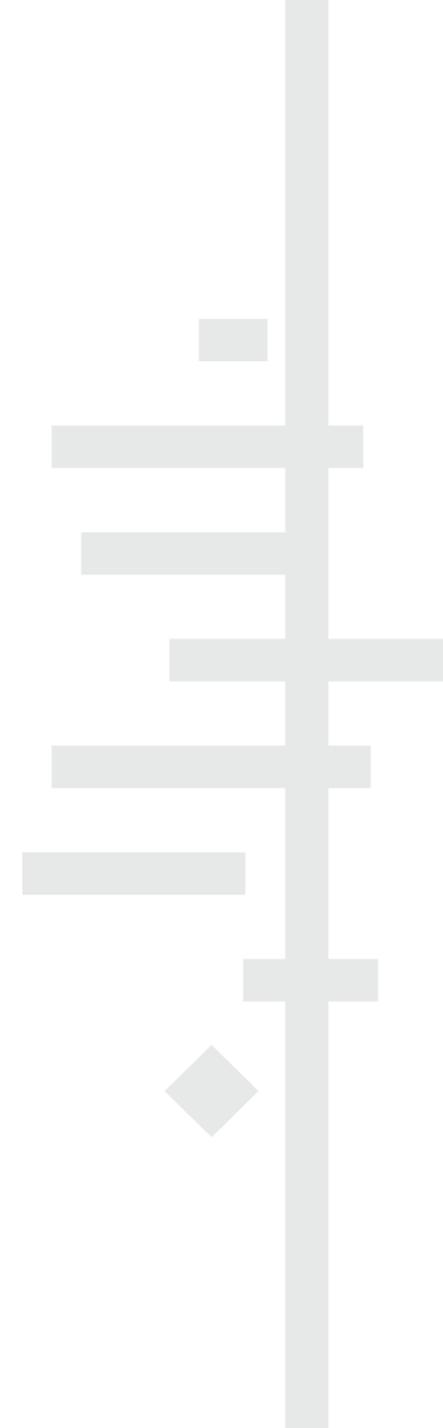
A. TRUE

B. FALSE

Selection and Extraction

- Use (at least) two people working independently

- Define in advance the process for resolving disagreements

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

- Seek key unpublished information that is missing from reports of included studies

Selection of studies

Review authors will independently review the title, abstract, and full text of all records located during the search process and assess each study to determine whether it meets the inclusion criteria for this review.

Selection of studies

Two review ~~Review~~ authors (NL and JH) will independently review the title, abstract, and full text of all records located during the search process and assess each study to determine whether it meets the inclusion criteria for this review. In the event of a disagreement between the authors, the full review team will discuss the decision regarding inclusion until it is resolved.

Risk of Bias

- Use (at least) two people working independently

- Must prepare to justify each decision

- Consider assessing key domains separately for different key outcomes

- Ensure good understanding of domains
  – Allocation Concealment versus Blinding;
  – Incomplete Outcome Data versus Selective Outcome Reporting)

- Draft empty 'shell' tables at Protocol Stage to be populated during review process

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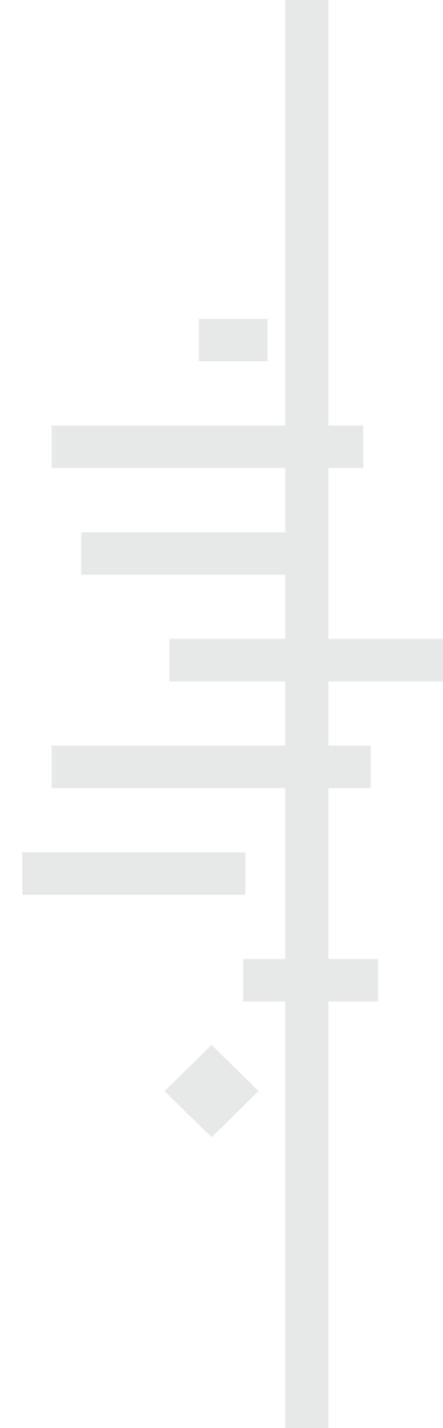
⊟ Risk of bias table 🔧

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk ▼	
Allocation concealment (selection bias)	Unclear risk ▼	
Blinding of participants and personnel (performance bias)	Unclear risk ▼	
Blinding of outcome assessment (detection bias) Investigator-assessed	Unclear risk ▼	
Blinding of outcome assessment (detection bias) Self-reported	Unclear risk ▼	
Incomplete outcome data (attrition bias) Investigator-assessed	Unclear risk ▼	
Incomplete outcome data (attrition bias) Self-reported	Unclear risk ▼	
Selective reporting (reporting bias)	Unclear risk ▼	
Other bias	Unclear risk ▼	

Poll Question #2

If a Study states "Participants were blinded to group allocation", review authors can use this to assess;

A. Allocation concealment

B. Blinding of Participants

Poll Question #3

If a study collects participant 'Pain' data, but fails to report it, review authors can use this information to assess;

A. Incomplete Outcome Data

B. Selective Outcome Reporting

Measures of treatment effect

- Clear plan to undertake (or display) a meta-analysis only if participants, interventions, comparisons and outcomes are judged to be sufficiently similar to ensure an answer that is clinically meaningful

- Ensure the planned effect measures match the outcomes of interest (e.g., time to event data)

Secondary outcomes

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)

Measures of treatment effect

Dichotomous data

For dichotomous outcome data (e.g. institutionalisation or death), we will calculate effect sizes as odds ratio (OR) with 95% confidence intervals (CIs).

Continuous data

We will convert continuous outcome data (e.g. cognitive abilities or behavioural problems) into standardised mean differences (SMDs) and present with 95% CIs, as it is assumed that study authors will use different measurement scales. If continuous outcome data is recorded using the same measurement scale, data will be converted into mean differences (MDs) and presented with 95% CIs. In the event of missing summary data, such as missing standard deviations, we will obtain these, where possible, using calculations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

We will extract both change scores (i.e. change from baseline) and final values. Studies with change-from-baseline outcomes will be combined in a meta-analysis with studies with final measurement outcomes by using the (unstandardised) mean difference method in RevMan ([Review Manager 2012](#)). We will present mean differences in change scores in one subgroup, mean differences in final values in another, and pool both subgroups for an overall analysis ([Higgins 2011](#)).

Time-to-event data

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

Assessment of heterogeneity

- Use of thresholds to diagnose heterogeneity should be avoided due to uncertainty in measures such as I-squared and tau-squared when there are few studies

Data synthesis

We will perform a meta-analysis on the results assuming that we find at least two studies suitable for inclusion. When a meta-analysis is not possible due to an insufficient number of studies, we will provide a narrative description of the study results alone.

We will pool data from studies which are sufficiently similar to make this appropriate. For example, we may pool data from studies studying the same class of drug if the populations are sufficiently similar to make this clinically informative. Where the I^2 measure of heterogeneity exceeds 40%, random effects model will be used.

Data synthesis

We will perform a meta-analysis on the results assuming that we find at least two studies suitable for inclusion. When a meta-analysis is not possible due to an insufficient number of studies, we will provide a narrative description of the study results alone.

We will pool data from studies which are sufficiently similar to make this appropriate. For example, we may pool data from studies studying the same class of drug if the populations are sufficiently similar to make this clinically informative. We will account for the expected heterogeneity among included studies by using a random-effects meta-analysis and the inverse variance weighting method in Review Manager 5 (Review Manager 2012). Where the I^2 measure of heterogeneity exceeds 40%, random effects model will be used.

Unit of Analyses and Missing Data

- Consider <u>all</u> potential Unit of Analysis issues
  - Cross over studies
  - Multiple arm studies
  - Cluster RCTS
  - Within Patient Trial designs

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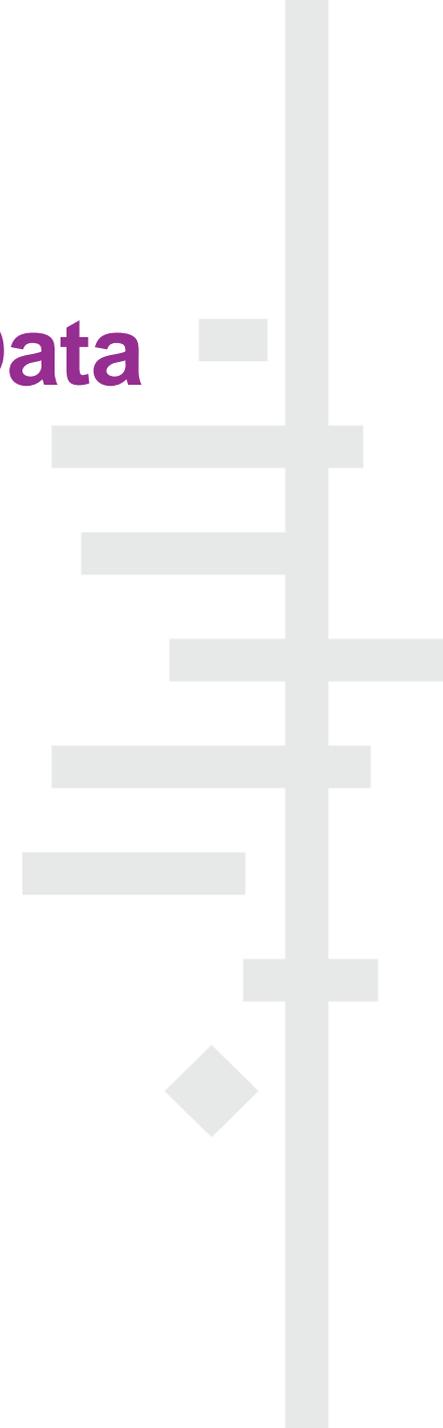
Subgroup Analyses

- Potential effect modifiers must be;
  - ➤ Predefined
  - ➤ Justified
  - ➤ Kept to a minimum

- If subgroup analyses are to be compared, use a <u>formal statistical test</u> to compare them

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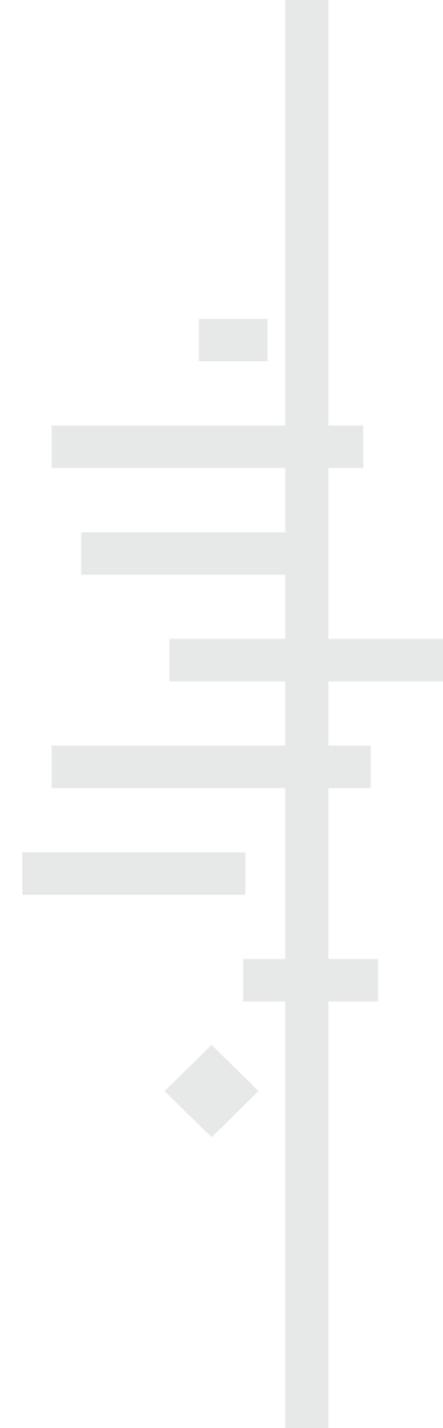
Subgroup analysis and investigation of heterogeneity

Providing that there is a sufficient number of studies, subgroup analyses will examine:

1. The differential effects of the different types of pharmacological intervention (e.g. donepezil versus galantamine);
2. The differential effects of baseline cognitive functioning (mild-to-moderate intellectual disability at baseline versus moderate-severe intellectual disability at baseline versus diagnosis of dementia at baseline);
3. The differential effects of interventions by stage of dementia (e.g. mild versus moderate versus severe); and
4. The differential effects of interventions by the age of the participant (e.g. young adult (18-30 years) versus mature adults (31 to 50 years), versus older adults (50 years plus).

Differences between subgroups will be assessed using the formal Test for Subgroup Differences in Review Manager 5 (Review Manager 2012).
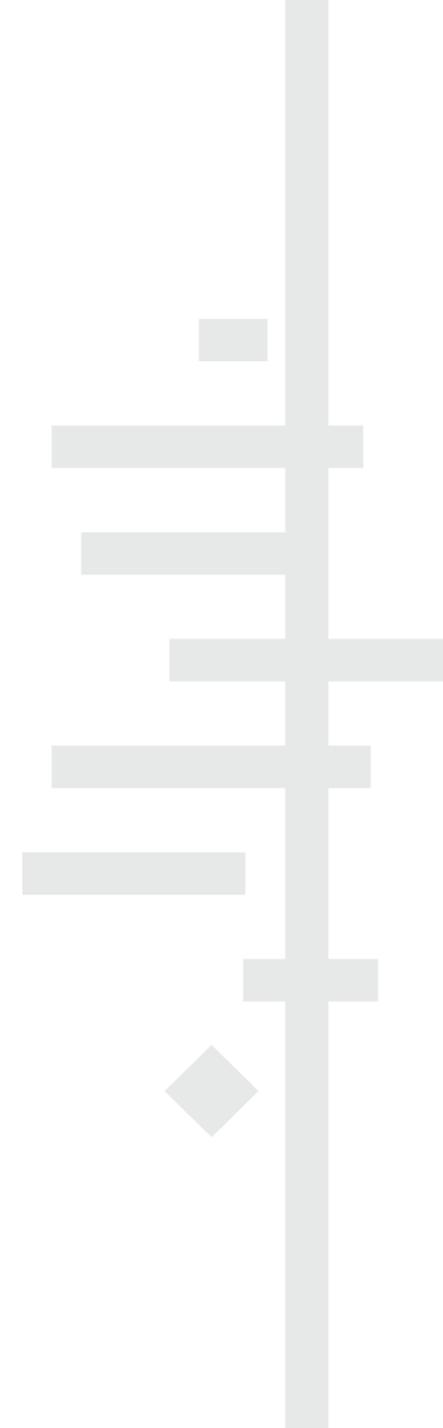
Sensitivity Analyses

- 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

Poll Question #4

'Exploring the difference between results from cluster RCTs and results from non-cluster RCTs' is a;

A. Sensitivity Analysis
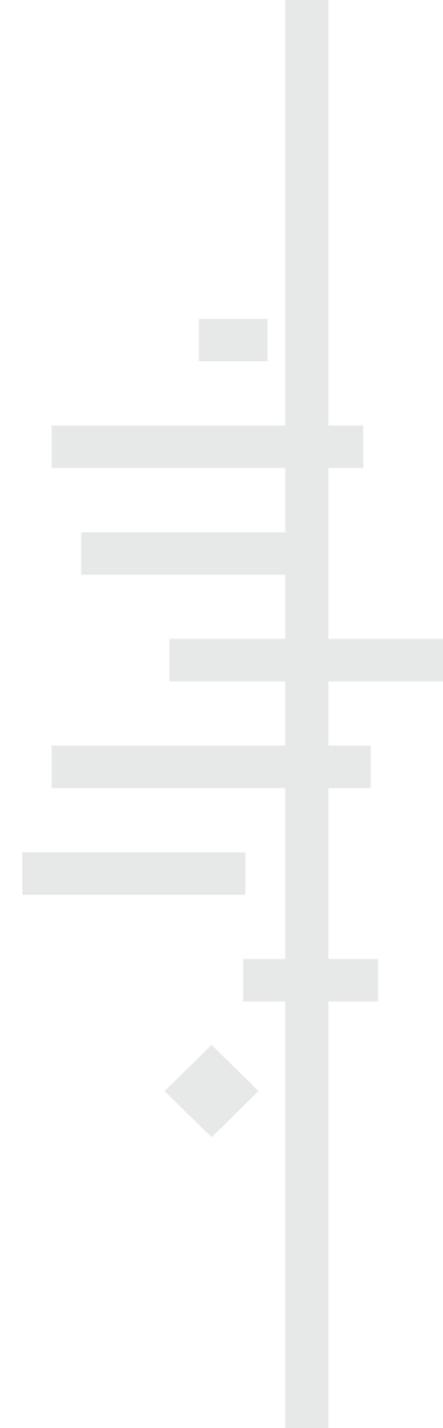
B. Subgroup Analysis

Poll Question #5

'Exploring the difference between results from male participants and results from female participants' is a;
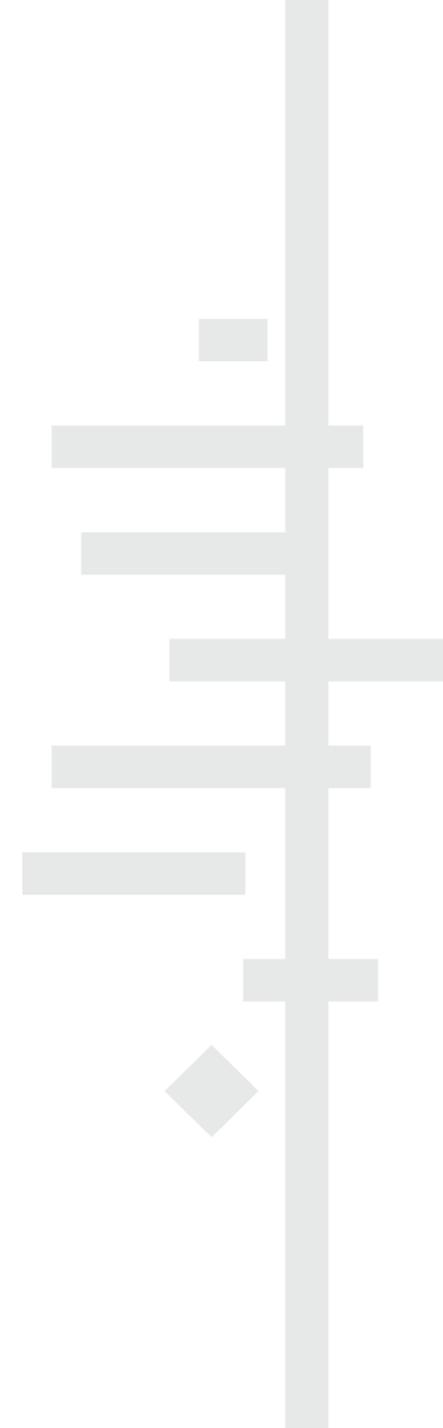
A. Sensitivity Analysis

B. Subgroup Analysis

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Poll Question #6

'Exploring the difference between results from blinded studies and results from unblinded studies' is a;

A.   Sensitivity Analysis

B.   Subgroup Analysis

Summary of Findings Table

- No plan in the protocol for including a SoF table

- Plan included as a brief sentence at the end of an existing section. No clear plan regarding:
  - Choice of comparisons and outcomes
  - How quality will be assessed using GRADE
  - Who will be involved in assessing quality

Avoiding SoF table common errors

- Separate, headed protocol section on SoF tables

- One table per comparison (not per outcome)

- Seven clinically important outcomes

  ➤ Consistent with review Objectives/PICO

  ➤ Balanced overview – showing both 'benefit' and 'harm'

- All GRADE considerations clearly described

- Quality assessed by two (unbiased) review authors

- Draft empty 'shell' tables at Protocol Stage to be populated during review process

Data synthesis

We will perform a meta-analysis on the results assuming that we find at least two studies suitable for inclusion. When a meta-analysis is not possible due to an insufficient number of studies, we will provide a narrative description of the study results alone.

We will pool data from studies which are sufficiently similar to make this appropriate. For example, we may pool data from studies studying the same class of drug if the populations are sufficiently similar to make this clinically informative.

We will classify the quality of the evidence into one of four categories according to the GRADE approach. We will present the results of the GRADE assessment in a 'Summary of findings' table.

⊟ *Data synthesis*

We will perform a meta-analysis on the results assuming that we find at least two studies suitable for inclusion. When a meta-analysis is not possible due to an insufficient number of studies, we will provide a narrative description of the study results alone.

We will pool data from studies which are sufficiently similar to make this appropriate. For example, we may pool data from studies studying the same class of drug if the populations are sufficiently similar to make this clinically informative.

~~We will classify the quality of the evidence into one of four categories according to the GRADE approach. We will present the results of the GRADE assessment in a 'Summary of findings' table.~~

'Summary of findings' table

Based on the methods described in Chapter 11 of the Cochrane Handbook for Systematic Reviews of Interventions (Schünemann2011), we will prepare a 'Summary of findings' table to present the meta-analysis results. Results of the meta-analysis will be presented for the main comparisons of the review, and the following outcomes;

- improvement in cognitive abilities
- Improvement in behavioural problems
- Adverse effects
- Carer stress
- Death

For each assumed risk cited in the table(s), we will provide a source and rationale, and the GRADE system will be used to rank the quality of the evidence using GRADEprofiler(GRADEpro) software (Schünemann2011). If meta-analysis is not possible, we will present results in a narrative 'Summary of findings' table format (drawing on Chan 2011 as an example).

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Comparison 1: donepezil versus placebo

Patient or population: people with Down syndrome
Setting: clinic
Intervention: donepezil
Comparison: placebo

Outcomes	Absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with donepezil**				
Cognitive abilities (*insert measurement tool*) Follow-up: (*X weeks*)						
Behavioural problems (*insert measurement tool*) Follow-up: (*X weeks*)						
Adverse events (*insert measurement tool*) Follow-up: (*X weeks*)						
Carer stress (*insert measurement tool*) Follow-up: (*X weeks*)						
Death (*insert measurement tool*) Follow-up: (*X weeks*)						

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; GRADE: Grades of Recommendations, Assessment, Development and Evaluation; RR: risk ratio; OR: odds ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
**Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

General errors

- Writing in past tense

- 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
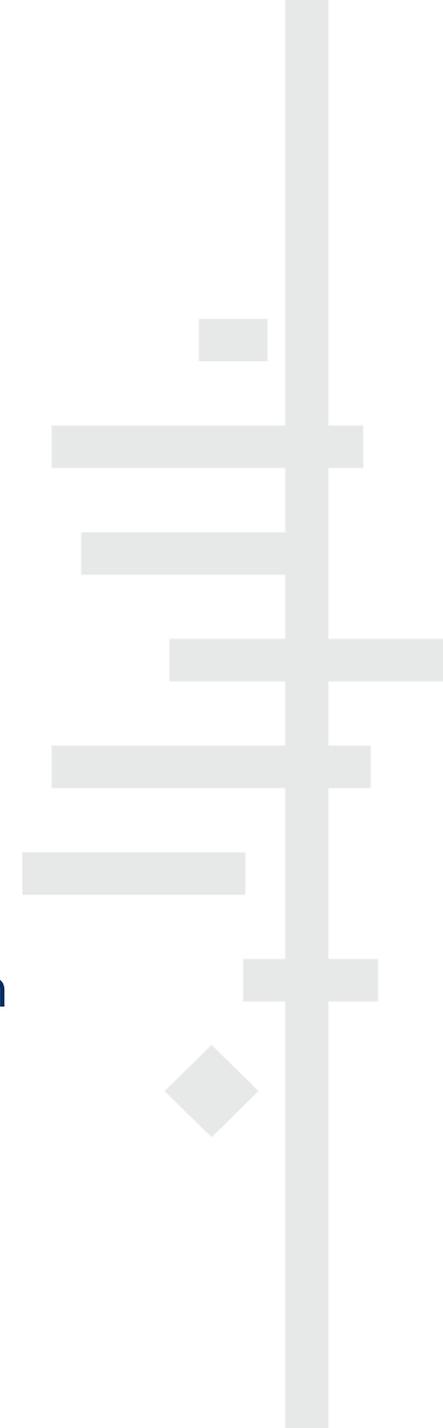
Any Questions?

(nlivingstone@cochrane.org)