Introduction to new Cochrane Handbook for Systematic Reviews of Interventions (Version 6)

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Senior Editor of Cochrane Handbook for Systematic Reviews of Interventions
Co-convenor of Cochrane Bias Methods Group

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Senior Editor of Cochrane Handbook for Systematic Reviews of Interventions
Co-convenor of Cochrane Qualitative and Implementation Methods Group
Outline

- Introduction and background to the Handbook (Julian)
- General structure and opening sections (James)
- Core quantitative topics (Julian)
- Specific perspectives on reviews (James)
- Some further topics (Julian)
- Online-only materials and closing remarks (James)
SECTION VI:
PREPARING AND MAINTAINING SYSTEMATIC REVIEWS
(The Cochrane Collaboration Tool Kit)

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Acknowledgements:
Kay Dickerson, Andrew Horsman, and Chris Muller were responsible for writing and editing this section of the Handbook. The contents of the Handbook have been reviewed by the members of the Steering Group who were involved in the preparation of the Tool Kit. The steering group includes a number of national and international experts in the field of systematic reviews. The handbook has been compiled by the Cochrane Collaboration, with the support of the Cochrane Library, a worldwide network of researchers working in the field of systematic reviews.
8 customer reviews

4.8 out of 5 stars

- 5 star: 88%
- 4 star: 12%
- 3 star: 0%
- 2 star: 0%
- 1 star: 0%

Review this product

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Write a customer review

Showing 1-8 of 8 reviews

Lea

Five Stars
26 June 2017
Format: Hardcover | Verified Purchase
quick and good quality

Ashleigh

Four Stars
5 January 2016
Format: Hardcover | Verified Purchase

Very thorough
Michael Smith

★★★★☆ Good review, though too advanced for beginners
July 28, 2017
Format: Hardcover | Verified Purchase

This is a very good book for systematic review (basically the gold standard), but my wife didn’t find it as useful as she had hoped because it was a little too advanced for her.

kinnickkinnick

★★★★☆ A worthwhile reference and study guide
September 17, 2015
Format: Hardcover | Verified Purchase

An excellent reference for pharmaceutical/medical writers as well as researchers in medicine and public health, possibly along with a good text on meta-analysis.

what2bee

★★☆☆☆ Just dull. That is the reason for the 3 stars
September 9, 2015
Format: Hardcover | Verified Purchase

This is the standard for meta-analyses. It is fairly thorough, just dull. That is the reason for the 3 stars. It is probably wrong to expect this to be something other than dull. Recent changes are available on the Cochrane web site.
Target audience

- Cochrane Review authors and editors
  - Traditionally many authors were novices at research, but not any more

- Non-Cochrane systematic review authors

- Researchers into methodology of systematic reviews

- Students

- Users of Cochrane Reviews
The Cochrane Handbook for Systematic Reviews of Interventions is the official document that describes in detail the process of preparing and maintaining Cochrane systematic reviews on the effects of healthcare interventions.
<table>
<thead>
<tr>
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<td>Brit J Anaesth</td>
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<td>BMC Med</td>
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<tr>
<td>Scientific Reports</td>
<td>69</td>
<td>Health Technol Assess</td>
<td>49</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>63</td>
<td>TOTAL JOURNAL ARTICLES</td>
<td>20,243</td>
</tr>
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</table>
Development of the new version

- Planning started in 2009 between Julian and Sally Green
  - direct correspondence with all CRGs
  - fleshed out a plan
  - instigated updates with Methods Groups or other authors

- Slow progress
  - change of editorial team in 2012
  - MECIR developed and integrated into version 5.2 (released June 2017)
  - recruited a new team…
The team

- Numerous contributing authors and Methods Groups
- Julian Higgins (Senior editor)
- James Thomas (Senior editor)
- Tianjing Li (Associate scientific editor)
- Matt Page (Associate scientific editor)
- Vivian Welch (Associate scientific editor)
- Miranda Cumpston (Implementation editor)
- Jackie Chandler (Managing editor)
- Laura Mellor (Editorial assistant)
General structure

James Thomas
Planning version 6

Part 1: Cochrane reviews
1. Introduction
2. Preparing a Cochrane review
3. Maintaining reviews: updates, amendments and feedback
4. Guide to the contents of a Cochrane protocol and review

Part 2: General methods for Cochrane reviews
5. Defining the review question and developing criteria for including studies
6. Searching for studies
7. Selecting studies and collecting data
8. Assessing risk of bias in included studies
9. Analysing data and undertaking meta-analyses
10. Addressing reporting biases
11. Presenting results and ‘Summary of findings’ tables
12. Interpreting results and drawing conclusions

Part 3: Special topics
13. Including non-randomized studies
14. Adverse effects
15. Incorporating economics evidence
16. Special topics in statistics
17. Patient-reported outcomes
18. Reviews of individual patient data
19. Prospective meta-analysis
20. Qualitative research and Cochrane reviews
21. Reviews in public health and health promotion
22. Overviews of reviews

Additional material
From version 5 to 6

Part 1: Cochrane Reviews
Chapter 1: Introduction
Chapter 2: Planning and preparation of a Cochrane review
Chapter 3: Maintaining reviews: updates, amendments and feedback
Chapter 4: Guide to the contents of a Cochrane protocol and review

Part 2: General methods for Cochrane Reviews
Chapter 5: Defining the review question and developing criteria for including studies
Chapter 6: Searching for studies
Chapter 7: Selecting studies and collecting data
Chapter 8: Assessing risk of bias in included studies
Chapter 9: Analysing data and undertaking meta-analyses
Chapter 10: Addressing reporting biases [PDF] new
Chapter 11: Completing ‘Summary of findings’ tables and grading the confidence in or quality of the evidence
Chapter 12: Interpreting results and drawing conclusions

Part 3: Special topics
Chapter 13: Including non-randomized studies
Chapter 14: Adverse effects
Chapter 15: Incorporating economics evidence
Chapter 16: Special topics in statistics
Chapter 17: Patient-reported outcomes
Chapter 18: Reviews of individual patient data
Chapter 19: Prospective meta-analysis
Chapter 20: Qualitative research and Cochrane reviews
Chapter 21: Reviews in public health and health promotion
Chapter 22: Overviews of reviews

Chapter I: Introduction
Chapter II: Planning a Cochrane review
Chapter III: Reporting a review
Chapter IV: Updating a review
Chapter V: Overviews of reviews
Core methods

1. Starting a review
2. Determining the scope of the review and the questions it will address
3. Defining the criteria for including studies and how they will be grouped for the synthesis
4. Searching for and selecting studies
5. Collecting data
6. Choosing effect measures and computing estimates of effect
7. Considering bias and conflicts of interest among the included studies
8. Assessing risk of bias in a randomized trial
9. Summarizing studies and preparing for the synthesis
10. Analysing data and undertaking meta-analyses
11. Undertaking network meta-analyses
12. Synthesizing and presenting findings using other methods
13. Assessing risk of bias due to missing results in a synthesis
14. Completing 'Summary of findings' tables and grading the certainty of the evidence
15. Interpreting results and drawing conclusions
From version 5 to 6

Part 1: Cochrane Reviews
Chapter 1: Introduction
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Chapter 16: Special topics in statistics
Chapter 17: Patient-reported outcomes
Chapter 18: Reviews of individual patient data
Chapter 19: Prospective meta-analysis
Chapter 20: Qualitative research and Cochrane reviews
Chapter 21: Reviews in public health and health promotion
Chapter 22: Overviews of reviews (now online Chapter V)

Specific perspectives in reviews
16. Equity and specific populations
17. Intervention complexity
18. Patient reported outcomes
19. Adverse effects
20. Economics evidence
21. Qualitative evidence

Other topics
22. Prospective approaches to cumulating evidence
23. Including variants on randomized trials
24. Including non-randomized studies
25. Assessing risk of bias in a non-randomized study
26. Individual participant data
Core methods
1. Starting a review
2. Determining the scope of the review and the questions it will address
3. **Defining the criteria for including studies and how they will be grouped for the synthesis**
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Specific perspectives in reviews
16. **Equity and specific populations**
17. **Intervention complexity**
18. Patient reported outcomes
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20. Economics evidence
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Other topics
22. **Prospective approaches to cumulating evidence**
23. Including variants on randomized trials
24. Including non-randomized studies
25. **Assessing risk of bias in a non-randomized study**
26. Individual participant data

About Cochrane Reviews
I. Introduction
II. Planning a Cochrane Review
III. Reporting a review
IV. Updating a review
V. Overviews of Reviews
Methodological expectations of Cochrane Intervention reviews (MECIR)

Methodological Expectations of Cochrane Intervention Reviews (MECIR)

Standards for the reporting of Plain language summaries in new Cochrane Intervention Reviews 2013
Opening sections

James Thomas
Starting a review

- Why do a systematic review?
- What is the review question?
- Who should do a systematic review?
  - Involving consumers and other stakeholders
- The importance of reliability
- Protocol development
- Data management and quality assurance
Determining the scope of the review and the questions it will address

- Rationale for well-formulated questions
- Aims of reviews of interventions
- Defining the scope of the review question
  - Consideration of the review’s PICO
  - Broad vs narrow reviews; ‘lumping’ vs ‘splitting’
- Ensuring the review addresses the right questions
  - Using priority-setting exercises to define review questions
  - Engaging stakeholders; considering issues relating to equity
- Methods and tools for structuring the review
  - Logic models
  - Economic data
The three stages of PICO

- The **review PICO** (planned at the protocol stage) is the PICO on which eligibility of studies is based (what will be included and what excluded from the review).

- The **PICO for each synthesis** (also planned at the protocol stage) defines the question that each specific synthesis aims to answer, determining how the synthesis will be structured, specifying planned comparisons (including intervention and comparator groups, any grouping of outcome and population subgroups).

- The **PICO of the included studies** (determined at the review stage) is what was actually investigated in the included studies.
Defining the criteria for including studies and how they will be grouped for synthesis

- Articulation of the review and comparison PICO
  - Defining type of participants: which people and populations?
  - Defining interventions and how they will be grouped
  - Defining which comparisons will be made
  - Selecting, prioritizing and grouping review outcomes
- Determining which study designing to include
  - Randomized trials & non-randomized studies
- Eligibility based on publication status and language
### Table 3.2.b: A process for planning intervention groups for synthesis

<table>
<thead>
<tr>
<th>Step</th>
<th>Considerations</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Identify intervention characteristics that may modify the effect of the intervention.</td>
<td>Consider whether differences in interventions characteristics might modify the size of the intervention effect importantly. Content-specific research literature and expertise should inform this step. The TIDieR checklist – a tool for describing interventions – outlines the characteristics across which an intervention might differ (Hoffmann et al 2014). These include ‘what’ materials and procedures are used, ‘who’ provides the intervention, ‘when and how much’ intervention is delivered. The ICAT-SR tool provides equivalent guidance for complex interventions (Lewin et al 2017).</td>
<td><strong>Exercise interventions</strong> differ across multiple characteristics, which vary in importance depending on the review. In a review of exercise for osteoporosis, whether the exercise is weight-bearing or non-weight-bearing may be a key characteristic, since the mechanism by which exercise is thought to work is by placing stress or mechanical load on bones (Howe et al 2011). Different mechanisms apply in reviews of exercise for knee osteoarthritis (muscle strengthening), falls prevention (gait and balance), cognitive function (cardiovascular fitness). The differing mechanisms might suggest different ways of grouping interventions (e.g. by intensity, mode of delivery) according to potential modifiers of the intervention effects.</td>
</tr>
</tbody>
</table>
Searching for and selecting studies

- General issues
  - The role of the information specialist / librarian
  - Minimising bias

- Sources to search
  - Bibliographic databases; trials registers; regulatory agency sources and clinical study reports

- Designing search strategies
  - Sensitivity vs precision; controlled vocabularies; identifying fraudulent studies / retracted publications

- Selecting studies
  - Software and new technologies
Core quantitative topics (bias, statistics etc)

Julian Higgins
Collecting data

- Collecting data from clinical study reports
- Semi-automation
  - “At the time of writing, we cannot recommend a specific tool for automating data extraction for routine systematic review production”
- Dealing with suspicions of misconduct
Effect measures

- A new chapter on effect measures
- Mostly a re-arrangement of existing material
- Includes computations to get data into the right format (SDs from P values, etc)
- Additional content on other effect measures for continuous outcomes (e.g. ratio of means)
Risk of bias

- Chapter 7: Considering bias and conflicts of interest among the included studies
- Chapter 8: Assessing risk of bias in a randomized trial
- Chapter 13: Assessing risk of bias due to missing results in a synthesis

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- Chapter 24: Including non-randomized studies
- Chapter 25: Assessing risk of bias in a non-randomized study
<table>
<thead>
<tr>
<th>RoB 1</th>
<th>RoB 2</th>
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<tbody>
<tr>
<td><strong>Outcome-based assessment</strong></td>
<td><strong>Result-based assessment</strong></td>
</tr>
<tr>
<td>Random sequence generation <em>(selection bias)</em></td>
<td>Bias arising from the randomization process</td>
</tr>
<tr>
<td>Allocation concealment <em>(selection bias)</em></td>
<td></td>
</tr>
<tr>
<td>Blinding of participants and personnel <em>(performance bias)</em></td>
<td>Bias due to deviations from intended interventions</td>
</tr>
<tr>
<td>Incomplete outcome data <em>(attrition bias)</em></td>
<td>Bias due to missing outcome data</td>
</tr>
<tr>
<td>Blinding of outcome assessment <em>(detection bias)</em></td>
<td>Bias in measurement of the outcome</td>
</tr>
<tr>
<td>Selective reporting <em>(reporting bias)</em></td>
<td>Bias in selection of the reported result</td>
</tr>
<tr>
<td>Other bias</td>
<td>[Not available]</td>
</tr>
<tr>
<td>[Not available]</td>
<td>Overall bias</td>
</tr>
<tr>
<td>Bias arising from the randomization process</td>
<td>Risk of bias judgement</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>1.1 Was the allocation sequence random?</td>
<td>Optional: What is the predicted direction of bias arising from the randomization process?</td>
</tr>
<tr>
<td>1.2 Was the allocation sequence concealed until participants were enro...</td>
<td></td>
</tr>
<tr>
<td>1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bias due to deviations from intended interventions</th>
<th>Risk of bias judgements</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Were participants aware of their assigned intervention during the trial?</td>
<td>Low / High / Some concerns</td>
</tr>
<tr>
<td>2.2 Were carers and people delivering the interventions aware of participants' allocated intervention during the trial?</td>
<td></td>
</tr>
<tr>
<td>2.3 If Y / PY / N / NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?</td>
<td></td>
</tr>
<tr>
<td>2.4 If Y / PY to 2.3: Were these deviations from intended intervention balanced between groups?</td>
<td></td>
</tr>
<tr>
<td>2.5 If N / PN / NI to 2.4: Were these deviations likely to has affected the outcome?</td>
<td></td>
</tr>
<tr>
<td>2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?</td>
<td></td>
</tr>
<tr>
<td>2.7 If N / PN / NI to 2.6: Was there potential for a substantial impact (on the result) of the unbalanced baseline?</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Bias judgement</th>
<th>Risk of bias judgements</th>
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<td>Optional: What is the predicted direction of bias due to deviations from intended intervention?</td>
<td>Low / High / Some concerns</td>
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<tr>
<th>Bias in measurement of the outcome</th>
<th>Risk of bias judgement</th>
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<tbody>
<tr>
<td>4.1 Was the outcome measured in the way that was planned?</td>
<td>Optional: What is the predicted direction of bias in measurement of the outcome?</td>
</tr>
<tr>
<td>4.2 Was the outcome measured in the way that was planned?</td>
<td>Low / High / Some concerns</td>
</tr>
<tr>
<td>4.3 If Y / PY / N / NI to 4.1: Could assessment of the outcome have been influenced by knowledge of the intervention?</td>
<td></td>
</tr>
<tr>
<td>4.4 If Y / PY / N / NI to 4.3: Could assessment of the outcome have been influenced by knowledge of the intervention?</td>
<td></td>
</tr>
<tr>
<td>4.5 If Y / PY / N / NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of the intervention?</td>
<td></td>
</tr>
</tbody>
</table>

**Risk of bias judgments**
- Low risk of bias
- Some concerns
- High risk of bias

**Signalling questions**
Answers Y / PY / N / PN / NI

**Distinction between effect of assignment to intervention and effect of adhering to intervention**

**Selection of reported result**
more specific than previous ‘selective reporting’ domain
Non-reporting not addressed

**Overall risk of bias**
Determined by ‘worst’ domain
Direction of travel

Concerns over conflicts of interest

TACIT

Risk of bias within studies
RoB 2; ROBINS-I

Risk of bias across studies
RoB-ME

Sources of heterogeneity

Study limitations

Publication bias

Inconsistency

Indirectness

GRADE
Meta-analysis and its alternatives

- New guidance on
  - fixed-effect vs random-effects models
  - interpreting random-effects meta-analysis using prediction intervals
  - better methods for random-effects meta-analysis
  - synthesis when meta-analysis can’t (or shouldn’t) be done
    - simple statistical tests
    - methods to avoid (e.g. vote counting statistical significance)
    - structured tables and plots

Awaiting implementation in RevMan
Network meta-analysis and indirect comparisons
Network meta-analysis and indirect comparisons
Specific perspectives on reviews

James Thomas
Equity and specific populations

- Defining health equity
  - (i.e. the absence of avoidable and unfair differences in health)
  - Using logic models and theories of change to articulate hypotheses about equity
  - Consideration of study designs and outcomes

- Consideration of equity throughout the review
Intervention complexity

- Intervention complexity, rather than ‘complex intervention’
- Three ways of understanding complexity
  - Number of intervention components
  - Interactions between components / context
  - The wider system within which the intervention is introduced
- Chapter mainly focuses on the first two
- Considers complexity throughout the review process, using a Cochrane review as an example
Patient-reported outcomes

- Introduction to patient-reported outcomes (PROs)
  - What are PROs?
  - Why use PROs?

- Consideration of PROs throughout the review process with a particular focus on:
  - Measurement
  - Reliability
  - Validity
  - Responsiveness
  - Reporting bias
  - How to select which PRO measure to use
Adverse effects

- All reviews should try to consider adverse aspects of interventions
- This is particularly important when evidence on the potential for harm may affect treatment or policy decisions
- Adverse effects data are not always handled with as much rigour as primary beneficial outcomes
- Authors need to consider issues such as inadequate monitoring and incomplete reporting
- The inclusion of non-randomized studies may be required if adverse effects are to be properly investigated
- The chapter gives guidance on this issue throughout the review process
Economics evidence

- Policy and practice decisions often need to be taken in the light of evidence about the (relative) costs of interventions
- Optimal decisions require best evidence on cost-effectiveness
- There are two possible methodological frameworks:
  - Brief economic commentary
  - Integrated full systematic review of economic evidence
- Chapter gives detailed guidance on how to construct brief economic commentaries in Cochrane reviews.
- Aims to provide guidance without requiring support from health economist
- Is a ‘minimal framework’ for including an economic perspective and we are currently discussing with the group where and how to include guidance on full integrated systematic reviews of economic evidence
Qualitative research and Cochrane Reviews

- How a qualitative evidence synthesis can add value
  - Understanding intervention complexity
  - Contextual variations
  - Implementation
  - Stakeholder preferences and experiences

- How a mixed-method / multicomponent design can be used to integrate a QES with a corresponding intervention review or within a single review

- Provides guidance throughout the review process – also signposts other key resources
Further topics

Julian Higgins
Prospective approaches to accumulating evidence

- New chapter covering
  - evidence surveillance and signals for updating
  - ‘living’ systematic reviews
  - prospectively planned meta-analyses
  - sequential approaches to meta-analysis
    - “Formal sequential meta-analysis approaches are discouraged for updated meta-analyses in most circumstances within the Cochrane context. They should not be used for the main analyses, or to draw main conclusions”
Non-standard trial designs and non-randomized studies

- Chapter 23: Including variants on randomized trials
  - cluster-randomized trials
  - cross-over trials
  - more than two treatment arms
- Chapter 24: Including non-randomized studies
- Chapter 25: Assessing risk of bias in a non-randomized study
  - ROBINS-I: core considerations for
    - follow-up studies
    - before-after studies (including interrupted time series)
    - controlled before-after studies
Online-only materials and closing remarks

James Thomas
Online chapters

- Introduction
- Planning a Cochrane Review
- Reporting a review
- Updating a review
- Overviews of Reviews
Overviews of Reviews

- What is a Cochrane Overview of Reviews?
- Specific characteristics:
  - Sufficiently up-to-date
  - Sufficiently homogeneous in terms of their PICO
  - Sufficiently homogeneous in terms of what and how outcome data are presented
  - Sufficiently low risk of bias or high methodological quality
- When a Cochrane Overview of Reviews is needed / appropriate
- Detailed methods for conducting a Cochrane Overview of Reviews
What happens next?

- Submission of book to Wiley later this week
- All chapters go up on intranet (PDFs) later this week
- Copy edits from Wiley get implemented
- Copy-edited version turned into open browseable version
- Book published later this year

- Anything can be implemented now (possibly CRG-dependent)
- Some methods to be implemented in RevMan Web
Thank you

Julian Higgins
James Thomas