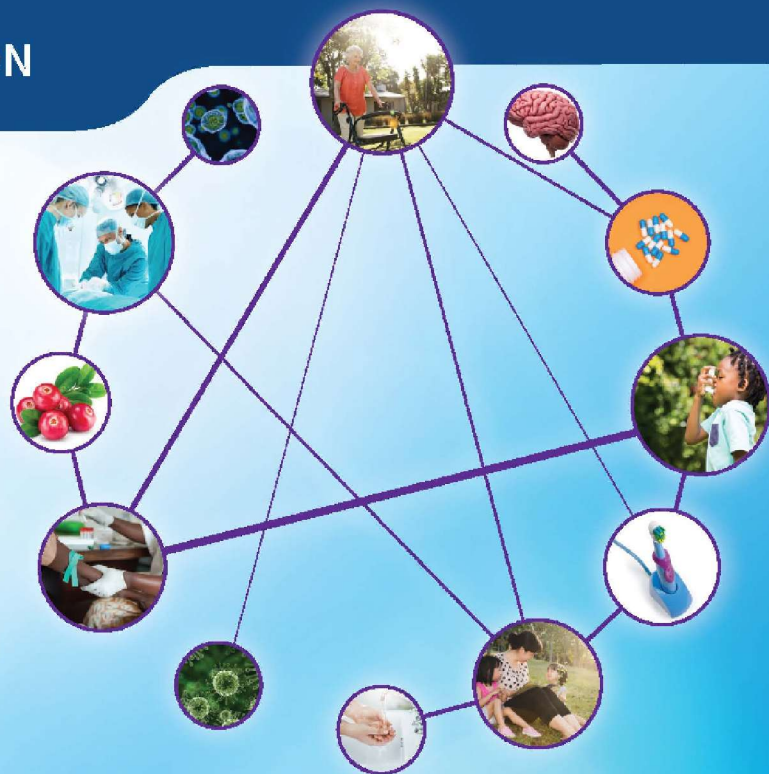


Cochrane Handbook for

Systematic Reviews of Interventions

SECOND EDITION



Edited by

Julian P. T. Higgins

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WILEY Blackwell

**Cochrane Handbook for
Systematic Reviews of
Interventions**

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Second Edition

*Edited by Julian P.T. Higgins, James Thomas,
Jacqueline Chandler, Miranda Cumpston, Tianjing Li,
Matthew J. Page and Vivian A. Welch*



WILEY Blackwell

This edition first published 2019
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This work is a co-publication between The Cochrane Collaboration and John Wiley & Sons Ltd.

Edition History

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Registered Office(s)

John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA

John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

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9600 Garsington Road, Oxford, OX4 2DQ, UK

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Library of Congress Cataloging-in-Publication Data

Names: Higgins, Julian P. T., editor. | Cochrane Collaboration, issuing body.

Title: Cochrane handbook for systematic reviews of interventions / edited by Julian P.T. Higgins, James Thomas, Jacqueline Chandler, Miranda Cumpston, Tianjing Li, Matthew J. Page, Vivian A. Welch.

Other titles: Cochrane book series.

Description: Second edition. | Hoboken, NJ : Wiley-Blackwell, 2019. | Series:

Cochrane book series | Includes bibliographical references and index. |

“This work is a co-publication between The Cochrane Collaboration and John Wiley & Sons Ltd.”—ECIP title page verso.

Identifiers: LCCN 2019024539 | ISBN 9781119536628 (hardback) | ISBN

9781119536611 (adobe pdf) | ISBN 9781119536659 (epub)

Subjects: | MESH: Outcome and Process Assessment (Health Care) |

Evidence-Based Medicine—methods | Meta-Analysis as Topic | Systematic Reviews as Topic

Classification: LCC RA427.3 | NLM W 84.41 | DDC 362.1—dc23 LC record available at <https://lccn.loc.gov/2019024539>

Cover image: © ittipon2002/iStock.com, © Eraxion/iStock.com, © Raycat/iStock.com, © atoss/iStock.com, © anmbph/iStock.com, © shapecharge/iStock.com, © adventr/iStock.com, © PeopleImages/iStock.com, © Abel Mitja Varela/iStock.com, © kiankhon/iStock.com, © Wavebreakmedia/iStock.com, © 9comeback/iStock.com, © leoniepow/iStock.com

Cover design by Wiley

Set in 10/12pt SourceSansPro by SPi Global, Pondicherry, India

Printed in the UK by Bell & Bain Ltd, Glasgow

HB printing 10 9 8 7 6 5 4 3 2 1

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Preface

‘First, do no harm’ is a principle to which those who would intervene in the lives of other people are often called to ascribe. However, in this era of data deluge, it is not possible for individual decision makers to ensure that their decisions are informed by the latest, reliable, research knowledge; and without reliable information to guide them, they can cause harm, even though their intentions may be good. This is the core problem that the founder of Cochrane, Sir Iain Chalmers, aimed to address through the provision of systematic reviews of reliable research.

By synthesizing the results of individual studies, systematic reviews present a summary of all the available evidence to answer a question, and in doing so can uncover important knowledge about the effects of healthcare interventions. Systematic reviews undertaken by Cochrane (Cochrane Reviews) present reliable syntheses of the results of multiple studies, alongside an assessment of the possibility of bias in the results, contextual factors influencing the interpretation and applicability of results, and other elements that can affect certainty in decision making. They reduce the time wasted by individuals searching for and appraising the same studies, and also aim to reduce research waste by ensuring that future studies can build on the body of studies already completed.

A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question. It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made. The key characteristics of a systematic review are:

- a clearly stated set of objectives with pre-defined eligibility criteria for studies;
- an explicit, reproducible methodology;
- a systematic search that attempts to identify all studies that meet the eligibility criteria;
- an assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias; and
- a systematic presentation, and synthesis, of the characteristics and findings of the included studies.

For twenty-five years, Cochrane Reviews have supported people making healthcare decisions, whether they are health professionals, managers, policy makers, or individuals making choices for themselves and their families. The *Cochrane Handbook for*

Systematic Reviews of Interventions (the Handbook) provides guidance to authors for this work.

About Cochrane

Cochrane is a global network of health practitioners, researchers, patient advocates and others, with a mission to promote evidence-informed health decision making by producing high quality, relevant, accessible systematic reviews and other synthesized research evidence (www.cochrane.org). Founded as The Cochrane Collaboration in 1993, it is a not-for-profit organization whose members aim to produce credible, accessible health information that is free from commercial sponsorship and other conflicts of interest.

Cochrane works collaboratively with health professionals, policy makers and international organizations such as the World Health Organization (WHO) to support the development of evidence-informed guidelines and policy. WHO guidelines on critical public health issues such as breastfeeding (2017) and malaria (2015), and the WHO Essential Medicines List (2017) are underpinned by dozens of Cochrane Reviews.

There are many examples of the impact of Cochrane Reviews on health and health care. Influential reviews of corticosteroids for women at risk of giving birth prematurely, treatments for macular degeneration and tranexamic acid for trauma patients with bleeding have demonstrated the effectiveness of these life-changing interventions and influenced clinical practice around the world. Other reviews of anti-arrhythmic drugs for atrial fibrillation and neuraminidase inhibitors for influenza have raised important doubts about the effectiveness of interventions in common use.

Cochrane Reviews are published in full online in the *Cochrane Database of Systematic Reviews*, which is a core component of the Cochrane Library (www.thecochranelibrary.com). The Cochrane Library was first published in 1996, and is now an online collection of multiple databases.

The evidence for Cochrane methodology

While Cochrane was one of the earliest organizations to produce and publish systematic reviews, there are now many organizations and journals doing so. One of the key elements that sets Cochrane apart is its rigorous methods, and Cochrane has played a unique role in fostering the development of methodology for systematic reviews throughout its history. Cochrane Methods Groups are voluntary collaborations of some of the world's leading methodological researchers in statistics, information retrieval, bias, qualitative methods, and many other specialist areas (see <https://methods.cochrane.org>). These Methods Groups support and disseminate methods research that identifies the most effective and efficient methods for systematic reviews, minimizing bias and increasing the appropriate analysis and interpretation of results.

The use of these rigorous methods is challenging and often time-consuming, but the recommendations are not made for their own sake. As McKenzie and colleagues wrote, "Our confidence in the findings of systematic reviews rests on the evidence base

underpinning the methods we use. Just as there are consequences arising from the choices we make about health and social care interventions, so too are there consequences when we choose the methods to use in systematic reviews.” (McKenzie et al, Cochrane Database of Systematic Reviews 2015; 7: ED00010)

With this in mind, the guidance in this *Handbook* has been written by authors who are international leaders in their fields, many of whom are supported by the work of Cochrane Methods Groups.

Ongoing challenges for systematic reviews

The landscape in which systematic reviews are conducted continues to evolve. Old and emerging challenges continue to spark debate, research and innovation.

The time required to complete a full systematic review, which is often more than two years, is a barrier both for author teams (representing a considerable commitment of often volunteer time) and for decision makers (who often require evidence within much shorter time frames). Methodology for undertaking reviews more rapidly is developing quickly. However, difficult choices are required in the trade-off between rigour and speed. The rise of technological solutions offers much potential, including collaboration tools, online crowd sourcing and automation of many aspects of the review process. Alongside consideration of appropriate ways to prioritize work, technology is also supporting more efficient approaches to keeping reviews up to date, with some reviews moving towards a ‘living’ systematic review model of very frequent, even continuous updates.

Cochrane Reviews have always encompassed complex questions of multi-component interventions, health systems and public health, and the challenging issues that arise from many of these reviews have prompted considerable thought and effort. Cochrane Reviews have always incorporated non-randomized studies where appropriate to the question, and a wider range of data sources is increasingly relevant to reviews, from the unpublished clinical study reports produced by pharmaceutical companies, to novel challenges in appraising and interpreting ‘big data’ repositories. The use of systematic reviews is expanding, and new methods developing, in areas such as environmental exposure and prognosis.

These conversations will continue, and new questions will continue to arise. Cochrane will continue to contribute actively to methodological development and application in each of these areas, continually striving to improve both the validity and usefulness of the reviews to decision makers.

Undertaking a Cochrane Review

Preparing a Cochrane Review is complex and involves many judgements. Authors work closely with Cochrane editorial teams in the production of reviews, supplying a highly structured format for both its protocols and reviews to guide authors on the information they should report. Cochrane groups and other research groups increasingly use priority-setting methods to engage stakeholders such as patients, the public, policy

makers and healthcare professionals to understand from them the most important uncertainties or information gap. Since its inception, Cochrane has advocated for routine updating of systematic reviews to take account of new evidence. In some fast-moving topics frequent updating is needed to ensure that review conclusions remain relevant.

While some authors new to Cochrane Reviews have training and experience in conducting other systematic reviews, many do not. Training for review authors is delivered in many countries by regional Cochrane groups or by the Cochrane Methods Groups responsible for researching and developing the methods used on Cochrane Reviews. In addition, Cochrane produces an extensive range of online learning resources. Detailed information is available via <https://training.cochrane.org>. Training materials and opportunities for training are continually developed and updated to reflect the evolving Cochrane methods and the needs of contributors.

About this *Handbook*

Work on a handbook to support authors of Cochrane Reviews began in 1993, and the first version was published in May 1994. Since then it has evolved and grown, through the stewardship of several editorial teams, with regular updating of its contents being punctuated by major new editions. This book represents Version 6 of the *Handbook*, the first major revision since the first print edition of the *Handbook* was published in 2008.

The book is divided into three parts. Part One provides the core methodology for undertaking systematic reviews on the effects of health interventions, with a particular emphasis on reviewing randomized trials. Part Two provides considerations for tackling these systematic reviews from different perspectives, such as when thinking about specific populations, or complex interventions, or particular types of outcomes. Part Three covers a range of further topics, including reviewing evidence other than straightforward randomized trials. The online version of the *Handbook* has an additional part, describing the particular organizational and procedural considerations when working specifically with Cochrane.

For this edition, each chapter that provides new or substantively updated guidance has been rigorously peer reviewed to ensure the guidance presented reflects the state of the science and is appropriate and efficient for use by Cochrane authors. The *Handbook* is updated regularly to reflect advances in systematic review methodology and in response to feedback from users. Please refer to <https://training.cochrane.org/handbook> for the most recent online version, for interim updates to the guidance and for details of previous versions of the *Handbook*. Feedback and corrections to the *Handbook* are also welcome via the contact details on the website.

What's new in this edition

In this edition, every chapter of the *Handbook* has been extensively revised, new chapters added, and authors familiar with previous versions will find it valuable to re-read any chapter of interest.

In particular, this edition incorporates the following major new chapters and areas of guidance:

- Expanded advice on assessing the risk of bias in included studies (Chapter 7), including Version 2 of the Cochrane Risk of Bias tool (Chapter 8) and the ROBINS-I tool for assessing risk of bias in non-randomized studies (Chapter 25).
- New guidance on summarizing study characteristics and preparing for synthesis (Chapters 3 and 9).
- New guidance on network meta-analysis (Chapter 11).
- New guidance on synthesizing results using methods other than meta-analysis (Chapter 12).
- Updated guidance on assessing the risk of bias due to missing results (reporting biases, Chapter 13).
- New guidance addressing intervention complexity (Chapter 17).

How to cite this book

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd Edition. Chichester (UK): John Wiley & Sons, 2019.

Acknowledgements

We thank all of our contributing authors and chapter editors for their patience and responsiveness in preparing this *Handbook*. We are also indebted to all those who have contributed to previous versions of the *Handbook*, and particularly to past editors Rachel Churchill, Sally Green, Phil Alderson, Mike Clarke, Cynthia Mulrow and Andy Oxman.

Many contributed constructive and timely peer review for this edition. We thank Zhenggang Bai, Hilda Bastian, Jesse Berlin, Lisa Bero, Jane Blazeby, Jacob Burns, Chris Cates, Nathorn Chaiyakunapruk, Kay Dickersin, Christopher Eccleston, Sam Egger, Cindy Farquhar, Nicole Fusco, Hernando Guillermo Gaitán Duarte, Paul Garner, Claire Glenton, Su Golder, Helen Handoll, Jamie Hartmann-Boyce, Joseph Lau, Simon Lewin, Jane Marjoribanks, Evan Mayo-Wilson, Steve McDonald, Emma Mead, Richard Morley, Sylvia Nalubega, Gerry Richardson, Richard Riley, Elham Shakibazadeh, Dayane Silveira, Jonathan Sterne, Alex Sutton, Özge Tunçalp, Peter von Philipsborn, Evelyn Whitlock, Jack Wilkinson. We thank Tamara Lotfi from the Secretariat for the Global Evidence Synthesis Initiative (GESI) and GESI for assisting with identifying peer referees, and Paul Garner and Taryn Young for their liaison with Learning Initiative for eXperienced Authors (LIXA).

Specific administrative support for this version of the *Handbook* was provided by Laura Mellor, and we are deeply indebted to Laura for her many contributions. We would also like to thank staff at Wiley for their patience, support and advice, including Priyanka Gibbons (Commissioning Editor), Jennifer Seward (Senior Project Editor), Deirdre Barry (Senior Editorial Assistant) and Tom Bates (Senior Production Editor).

We thank Ella Flemyng for her assistance and Elizabeth Royle and Jenny Bellorini at Cochrane Copy Edit Support for their assistance in copy editing some chapters of the *Handbook*. Finally, we thank Jan East for copy editing the whole volume, and Nik Prowse for project management.

This *Handbook* would not have been possible without the generous support provided to the editors by colleagues at the University of Bristol, University College London, Johns Hopkins Bloomberg School of Public Health, Cochrane Australia at Monash University, and the Cochrane Editorial and Methods Department at Cochrane Central Executive. We particularly thank David Tovey (former Editor in Chief, The Cochrane Library), and acknowledge Cochrane staff Madeleine Hill for editorial support, and Jo Anthony and Holly Millward for contributing to the cover design.

Finally, the Editors would like to thank the thousands of Cochrane authors who volunteer their time to collate evidence for people making decisions about health care, and the methodologists, editors and trainers who support them.

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