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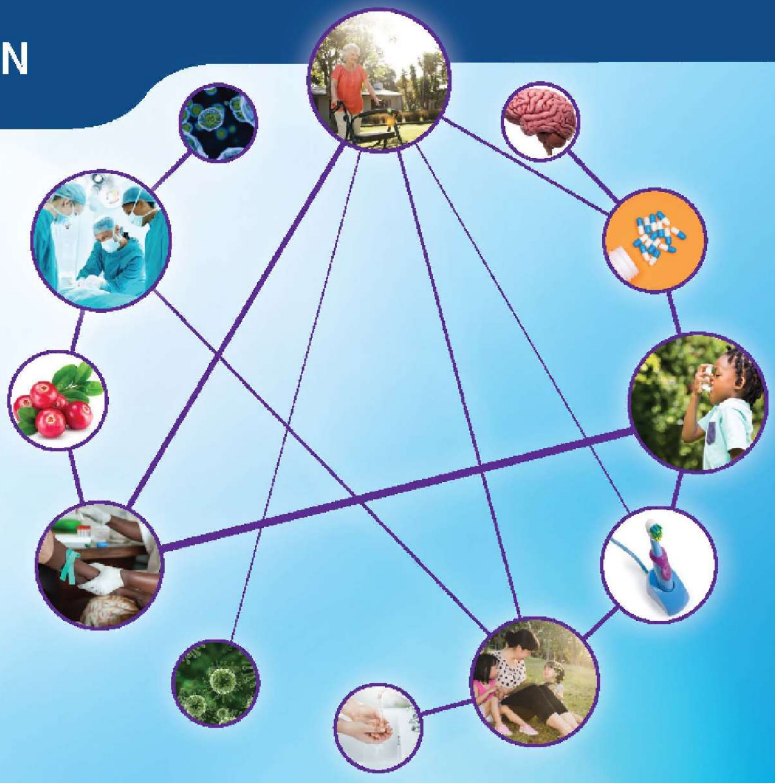
Cochrane Handbook for Systematic Reviews of Interventions

SECOND EDITION



Edited by

Julian P. T. Higgins

James Thomas

Associate Editors

Jacqueline Chandler · Miranda Cumpston

Tianjing Li · Matthew J. Page · Vivian A. Welch

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Contents

Contributors

Akl, Elie A
Department of Internal Medicine
American University of Beirut Medical Center
Beirut
Lebanon

Altman, Douglas G*
Centre for Statistics in Medicine
University of Oxford
Oxford
UK

Aluko, Patricia
Institute of Health and Society
Newcastle University
Newcastle upon Tyne
UK

Askie, Lisa M
NHMRC Clinical Trials Centre
University of Sydney
Sydney
Australia

Beaton, Dorcas E
Institute for Work & Health
Toronto, Ontario
Canada

Berlin, Jesse A
Department of Epidemiology
Johnson & Johnson
Titusville, NJ
USA

Bhaumik, Soumyadeep
The George Institute for Global Health
New Delhi
India

Bingham III, Clifton O
Department of Rheumatology
Johns Hopkins University
Baltimore, MD
USA

Boers, Maarten
Department of Epidemiology and Biostatistics
Amsterdam UMC
Vrije Universiteit Amsterdam
Amsterdam
The Netherlands

Booth, Andrew
School of Health and Related Research
University of Sheffield
Sheffield
UK

Boutron, Isabelle
METHODS team, Centre of Research in Epidemiology and Statistics (CRESS-UMR1153), INSERM/Paris Descartes University;

* Deceased 3 June 2018

Centre d' Epidémiologie Clinique
Assistance Publique des hôpitaux de Paris;
Cochrane France
Paris
France

Brennan, Sue E
Cochrane Australia
School of Public Health and Preventive Medicine
Monash University
Melbourne
Australia

Briel, Matthias
Department of Clinical Research
University of Basel
Basel
Switzerland

Briscoe, Simon
College of Medicine and Health
University of Exeter
Exeter
UK

Busse, Jason W
Department of Anesthesia
McMaster University
Hamilton, Ontario
Canada

Caldwell, Deborah M
Population Health Sciences
Bristol Medical School
University of Bristol
Bristol
UK

Cargo, Margaret
Health Research Institute
University of Canberra
Canberra
Australia

Carrasco-Labra, Alonso
Department of Health Research Methods, Evidence and Impact (HEI)
McMaster University
Hamilton, Ontario
Canada
Department of Oral and Craniofacial Health Science
University of North Carolina at Chapel Hill
Chapel Hill, NC
USA

Chaimani, Anna
METHODS team Centre of Research in Epidemiology and Statistics
Sorbonne Paris Cité (CRESS-UMR1153), INSERM/Paris Descartes University
Paris
France

Chandler, Jacqueline
Wessex Academic Health Science Network
University Hospital Southampton
Southampton
UK

Christensen, Robin
Musculoskeletal Statistics Unit
The Parker Institute
Bispebjerg and Frederiksberg Hospital
Copenhagen
Denmark

Clarke, Mike
Northern Ireland Methodology Hub
Centre for Public Health
Queen's University Belfast
Belfast
Northern Ireland

Craig, Dawn
Institute of Health and Society
Newcastle University
Newcastle upon Tyne
UK

da Costa, Bruno R
Applied Health Research Centre
St. Michael's Hospital
Toronto, Ontario
Canada

Deeks, Jonathan J
Institute of Applied Health Research
University of Birmingham
Birmingham
UK

Devji, Tahira
Department of Health Research Methods, Evidence and Impact (HEI)
McMaster University
Hamilton, Ontario
Canada

Drummond, Michael
Centre for Health Economics
University of York
York
UK

Elbers, Roy G
Population Health Sciences
Bristol Medical School
University of Bristol
Bristol
UK

El Dib, Regina
Institute of Science and Technology
UNESP - Univ Estadual Paulista
São José dos Campos
Brazil

Eldridge, Sandra
Centre for Primary Care and Public Health
Blizard Institute
Barts and The London
School of Medicine and Dentistry
Queen Mary University of London
London
UK

Elliott, Julian H
Cochrane Australia
Monash University
Melbourne
Australia

Flemming, Kate
Department of Health Sciences
University of York
York
UK

Gagnier, Joel J
Department of Orthopaedic Surgery
Epidemiology
University of Michigan
Ann Arbor, MI
USA

Garside, Ruth
European Centre for Environment and Human Health
University of Exeter Medical School
University of Exeter
Truro
UK

Ghersi, Davina
Research Policy and Translation
National Health and Medical Research Council
Canberra
Australia

Glanville, Julie
York Health Economics Consortium
York
UK

Glasziou, Paul
Institute for Evidence-Based Healthcare
Bond University
Queensland
Australia

Golder, Su
Department of Health Sciences
University of York
York
UK

Graybill, Erin
Department of Economics
Newcastle University
Business School
Newcastle upon Tyne
UK

Guyatt, Gordon H
Department of Health Research Methods, Evidence and Impact (HEI)
McMaster University
Hamilton, Ontario
Canada

Hannes, Karin
Social Research Methodology Group
Faculty of Social Sciences
KU Leuven
Leuven
Belgium

Harden, Angela
Institute of Health and Human Development
University of East London
London
UK

Harris, Janet
School of Health and Related Research
University of Sheffield
Sheffield
UK

Hartling, Lisa
Department of Pediatrics, Faculty of Medicine & Dentistry
University of Alberta
Edmonton, Alberta
Canada

Henderson, Catherine
Personal Social Services Unit
London School of Economics and Political Science
London
UK

Hernán, Miguel A
Departments of Epidemiology and Biostatistics
Harvard T.H. Chan School of Public Health
Boston, MA
USA

Higgins, Julian PT
Population Health Sciences
Bristol Medical School
University of Bristol
Bristol
UK

Hróbjartsson, Asbjørn
Centre for Evidence-Based Medicine Odense (CEBMO)
Odense University Hospital
Odense
Denmark

Johnston, Bradley C
Department of Community Health and Epidemiology
Dalhousie University
Halifax, Nova Scotia
Canada

Johnston, Renea V
Monash Department of Clinical Epidemiology, Cabrini Institute
School of Public Health and Preventive Medicine, Monash University
Melbourne
Australia

Jull, Janet
School of Rehabilitation Therapy
Queen's University
Kingston, Ontario
Canada

Junqueira, Daniela R
Faculty of Medicine and Dentistry
University of Alberta
Edmonton, Alberta
Canada

Klassen, Terry
Manitoba Institute of
Child Health
Winnipeg, Manitoba
Canada

Kneale, Dylan
EPPI-Centre, Institute of Education
University College London
London
UK

Kristjansson, Elizabeth
School of Psychology
Faculty of Social Sciences
University of Ottawa
Ottawa, Ontario
Canada

Lasserson, Toby J
Editorial & Methods Department
Cochrane Central Executive
London
UK

Lefebvre, Carol
Lefebvre Associates Ltd
Oxford
UK

Li, Tianjing
Department of Epidemiology
Johns Hopkins Bloomberg School of
Public Health
Baltimore, MD
USA

Littlewood, Anne
Cochrane Oral Health
University of Manchester
Manchester
UK

Loke, Yoon Kong
Norwich Medical School
University of East Anglia
Norwich
UK

Lundh, Andreas
Centre for Evidence-Based
Medicine Odense (CEBMO)
Odense University Hospital
Odense
Denmark

Lyddiatt, Anne
Ingersoll, Ontario
Canada

Marshall, Chris
Institute of Health and Society
Newcastle University
Newcastle upon Tyne
UK

Maxwell, Lara J
University of Ottawa
Ottawa, Ontario
Canada

McAleenan, Alexandra
Population Health Sciences
Bristol Medical School
University of Bristol
Bristol
UK

McKenzie, Joanne E
School of Public Health and
Preventive Medicine
Monash University
Melbourne
Australia

Metzendorf, Maria-Inti
Institute of General Practice
Medical Faculty of the
Heinrich-Heine-University Düsseldorf
Düsseldorf
Germany

Noel-Storr, Anna
Radcliffe Department of Medicine
University of Oxford
Oxford
UK

Noyes, Jane
School of Health Sciences
Bangor University
Bangor
UK

Ostelo, Raymond W
Department of Epidemiology and Biostatistics
Amsterdam UMC
Vrije Universiteit Amsterdam
Amsterdam
The Netherlands

Page, Matthew J
School of Public Health and Preventive Medicine
Monash University
Melbourne
Australia

Pantoja, Tomás
Department of Family Medicine
Faculty of Medicine
Pontificia Universidad Católica de Chile
Santiago
Chile

Pardo Pardo, Jordi
Cochrane Musculoskeletal Group
University of Ottawa
Ottawa, Ontario
Canada

Patrick, Donald L
Health Services and Epidemiology
University of Washington
Seattle, WA
USA

Peryer, Guy
University of East Anglia
Norwich
UK

Petkovic, Jennifer
Bruyère Research Institute
University of Ottawa
Ottawa, Ontario
Canada

Petticrew, Mark
Faculty of Public Health and Policy
London School of Hygiene and Tropical Medicine
London
UK

Rader, Tamara
Evidence Standards
Canadian Agency for Drugs and Technologies in Health
Ottawa, Ontario
Canada

Reeves, Barnaby C
Translational Health Sciences
Bristol Medical School
University of Bristol
Bristol
UK

Rehfuess, Eva
Pettenkofer School of Public Health
Institute for Medical Information Processing, Biometry and Epidemiology
LMU Munich
Munich
Germany

Robalino, Shannon
Institute of Health and Society
Newcastle University
Newcastle upon Tyne
UK

Ryan, Rebecca E
Cochrane Consumers and Communication Group
Centre for Health Communication and Participation
La Trobe University
Melbourne
Australia

Salanti, Georgia
Institute of Social and Preventive Medicine
University of Bern
Bern
Switzerland

Santesso, Nancy
Department of Health Research Methods Evidence and Impact (HEI)
McMaster University
Hamilton, Ontario
Canada

Savović, Jelena
Population Health Sciences
Bristol Medical School
University of Bristol
Bristol
UK

Schünemann, Holger J
Departments of Health Research Methods, Evidence, and Impact (HEI) and of Medicine
McMaster University
Hamilton, Ontario
Canada

Shea, Beverley
Department of Medicine,
Ottawa Hospital Research Institute;
School of Epidemiology and Public Health, University of Ottawa
Ottawa, Ontario
Canada

Shemilt, Ian
EPPI-Centre
University College London
London
UK

Shokraneh, Farhad
Cochrane Schizophrenia Group
Division of Psychiatry and Applied Psychology
Institute of Mental Health
School of Medicine
University of Nottingham
Nottingham
UK

Simmonds, Mark
Centre for Reviews and Dissemination
University of York
York
UK

Singh, Jasvinder
School of Medicine
University of Alabama at Birmingham
Birmingham, AL
USA

Skoetz, Nicole
Department of Internal Medicine
University Hospital of Cologne
Cologne
Germany

Sterne, Jonathan AC
Population Health Sciences
Bristol Medical School
University of Bristol
Bristol
UK

Stewart, Lesley A
Centre for Reviews and Dissemination
University of York
York
UK

Stott, David J
Academic Section of Geriatric Medicine
Institute of Cardiovascular and Medical Sciences
University of Glasgow
Glasgow
UK

Takwoingi, Yemisi
Institute of Applied Health Research
University of Birmingham
Birmingham
UK

Terwee, Caroline B
Department of Epidemiology and Biostatistics
Amsterdam Public Health Research Institute
Amsterdam UMC
Vrije Universiteit Amsterdam
Amsterdam
The Netherlands

Thomas, James
EPPI-Centre, Department of Social Science
University College London
London
UK

Thomson, Denise
Department of Pediatrics
Faculty of Medicine and Dentistry
University of Alberta
Edmonton, Alberta
Canada

Thomson, Hilary J
MRC/CSO Social and Public Health Sciences Unit
University of Glasgow
Glasgow
UK

Tierney, Jayne F
MRC Clinical Trials Unit at UCL
Institute of Clinical Trials and Methodology
London
UK

Tugwell, Peter
Department of Medicine & School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa;
Clinical Epidemiology Program, Ottawa Hospital Research Institute
Ottawa, Ontario
Canada

Ueffing, Erin
Centre for Practice-Changing Research
Ottawa Hospital Research Institute
Ottawa, Ontario
Canada

Vale, Luke
Health Economics Group
Institute of Health and Society
Newcastle University
Newcastle upon Tyne
UK

Vist, Gunn E
Department of Preventive, Health Promotion and Organisation of Care
Norwegian Institute of Public Health
Oslo
Norway

Vohra, Sunita
Department of Pediatrics
Faculty of Medicine & Dentistry
University of Alberta
Edmonton, Alberta
Canada

Welch, Vivian A
Bruyère Research Institute
Ottawa, Ontario
Canada

Wells, George A
School of Epidemiology and Public Health, University of Ottawa;
University of Ottawa Heart Institute
Ottawa, Ontario
Canada

Wieland, L Susan
Center for Integrative Medicine
Department of Family and Community Medicine
University of Maryland School of Medicine
Baltimore, MD
USA

Williams, Katrina
Department of Paediatrics, Monash University;
Developmental Paediatrics, Monash Children's Hospital;
Neurodisability and Rehabilitation, Murdoch Children's Research Institute
Melbourne
Australia

Williamson, Paula R
Department of Biostatistics
University of Liverpool
Liverpool
UK

Wilson, Edward CF
Health Economics Group
Norwich Medical School
University of East Anglia
UK

Young, Camilla
Institute of Cardiovascular and Medical Sciences
University of Glasgow
Glasgow
UK

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 multicomponent 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 addition 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).

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The *Handbook* editorial team

Julian P.T. Higgins (*Senior Editor*) is Professor of Evidence Synthesis at the University of Bristol, UK.

James Thomas (*Senior Editor*) is Professor of Social Research & Policy, and Associate Director of the EPPI-Centre at UCL, London, UK.

Jacqueline Chandler (*Managing Editor*) is Evaluation Programme Manager (Qualitative Evaluation) at Wessex Academic Health Science Network, University Hospital Southampton, Southampton, UK.

Miranda Cumpston (*Implementation Editor*) is an Editor at Cochrane Public Health in the School of Medicine and Public Health, University of Newcastle, and the School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia.

Tianjing Li (*Associate Scientific Editor*) is an Associate Professor of Epidemiology at Johns Hopkins Bloomberg School of Public Health, Baltimore, USA. She is a Coordinating Editor for Cochrane Eyes and Vision.

Matthew J. Page (*Associate Scientific Editor*) is a Research Fellow in the Research Methodology Division of the School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia.

Vivian A. Welch (*Associate Scientific Editor*) is Editor in Chief of the Campbell Collaboration, Scientist at Bruyère Research Institute, Ottawa, Canada; Associate Professor at the School of Epidemiology and Public Health, University of Ottawa, Canada.