Principles and Practice of Systematic Reviews and Meta-Analysis
Evidence-Based Medicine (EBM) is at the core of modern medicine [1, 2]. EBM is the integration of individual clinical expertise with the best available clinical evidence from systematic research and patient’s values and expectations [1, 2]. EBM requires that decisions should be taken based on the body of evidence, and not just a single study [3]. Systematic reviews offer evidence that is as good as the best available evidence summarized by the review [3]. Systematic reviews are “the most reliable and comprehensive statement about what works,” and involve identifying, synthesizing, and assessing all available evidence, quantitative and/or qualitative, to generate a robust, empirically derived answer to a focused research question [4]. Since their introduction in medical sciences in 1970s, systematic reviews have been adopted in a wide range of fields, from astronomy, international development, and global health, to zoology [5–7]. The importance of systematic reviews with meta-analyses as the best source of evidence cannot be overemphasized considering that health care staff, public health policy-makers, and researchers have limited time to catch up with and critically appraise the vast amount of literature that gets added every day [8].

Written by clinicians, the objective of this reader-friendly book is to introduce the readers from various faculties of science to the principles and practice of systematic reviews and meta-analysis. Our aim is to help them in developing skills to use this precious tool for guiding their clinical practice and research [8].

Perth, WA, Australia
Sanjay Patole
References

7. Schlosser RW. The role of systematic reviews in evidence-based practice, research, and development. Focus—A Publication of the National Center for the Dissemination of Disability Research (NCDDR) 2006; Technical Brief No 15: 1–4.
Acknowledgments

I would like to express my sincere gratitude to the Associate Editor of this book, A/Prof. Shripada Rao. This book would not have been completed without his significant contribution in every aspect, from concept to completion.

Sanjay Patole, MD, FRACP, DrPH
## Contents

<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic Reviews, Meta-Analysis, and Evidence-Based Medicine</td>
<td>1</td>
</tr>
<tr>
<td>Sanjay Patole</td>
<td></td>
</tr>
<tr>
<td>Literature Search for Systematic Reviews</td>
<td>11</td>
</tr>
<tr>
<td>Shripada Rao and Kwi Moon</td>
<td></td>
</tr>
<tr>
<td>Assessing and Exploring Heterogeneity</td>
<td>33</td>
</tr>
<tr>
<td>Sven Schulzke</td>
<td></td>
</tr>
<tr>
<td>Assessment of the Risk of Bias</td>
<td>43</td>
</tr>
<tr>
<td>Kwi Moon and Shripada Rao</td>
<td></td>
</tr>
<tr>
<td>Assessment of Publication Bias</td>
<td>57</td>
</tr>
<tr>
<td>Sven Schulzke</td>
<td></td>
</tr>
<tr>
<td>Data Extraction from Included Studies</td>
<td>65</td>
</tr>
<tr>
<td>Kwi Moon and Shripada Rao</td>
<td></td>
</tr>
<tr>
<td>Fixed and Random-Effects Models for Meta-Analysis</td>
<td>73</td>
</tr>
<tr>
<td>Ravisha Srinivasjois</td>
<td></td>
</tr>
<tr>
<td>Forest Plots in a Meta-Analysis</td>
<td>79</td>
</tr>
<tr>
<td>Sanjay Patole</td>
<td></td>
</tr>
<tr>
<td>Sensitivity and Subgroup Analyses</td>
<td>89</td>
</tr>
<tr>
<td>Mangesh Deshmukh</td>
<td></td>
</tr>
<tr>
<td>Rating Certainty of the Evidence Using GRADE Guidelines</td>
<td>99</td>
</tr>
<tr>
<td>Abhijeet Rakshasbhuvankar</td>
<td></td>
</tr>
<tr>
<td>Reporting of Meta-Analysis (PRISMA)</td>
<td>111</td>
</tr>
<tr>
<td>Sam Athikarisamy and Sanjay Patole</td>
<td></td>
</tr>
<tr>
<td>Critical Appraisal of Systematic Reviews and Meta-Analyses</td>
<td>125</td>
</tr>
<tr>
<td>Sanjay Patole</td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>Page</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Systematic Reviews and Meta-Analyses of Non-randomised Studies</td>
<td>139</td>
</tr>
<tr>
<td>Sanjay Patole</td>
<td></td>
</tr>
<tr>
<td>Individual Participant Data (IPD) Meta-Analysis</td>
<td>147</td>
</tr>
<tr>
<td>Abhijeet Rakshashbhuvankar</td>
<td></td>
</tr>
<tr>
<td>Systematic Reviews of Diagnostic Test Accuracy</td>
<td>157</td>
</tr>
<tr>
<td>Mohan Pammi and Yemisi Takwoingi</td>
<td></td>
</tr>
<tr>
<td>Network Meta-Analysis</td>
<td>169</td>
</tr>
<tr>
<td>Sanjay Patole</td>
<td></td>
</tr>
<tr>
<td>Systematic Reviews of Animal Studies</td>
<td>177</td>
</tr>
<tr>
<td>Gayatri Athalye-Jape</td>
<td></td>
</tr>
</tbody>
</table>
Contributors

Gayatri Athalye-Jape Neonatal Directorate, King Edward Memorial Hospital, Perth, WA, Australia; School of Medicine, University of Western Australia, Perth, Australia

Sam Athikarisamy Neonatal Directorate, King Edward Memorial Hospital for Women, Perth, WA, Australia; School of Medicine, University of Western Australia, Perth, WA, Australia

Mangesh Deshmukh Department of Neonatology, Fiona Stanley Hospital, School of Medicine, Curtin and University of Western Australia, Perth, WA, Australia

Kwi Moon Department of Pharmacy, Perth Children’s Hospital, Perth, WA, Australia; School of Medicine, University of Western Australia, Perth, WA, Australia

Gillian Northcott Graphic Design, Medical Illustration, Perth Children’s Hospital, Perth, WA, Australia

Mohan Pammi Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA

Sanjay Patole Neonatal Directorate, King Edward Memorial Hospital for Women, Perth, WA, Australia; School of Medicine, University of Western Australia, Perth, WA, Australia

Abhijeet Rakshasbhuvankar School of Medicine, Neonatal Directorate, King Edward Memorial Hospital for Women, University of Western Australia, Perth, WA, Australia

Shripada Rao School of Medicine, Neonatal Directorate, Perth Children’s Hospital, University of Western Australia, Perth, WA, Australia

Sven Schulzke Neonatologist, Director of Research, University Children’s Hospital Basel UKBB, Basel, Switzerland
Contributors

**Ravisha Srinivasjois**  School of Medicine, University of Western Australia, Perth, WA, Australia

**Yemisi Takwoingi**  Institute of Applied Health Research, Public Health Building, University of Birmingham, Birmingham, UK
Abstract  Evidence-based medicine (EBM) is at the core of current clinical practice. The philosophical origins of EBM date as far back as the mid-19th century earlier. David Sackett (1934-2015) considered as the father of EBM, described it as ‘the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients’. EBM requires that clinical decisions should be based on the evidence in totality, and not on just a single study. Systematic reviews offer the best available evidence for decision making in clinical practice. They are ‘the most reliable and comprehensive statement about what works’, and involve identifying, synthesising and assessing all available evidence by a systematic approach, to generate a robust, empirically derived answer to a focused research question. A systematic review may or may not contain a statistical analysis (Meta-analysis) depending on whether it is possible, and importantly, sensible to combine data from different studies on the same subject, or not. This chapter covers the history, principles and characteristics of systematic reviews and meta-analysis in the context of EBM.

Keywords  Evidence-based medicine · Systematic reviews · Narrative reviews · Meta-analysis · History · Principles · Practice · Hierarchy

Introduction

Evidence-based medicine (EBM) is at the core of current clinical practice (http://www.senseaboutscience.org/pages/evidence-based-medicine.html; Guyatt et al. 2000). The philosophical origins of EBM date as far back as the mid-19th century
Paris and earlier (Anderson 2015). David Sackett (1934-2015) considered as the father of EBM, described it as ‘the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients’ (Anderson 2015; Sackett 1997). To him, the practice of EBM meant ‘integration of individual clinical expertise with the best available external clinical evidence from systematic research’. EBM requires that clinical decisions should be based on the evidence in totality, and not on just a single study (Guyatt et al. 2002). The role of a systematic review is to offer the best available evidence for decision making in clinical practice (Guyatt et al. 2002).

**Narrative Reviews**

Narrative reviews often reflect ‘Eminence-based medicine’ as they are mostly written by invited experts (Isaacs and Fitzgerald 1999). Needless to say, they are influenced by the author’s intuition, experience, and inevitably, their bias. Critics point out that narrative reviews are a quick, easy, and an inexpensive way to reach desired conclusions! (Isaacs and Fitzgerald 1999).

The definition of what constitutes ‘evidence’ is subjective. Narrative reviews could be evidence-based, but still not truly useful as scientific evidence. In the absence of a clear section titled ‘methods’, it is difficult to understand how the evidence was derived and interpreted in narrative reviews. The lack of clarity and transparency and the element of subjectivity make it challenging to derive reliable, unbiased interpretation and conclusions on a specific topic when appraising narrative reviews (Isaacs and Fitzgerald 1999). For example, a comparison of seven narrative reviews, including the same studies showed that different reviewers reached different conclusions!!(Cipriani and Geddes 2003) The case of vitamin C as an intervention for cold illustrates the issues with narrative reviews quite well. The narrative review of vitamin C (‘How to live longer and feel better, Linus Pauling 1986’) had concluded that “We should be getting 200 times the amount of vitamin C that the Food and Nutrition Board recommends” (Linus Planning 2006). The author, Linus Pauling, was one of the founders of quantum chemistry and molecular biology, and one of the 20 greatest scientists of all time who went on to win the Nobel Prize in Chemistry in 1954 (Global Firsts and Facts 2017). Furthermore in the year 2000 he was acknowledged as the 16th most influential scientist in history. A subsequent systematic review of vitamin C for the cold by investigators from Oxford involved an exhaustive search of databases, journals and special collections (Knipschild 1995). It identified 61 trials, of which 15 were methodologically sound. The results of this systematic review suggested that even in megadoses Vitamin C cannot prevent a cold, though it might shorten its duration if already infected. The reviewers pointed out that the narrative review had missed five of the 15 methodologically sound trials, and had referred to other two only in passing (Knipschild 1995). Considering their limitations, narrative reviews are becoming less and less prevalent in the era of EBM.
Systematic Reviews

Systematic reviews are ‘the most reliable and comprehensive statement about what works’, and involve identifying, synthesising and assessing all available evidence by a systematic approach, to generate a robust, empirically derived answer to a focused research question (Isaacs and Fitzgerald 1999). Systematic reviews have been used in a wide range of fields, ‘from astronomy and zoology’ to international development, and global health, and were introduced to the medical field only in the 1970s (Petticrew 2001; Malletta et al. 2012; Schlosser 2006; O’Rourke 2007).

A Brief History of Systematic Reviews

The phrase ‘systematic review’ was mentioned in the early and mid-19th century in few publications on the classification of species in biology and zoology (Mees 1957; Alm 1916). In the late 1970s and early 1980s a group of health researchers in Oxford prepared the ground for EBM by beginning a programme of systematic reviews on the effectiveness of health care interventions.

Archie Cochrane called for developing medicine based on randomised controlled trials (RCTs) in his seminal book in 1972 titled ‘Effectiveness and Efficiency: Random Reflections on Health Services’ (Cochrane 1972). Later, his call for the critical summary of all RCT’s (1979) led to the establishment of a collaborative database of perinatal trials (The Cochrane Collaboration 2017). Systematic reviews of RCTs started to get published in the 1980s, and in 1987 he encouraged others to adopt the methodologies used in these reviews. Archie Cochrane’s untiring efforts and the increasing acceptance of EBM subsequently led to the opening of the Cochrane Collaboration Centre in Oxford, the UK in 1992, shortly after his death (Cochrane 1972; EPPI 2017; Brent Thoma 2013). The push for systematic reviews in the medical world started with the meeting organised by the British Medical Journal and the Cochrane Centre in London in 1993 (Chalmers and Altman 1995). The group at this meeting aimed to improve the scientific rigour of reviews in clinical medicine for a reliable and evidence-based approach in advising treatments. They believed that in the absence of scientific methods, advice on some lifesaving therapies had been delayed for over a decade, while others shown to be harmful in controlled trials continued to be offered (Oxman and Guyatt 1988). Systematic reviews, as we understand them today, represent the structured approach to undertaking literature reviews on earlier research studies and they are tied closely to meta-analyses, i.e. a statistical method for combining the data from the previous studies. We will learn more about meta-analysis later in this book.

The importance of systematic reviews as the best source of evidence for practising EBM cannot be overemphasised considering that health care providers, public health policymakers, and researchers often have limited time to catch up with and critically appraise the vast amount of literature that gets added every day.
Malletta et al. 2012; Glasziou et al. 2004). RCTs are considered as the gold standard in clinical research as they address the issue of not only the known but also the unknown confounders, something that other study designs (‘Non-RCTs’: cohort studies, case-control studies) cannot do. Systematic reviews of RCTs are, therefore, at the top of the pyramid of the hierarchy of evidence in EBM. However, assessing the risk of bias in various domains (e.g. randomisation, allocation concealment) of the included trials is important before accepting systematic reviews of RCTs as the gold standard in EBM (Fig. 1).

**Fig. 1  Hierarchy of evidence pyramid**

(Malletta et al. 2012; Glasziou et al. 2004). RCTs are considered as the gold standard in clinical research as they address the issue of not only the known but also the unknown confounders, something that other study designs (‘Non-RCTs’: cohort studies, case-control studies) cannot do. Systematic reviews of RCTs are, therefore, at the top of the pyramid of the hierarchy of evidence in EBM. However, assessing the risk of bias in various domains (e.g. randomisation, allocation concealment) of the included trials is important before accepting systematic reviews of RCTs as the gold standard in EBM (Fig. 1).

**What Does Systematic Review Involve?**

A systematic review involves systematic identification and evaluation of all the available relevant evidence to guide clinical practice, research, and policy. A systematic review focuses on a specific question; uses clearly stated, prespecified scientific methods to identify, select, assess, and summarise the findings of similar but separate studies. As Gene Glass said ‘a systematic review is an analysis of analyses’. It is important to know that a systematic review may or may not contain a statistical analysis (Meta-analysis) depending on whether it is possible, and importantly, sensible to combine data from different studies on the same subject, or not (Douglas Altman 2013; Chinchilli 2007).
**Why Do We Need Systematic Reviews?**

Limited time to catch up with and critically appraise the vast amount of literature is not the only reason why we need systematic reviews. A comprehensive search and unbiased interpretation of the best available evidence—a critical component of EBM, is difficult without being systematic. Systematic reviews are useful in interpreting conflicting results of primary studies, synthesising results of a large number of primary studies, and judging external applicability of the evidence, especially when there are only a few primary studies. Reproducibility of results is another important benefit of systematic reviews given the transparency and clarity of their methodology. Systematic reviews help us know existing research (and its quality) in our area of interest, prevent duplication of efforts by letting us know what has already been done, and provide insights through the comparison and/or combination of different studies (Oakley et al. 2005).

**What Are the Principles of Systematic Reviews?**

A systematic review needs to have a focused, well defined, useful, and importantly, an answerable question. It requires a clear title and objectives with explicit and justified predefined inclusion and exclusion criteria. The question needs to convey, with clarity, the patients (P), intervention (I), control/comparison (C), the outcome of interest (O), and the study design (S). This is the PICOS format of the question that the systematic review is addressing. Some prefer to add the study time frame (T) to the phrased question, resulting in the abbreviation PICOT.

Considering the aim is to provide comprehensive and best available evidence, it should have a clearly documented and comprehensive search strategy for tracing all relevant studies—published as well as unpublished. Providing details of the search strategy makes it possible to reproduce the search results, increasing the validity of search methodology. To assure minimisation of bias, it should have a pre-stated method for critical appraisal of included studies using pre-stated methods.

The type of synthesis of the results (Quantitative, i.e. meta-analysis or Qualitative) depends on whether it is possible, and sensible to combine the data from ‘more or less similar; but different individual studies together. This is perhaps the most important step in systematic reviews.

Unbiased interpretation and conclusions and putting research into context are important. Finally, systematic reviews are required to have a structured report for the dissemination of results with clarity to the broader community.

As discussed above, assuring transparency, clarity, and objectivity at each step of the systematic review is important (Table 1). The practical approach to a systematic review is summarised in Table 2. The approach can be summarised in a sentence: *Ask a focussed question; tell the readers what exactly you did in an attempt to answer it, how and why?* Baumeister et al. have emphasised the
importance of an additional aspect—the mindset of a systematic reviewer (Baumeister 2013). The responsibility of systematic reviewers is to provide the comprehensive and best available evidence in the context of current clinical practice and let the reader judge the applicability (safety and efficacy) of the evidence to their patient. Considering human behaviour, it is not uncommon for reviewers to take sides, consciously or subconsciously!

It is important to know what systematic reviews tell us and what they don’t. If conducted and reported using a robust methodology, systematic reviews tell us in a scientific, structured, and transparent way as to Who did what, why, and for whom? How? What did they find? What does it mean in the current context? What needs to be done? Systematic reviews do NOT tell what one should do for an individual patient. That process is left to the health care provider and the patient as a shared responsibility.

### What Is a Meta-Analysis?

Systematic reviews represent the structured scientific approach for undertaking literature reviews on earlier research studies addressing the desired focussed and properly framed question (PICOS/T). They are tied closely to meta-analyses, i.e. a statistical method for combining the data from the previous studies. A systematic review may or may not contain a meta-analysis depending on whether the data from previous studies addressing the desired question can or cannot be combined. When meta-analysis is possible, it’s a systematic review with meta-analysis’ (i.e. quantitative systematic review); otherwise, it is only a systematic review. When

---

### Table 1 Characteristics of a systematic review*

- **T**: Transparency at each step
- **R**: Reproducible and robust methodology
- **U**: Unbiased (Best precautions at each step to minimise bias)
- **E**: Explicit objective criteria for each step (e.g. inclusion)

*Systematic reviews have to be ‘truly’ systematic

### Table 2 Practical approach to a systematic review

- Ask a useful and answerable question
- Before you start, check if it has been answered already!
- Be specific in deciding the type of studies (PICOS) you wish to search for
- Be comprehensive in the literature search
- Get help (Subject experts, Methodologist)
- Avoid the temptation to conduct a ‘Meta-analysis’ just to impress!
- Don’t combine apples with oranges unless assessing ‘fruits in general’
- Keep the mindset of a judge and jury (Fair judgement), rather than a lawyer (Make the best case for one side (Baumeister 2013))
meta-analysis is not done for various reasons, the reviewers take a structured descriptive/narrative approach to discuss various aspects of the included studies. Such a systematic review without meta-analysis is called as a qualitative systematic review.

There is no reason why data from different ‘more or less similar’ studies answering the desired question cannot be combined using the technique of meta-analysis, however, the evidence from such a meta-analysis will not be reliable if the included studies are not derived by a systematic review. Appreciating the importance of a systematic review for identifying the studies included in a meta-analysis is critical.

It is important to know that meta-analysis can be used to synthesise results from RCTs, as well as non-RCTs (‘Observational studies’) and epidemiological studies.

A Brief History of Meta-Analyses

The 17th-century French mathematician Blaise Pascal developed methods to determine the value of possible gambles and to compare and combine observations by different astronomers (https://www.biography.com/people/blaise-pascal-9434176) (Table 3). Later, the 18th and 19th-century astronomers and mathematicians such as Gauss and Laplace dealt with the concept of summarising the results from different studies (https://en.wikipedia.org/wiki/Carl_Friedrich_Gauss; https://en.wikipedia.org/wiki/Pierre-Simon_Laplace). These were presented in a book published by the British Royal Astronomer George Biddell Airy (Wright 1988). The British statistician Karl Pearson (1904) is considered to be the first person to combine observations from different studies using special methods (http://adsabs.harvard.edu/full/; Shannon 2008; Pearson 1900). Pearson compared infection and mortality among soldiers who had volunteered for vaccination against typhoid fever with those who had not volunteered. It is remarkable that he commented not only on the ‘significance’ of results, irregularity of correlation (i.e. heterogeneity) between vaccination and mortality, and the ‘lowness’ of the values (poor efficacy) reflecting the need for a better vaccine but also on the need for a better method (direction for further research) to get unbiased results (http://adsabs.harvard.edu/full/; Shannon 2008; Pearson 1900). Sir Ronald Aylmer Fisher (1890–1962), the famous English statistician and biologist who used mathematics to combine Mendelian genetics and natural selection, developed the combined probability test for combining data the, i.e. conducting “meta-analysis” (analysis of analyses) (Pearson 1904; Ronald Fisher 2017; Fisher 1925). The test is used to combine the results from several independent tests bearing upon the same overall hypothesis (H0). The credit for coining the term ‘meta-analysis’ is given to Gene Glass, an American statistician and researcher in educational psychology and social sciences (Mosteller and Fisher 1948; Gene 2017; Glass 1976). It is said that he used the term for the first time in his presidential address to the American Educational Research Association in San Francisco in April, 1976 (Mosteller and Fisher 1948).
One of the earliest books on meta-analysis is said to have been published in 1981. Subsequent statisticians have contributed to further development of the methods for meta-analysis. The most recent milestone in the journey of EBM is the development of the Cochrane Collaboration devoted to systematic reviews and meta-analyses of clinical studies to guide clinical practice and research.

The next chapters in this book are devoted to the various steps in systematic reviews and meta-analysis of RCTs. Except for a few differences, the principles for systematic reviews and meta-analysis of non-RCTs, diagnostic studies, and animal studies are similar to those for RCTs. We have covered the essentials of the methodology for systematic reviews of these three different types of studies as a detailed discussion on them is beyond the scope of this book.

**References**

Alm G. Monography of Swedish fresh water ostracoda along with the systematic review of Tribus Podocopa. Zoologiska Bidrag Från Uppsala. 1916; 4. 1–248.


