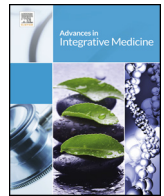




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Review

Systematic reviews in integrative medicine: A clinician’s guide to publication

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ABSTRACT

The role of evidence-based medicine in integrative medicine is becoming increasingly important, and with this increasing comes a need for succinct summaries of research evidence. Systematic reviews are essential to summarise evidence relating to efficacy and safety of healthcare and to summarise health care trends and phenomena accurately and reliably. However, reviews can bring with them numerous biases and methodological issues, particularly related to the sourcing of information used, and therefore need to be conducted in a systematic and methodical process. Specialised fields such as integrative medicine bring with them their own unique challenges in conducting an accurate and reliable review. This article describes practical and academic insights into writing a systematic review for publication.

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1. Introduction

Evidence-based medicine (EBM) focuses on ensuring that clinical decisions about individual patients are made on the basis of the most up-to-date, solid, reliable scientific evidence, and is equally as important for integrative medicine as it is for any other clinical field [1]. Whilst available research evidence, clinical experience and patient needs and expectations are *all* important considerations in EBM, access to contemporary research summaries are an essential part of this process. However, the growth and decentralisation of medical research literature occurs at an increasing rate, adding millions of research papers each year to the body of medical knowledge [2]. Such growth is clearly unwieldy and inaccessible for most clinicians, and clinical reviews have become increasingly important as a method of keeping up to date with research developments in clinical practice. Systematic reviews in particular are essential tools for summarising evidence accurately and reliably. In an era in which EBM is becoming increasingly important, systematic reviews help clinicians keep up to date; provide evidence for policy and decision makers; provide valuable starting points for clinical practice guidelines and provide summaries of previous research for funders and researchers.

1.1. What is a systematic review?

In its most basic definition, a systematic review is a comprehensive high-level summary of primary research on a specific research question that attempts to identify, select, synthesise, and appraise all high quality evidence relevant to that specific question [3,4]. Before systematic reviews become the norm, authors were free to pick and choose the research papers that supported their particular viewpoint. This clearly biased approach led to reviews that in turn led to poor decisions being made about healthcare – as highlighted by Antman et al.'s seminal *JAMA* study comparing meta-analyses results with clinical expert opinions on the treatment of myocardial infarction [5]. The systematic review was specifically developed to try to reduce the influence of the reviewer's own individual bias, and does so by deciding in advance what evidence to include and how it should be used. Just as case reports become a more important research tool once standardised approaches to case reports had been developed [6], reviews become more accepted and integrated into EBM once clear standards had been developed, and are now near the top of the research evidence hierarchy [3,4]. Many journals, including *Advances in Integrative Medicine*, are increasingly hesitant to publish non-systematic reviews, as not only may they be intentionally or unintentionally biased, but the lack of methodical and systematic process make them difficult to replicate, update or compare.

1.2. Other types of systematic reviews and meta-analyses

Some reviews are called 'critical reviews' or 'integrative reviews'. These are an extension of systematic reviews, and differ largely where the research question will not return the same kinds of studies or have multiple outcome measures over differing methodologies, which requires additional critical analysis of results. However, they remain systematic and employ the same methodological process as any other systematic review. For example, exploring the factors associated with integrative medicine use in rural areas [7] or the indirect risks associated with integrative medicine use [8] may require a critical review as they will report findings of multiple studies using multiple methodologies, whereas exploring the impact of a specific integrative therapy (e.g. yoga) that are most effective at treating a specific condition (e.g. depression) [9] will require a

systematic review as the studies will report only the findings from interventional studies.

Although the terms are often used interchangeably, systematic reviews and meta-analyses are not the same. A meta-analysis utilises statistical methods to quantitatively evaluate pooled data from single studies. Often, meta-analyses are included as part of systematic reviews. Heterogeneity is also a factor that differentiates systematic reviews from meta-analyses. It would be wholly inappropriate – from a statistical point of view – to pool dissimilar studies in a meta-analysis, but it may be appropriate to undertake a systematic, critical or integrative review. The issue of heterogeneity ought to be considered before developing a research question, as it can be a double-edged sword which improves external validity at the cost of internal validity. In other words, the more narrow the inclusion criteria the more homogenous the data will become, but this necessitates exclusion of patients with certain characteristics and exposures (e.g. multiple medications), which may make the results less generalisable.

Recently, there has been focus on conducting systematic reviews of systematic reviews, as the amount of information (and reviews) available becomes overwhelming [10]. However, these can be problematic. Systematic reviews do have considerable weaknesses – notably that they can come to quite contrasting conclusions depending on the quality control tools or scales used in assessing trials [11]. These scales have rarely been tested for inter-rater variability, there is generally lack of agreement between scales as to what is being measured, and scales differ considerable on number of items included and the importance of each item. Yet these tools and scales are highly relevant to the outcomes of systematic reviews, as they determine which trials will be incorporated in the review. For example, analysis of the efficacy of homoeopathy as a treatment has been demonstrated to show it can be both highly effective or highly ineffective depending on which trials are included or excluded in a review based on differing interpretations of quality scales [12]. The strength of a systematic review – using a unified approach to evaluate and assess numerous articles on a given topic – is lost when comparing *across* systematic reviews, as systematic reviews are usually as heterogeneous as individual articles, but are harder to systematically synthesise in a coherent, concise and rigorous manner.

2. Finding and reviewing the literature

The fidelity and value of a literature review rests heavily upon the process undertaken in both finding and reviewing the literature in question. Whilst there are guidelines which outline the process of reporting a literature review when preparing a manuscript for publication (e.g. the PRISMA statement), these guidelines are only of value if the correct process has been followed from the start. The following steps should be followed when undertaking a literature review to ensure the result is as comprehensive and relevant as possible.

2.1. Clarifying the question

A clear and descriptive research question should be articulated from the outset to allow the research team to build the search terms and identify the appropriate evaluation tools. To develop a research question the specific topic must be identified. In addition, the research team needs to determine whether date or language restrictions will be applied. Date restrictions are used when a literature review has been already been conducted in the past and the intended review is an update on this previous work, or changes between historical and contemporary practices in the field would detract from the overall findings if combined. Whilst it is common for review articles to restrict primarily to English language articles,

it is important that when a significant body of work is known to have been conducted in a non-English speaking country that the language restrictions allow for articles written in other relevant languages to be included. The process of developing and clarifying a research question can often be an iterative process which draws on the existing literature in the field and previous publications to inform the final research question.

2.2. Identifying search terms

Once a research question has been defined the research team must then decide on search terms to be used to find the relevant articles. The use of appropriate search terms is vital to ensure important publications are not missed. Familiarity with the field of study is necessary for this step as search terms should always include related synonyms (e.g. complementary medicine, complementary therapies, alternative medicine, alternative therapies, integrative medicine, natural medicine, herbal medicine, holistic health and holistic medicine may all be used for a complementary medicine literature review topic). Ideas for search terms can be gleaned from subject heading lists on databases (e.g. MeSH terms on Medline/PubMed) as well as from the methodology section of previous literature reviews on similar topics.

2.3. Locating papers

2.3.1. Databases

Peer-reviewed publications are primarily accessed through bibliographic databases and it is important in any literature review that the broadest sweep of databases as is practical and possible is undertaken to ensure all relevant articles are located. The three major research databases used for literature reviews are MEDLINE/PubMED, EMBASE and Cochrane Central. However, it is essential in specialised fields such as complementary medicine (CM) and integrative medicine (IM) that other databases publishing topical research are included and a recent analysis of controlled clinical trials of CM found an additional five databases which yielded records not listed on MEDLINE [13] (see Table 1). Even in conventional specialist fields (such as physiotherapy), failing to extend searches to specialised databases can result in missing one in ten research papers [14].

2.3.2. Registries

Prospective registration of clinical studies is being increasingly mandated by journals, funding agencies and ethics committees [15]. As such, searches for systematic reviews of therapeutic interventions should also extend to study registries, such as the World Health Organization's International Clinical Trials Registry Platform (which includes data from national databases such as clinicaltrials.gov from the United States or the Australian and New Zealand Clinical Trial Registry), to include data which may not be

yet published. Searching these databases are mandated for Cochrane Reviews, for example, to help reduce the impact of publication bias [16]. These searches should be considered as equally important as bibliographic databases, as they often uncover unpublished trials that, if not included, would not give an accurate overview of the efficacy of therapies [17].

Just as registration of trials is important, registration of systematic reviews is also increasingly common, to help avoid duplication of effort and encourage researchers to publish results irrespective of outcome. Before beginning a systematic review, prospective reviewers should check the internationally recognised systematic review registry PROSPERO [18] to ensure their research topic is not already being undertaken, and reviewers should register their own review once the decision has been made to move forward.

2.3.3. Manual searching

In addition to the use of bibliographic databases, it is also appropriate to use 'manual searching' to identify potential papers for review. The process of manual searching involves a targeted exploration of specific journals or other sources. This may include searching past issues of a peer-reviewed journal which is particularly topical to the research question but may not be listed on the selected databases. Alternatively, websites which are known to list published research on the chosen topic may also be searched to identify any possible 'missed' papers for inclusion in the review.

2.4. Downloading and filtering papers

All manuscripts located through database searching are downloaded to a reference management software programme (e.g. Endnote, Refworks, Mendeley, etc.). This will include a large number of irrelevant papers which will be filtered and sorted *after* downloading. The total number of papers downloaded from each database must be recorded for reporting in the final manuscripts. Once downloaded, the located records must be filtered to identify the relevant papers to be included in the review. The process involved in sorting and filtering is as follows:

1. *Remove duplications* – all records which have been downloaded more than once (due to indexing on multiple databases) are removed so that only one record for each manuscript remains. The number of duplicates removed must be recorded.
2. *Filter by title* – the title of each record is reviewed to identify records which are irrelevant to the research question. The number of records removed based on their title must be recorded.
3. *Filter by abstract* – the abstract of each remaining record is reviewed to identify records which do not fit within the specific restrictions of the research question. It is good practice to take

Table 1

Bibliographic databases for use in complementary and integrative medicine literature reviews.

Bibliographic database	Description
MEDLINE/PubMed	MEDLINE contains journal citations and abstracts from biomedical literature. PubMed provides free access to MEDLINE
EMBASE	Indexes biomedical evidence within published, peer-reviewed literature, in-press publications and conference abstracts
Cochrane CENTRAL	Reports of randomised controlled trials
AMED (The Allied and Complementary Medicine Database)	Indexes bibliographic records for research associated with complementary and integrative medicine, hosted by the British Library
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	Focuses on nursing and allied health journals
PsycINFO	Centres on psychology and the behavioural and social sciences
Acubriefs	References on acupuncture in the English language
MANTIS (The Manual, Alternative and Natural Therapy Information System)	Indexes bibliographic records for research associated with complementary and integrative medicine

note not only the number of records removed in this step, but also the broad categories of reasons for which they were removed. For example, were there a number of manuscripts which employed a different research design, or a different population sample compared with those intended to be examined through this review?

4. *Filter by full-text* – the full-text of each remaining record must be accessed for this final stage to verify the relevance of the article for inclusion in the review. As with the previous step, it is necessary to document the number and reasons any manuscripts were removed at this point.

2.4.1. Inclusion and exclusion criteria

Inclusion and exclusion criteria ideally should be established in the protocol development stage and should inform the development of a checklist for deciding which studies to include and which ones to exclude. These criteria need to be closely linked to the research question that you have specified in your protocol – they may be based on: study design (e.g. randomised or controlled trials only); participants (e.g. patients who have experienced the symptom for a period longer than six months); the intervention (e.g. Chinese medicine acupuncture rather than broader ‘needling’ therapy); language (e.g. studies in English); types of control or types of outcomes (these last two may allow for further meta-analysis). You may wish to include only those articles with data, rather than commentary or other reviews, though these latter may be useful for identifying additional articles for inclusion.

2.4.2. Language

Language is a particularly relevant concern for integrative medicine, as much of the evidence may not be published in the English language. Limiting searches to English in integrative medicine treatments tends to result in reviews and meta-analyses that underestimate the effectiveness of integrative therapies [19]. This is obvious in therapies associated with traditional medicine, where much research will be located in journals in the languages most relevant to the traditions from which these therapies emerged. This has been demonstrated in trials of Chinese medicine, for example [20]. However, the importance of extending language filters is relevant even in interventions not typically associated with one tradition. The first meta-analysis of St John’s Wort published in the *British Medical Journal* in 1996, for example, noted that had it not extended its search beyond the English language (most articles were in German) it would not have included a single study before 1994 (it eventually included 23) [21].

2.5. Data extraction

Once the papers to be included in the review have been identified, the research team must then extract the relevant information from each manuscript to summarise and discuss for the literature review. This is often achieved through a summary table which includes information regarding the manuscript author/s, country where the research was conducted, research method employed, participant/dataset information, target population, sample size, and other details relevant to the specific review question.

2.6. Appraising the data

A quality literature review requires not only summary of the included papers but also critically appraisal of the research design, methodology and report of findings of each paper. Critical appraisal of research through a literature review assists the readers in determining the value to be placed on the findings

of included studies and is used as a platform for identifying gaps in the research for future enquiry. It is also a necessary element in a literature review which aims to inform changes to policy and practice to ensure recommendations are based on sound findings from rigorous research. A number of critical appraisal tools have been developed by expert researchers to assist with this process and provide consistency across reviews (see [Table 2](#)).

2.7. Reporting the data

As in all other articles, care should be taken to ensure that the systematic review is written in a scholarly or academic tone. Further ‘writing style’ recommendations can be seen in the first article of the methodology series on case studies [6]. In addition to stylistic considerations, the PRISMA statement [4] offers a checklist of items to be included in a systematic review.

Title: The title should include the words systematic review (and meta-analysis, if it includes one) or critical or integrative review.

Abstract: The abstract should be a structured summary which includes: background; objectives; data sources; study eligibility criteria, participants and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings.

Introduction: The introduction should include the rationale for the review in the context of what is already known about the topic of the review, and should provide an explicit statement of questions being addressed with reference to PICOS.

Methods: The methods section of a systematic review should be as rigorous as that of any other piece of research. It should specify: eligibility criteria; all information sources (e.g. databases and journals hand-searched); a full electronic search strategy for at least one database (usually MEDLINE, and usually attached as an appendix); the process for selecting studies (i.e. screening, eligibility for inclusion in the review); details of the data collection and extraction process; details of the variables for which all data was sought; methods used for assessing risk of bias in individual studies; the principal summary measures (e.g. risk ratio, difference in means); a description of synthesis of results (i.e. the methods of handling data and combining results of studies); and any assessment of risk of bias that may affect cumulative evidence (e.g. publication bias, selective reporting within studies).

Results: The results section should include a flow diagram ([Fig. 1](#)) which presents numbers of studies screened, assessed for eligibility, included in the review, with reasons for exclusion at each stage. Study characteristics (e.g. study size, PICOS) should be presented with citations to the source articles. Data on risk of bias should be included for each study. For all outcomes considered a simple summary data for each intervention group should be presented.

Discussion: In the discussion section the main findings including the strength of evidence for each main outcome should be discussed in relation to their relevance to key groups (e.g. healthcare providers, users and policy makers). Limitations at both study level (e.g. risk of bias in included studies) and at review level (e.g. incomplete retrieval of identified research, reporting bias) should be adequately and appropriately discussed. A general interpretation of the results in the context of other evidence, and implications for future research should be discussed in a manner that is consistent with the results (i.e. does not ‘speak beyond the data’).

Funding: If your project has received some funding this should be acknowledged in the article.

Table 2
Critical appraisal tools for literature reviews.

Study type	Title	Description	Link/reference
Cohort and cross-sectional studies	CASP Cohort Study Appraisal Tool	A methodological checklist which provides key criteria relevant to cohort studies	http://media.wix.com/ugd/dded87_e37a4ab637fe46a0869f9f77dacf134.pdf
	NIH Quality Assessment Tool for Observational Cohort and Cross-sectional studies	A checklist for appraising observational study designs including cohort and cross-sectional studies	https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiopvascular-risk-reduction/tools/cohort
Qualitative research	CASP Qualitative Research Appraisal Tool	A methodological checklist which provides key criteria relevant to qualitative research studies	http://media.wix.com/ugd/dded87_29c5b002d99342f788c6ac670e49f274.pdf
	McMaster University Critical Review Form for Qualitative Studies	A generic qualitative appraisal tool, accompanied by detailed guidelines for usage	http://www.unisa.edu.au/Global/Health/Sansom/Documents/iCAHE/CATs/McMasters_qualreview_version2%200.pdf
Mixed methods research	A Scoring system for Mixed Methods Research and Mixed Studies Reviews	This scoring system assesses Qualitative, Quantitative experimental, Quantitative observational and Mixed Methods at the one time	Pluye et al. (2009) <i>International Journal of Nursing Studies</i> 46:529–546
	HCRPRU Evaluation Tool for Mixed Methods Studies	Allows appraisal of both the qualitative data collection and analysis component and the wider quantitative research design. It is applicable where the aim of the qualitative component is to draw out the informants understandings and perceptions	http://usir.salford.ac.uk/13070/1/Evaluative_Tool_for_Mixed_Method_Studies.pdf
Case control studies	CASP Case Control Studies	A methodological checklist which provides key criteria relevant to case control studies	http://media.wix.com/ugd/dded87_63fb65dd4e0548e2bfd0a982295f839e.pdf
Case Reports	The Single-Case Experimental Design (SCED) Scale	Developed to assess the methodological quality of single-subject designs. It is a validated scale that can also be used as a single-subject case study design checklist	http://www.psychbite.com/docs/The_SCED_Scale.pdf
Randomised-controlled trials	CASP Randomised-controlled trials	A methodological checklist which provides key criteria relevant to randomised controlled trials	http://media.wix.com/ugd/dded87_40b9ff0bf53840478331915a8ed8b2fb.pdf
	The Consort Statement	A detailed document which outlines an explanation and elaboration of the CONSORT statement for reporting randomised controlled trials and includes a critical appraisal tool	http://www.consort-statement.org/downloads
	The Delphi List	A set of generic core items for the quality assessment of RCTs	Verhagen et al. (1998) <i>Journal of Clinical Epidemiology</i> . 51:1235–1241
	The JADAD Scale	Assesses the quality of published clinical trials based methods relevant to random assignment, double blinding, and the flow of patients	http://onlinelibrary.wiley.com/doi/10.1002/9780470988343.app1/pdf
Non-randomised Controlled Trials	The Trend Statement	A 22-item checklist specifically developed to guide standardised reporting of non-randomised controlled trials	http://www.cdc.gov/trendstatement/docs/AJPH_Mar2004_Trendstatement.pdf

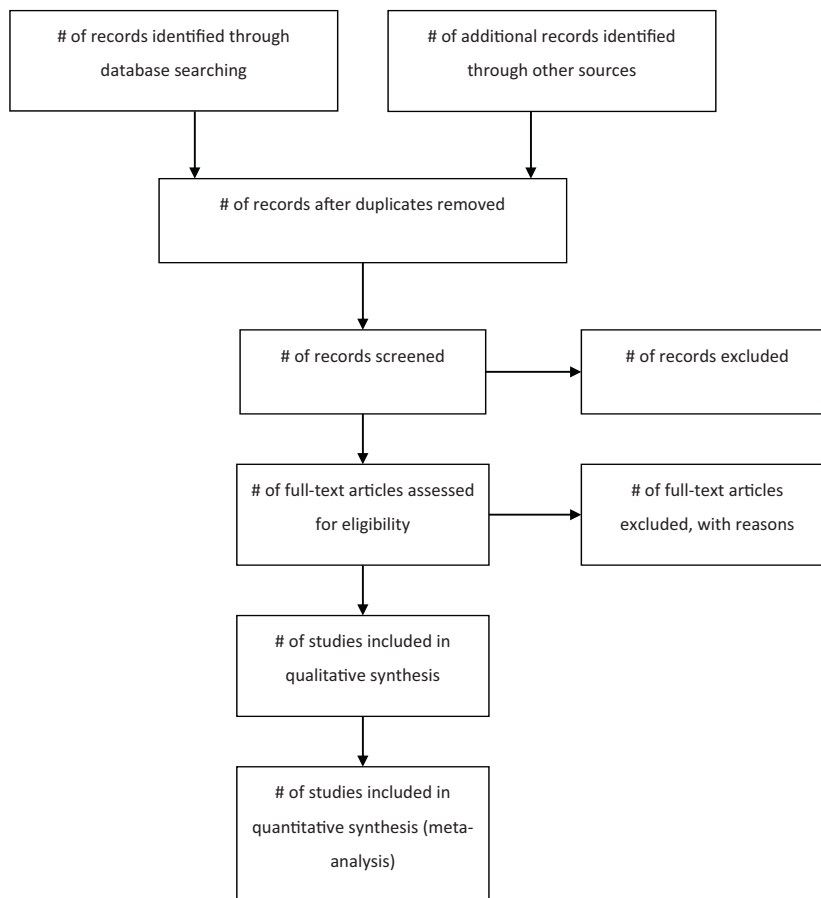


Fig. 1. Flow of information through the different stages of a systematic review [3].

3. Summary

Systematic reviews are sometimes erroneously considered to represent less effort than a primary clinical study, however, as can be seen in this article, a quality systematic review requires considerable and significant preparation and planning. A methodical and rigorous approach is incredibly important, however, as a less than thorough review may miss important studies, which can significantly affect conclusions. In a specialised field such as integrative medicine this is particularly important, as much of the research may be 'hidden' in specialist databases. However, a well-conducted review of good primary data can be both satisfying to the researchers in addition to being beneficial to patient care. In a field such as integrative medicine, where the need for clinical evidence summaries is so pronounced, they can also assist with the development of the field.

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