



How to write a systematic literature review: a guide for medical students

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Why write a systematic review?

When faced with any question, being able to conduct a robust systematic review of the literature is an important skill for any researcher to develop; allowing identification of the current literature, its limitations, quality and potential. In addition to potentially answering the question, the information will give guidance to the planning and suggestion of the value of novel research.

Significant experimental endeavours should be preceded by a comprehensive review of the subject and should exhibit the same rigour as any laboratory experiment in the assessment of both quantitative and qualitative data.

Recent decades have seen the replacement of authoritative reviews by fully systematic assessment of the literature. Enthusiasts of the authoritative/opinionated review would argue that this method allows the reviewer to negate poorly conducted research from both quantitative and qualitative consideration, but such a method inappropriately allows the biased, imprecise and 'unreliable' presentation of evidence.

Poorly conducted systematic reviews can mislead just like any other experimental study, yet meticulous planning and execution of the study design can minimise the compromising factors.



Important definitions:

A **systematic literature review** attempts *'to identify, appraise and synthesize all the empirical evidence that meets pre-specified eligibility criteria to answer a given research question'* (Cochrane definition, 2013).

A **meta-analysis** is a statistical assessment of the data provided from multiple studies or sources that attempt to ask/answer the same question.

Objectives

This guide aims to serve as a practical introduction to:

- the rationale for conducting a systematic review of the literature
- how to search the literature
- qualitative and quantitative interpretation
- how to structure a systematic review manuscript



Generating a hypothesis

Like an experimental investigation, review of the literature and assessment of previously acquired data is conducted to test a hypothesis. In this regard, a review does not differ in attempting to test hypotheses, synthesise a new idea or reach a conclusion.

A vague question is likely to lead to a vague answer. It may be advised, therefore, to limit the review question and/or aims in synchrony with a limited systematic search, discussed in the next section.

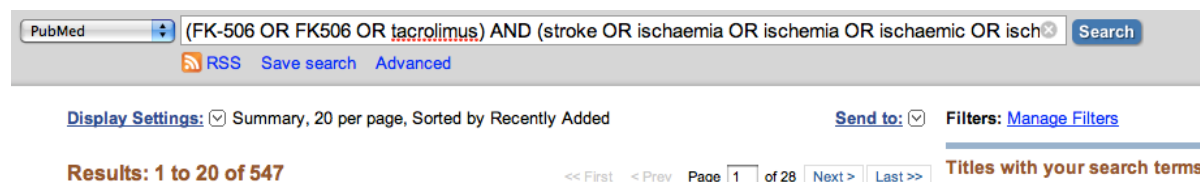
Important definition:

A **hypothesis** is a proposed explanation for an observation, one that may be investigated (**scientific hypothesis**) or may be carried forward (**working hypothesis**).

Searching the literature

What to search

Literature search engines work by automatic, algorithmic assessment of a search string. Despite the many advantages of this approach, it is often difficult to strike a balance between broad and specific searching. Subjects of high interest such as stroke are heavily investigated, so a simple search of ‘stroke’ generates over ten-thousand results. Therefore a specific search using a well thought out collection of keywords (or ‘search string’) is required to whittle down hundreds, if not thousands, of published studies in any one paradigm.



The screenshot shows a PubMed search bar with the query: (FK-506 OR FK506 OR tacrolimus) AND (stroke OR ischaemia OR ischemia OR ischaemic OR isch). Below the search bar are options for RSS, Save search, and Advanced. The results section shows 'Results: 1 to 20 of 547' and navigation links for First, Prev, Page 1 of 28, Next, and Last. There are also links for Display Settings, Send to, and Filters.

A suitable ‘search-string’ for a search engine is specific, inclusive and aware of the variability in terminology/reporting. For the example, a search for investigating the efficacy of a neuroprotective drug: *(drug-x OR drug-x-alternative-name(s) OR drug-x-alternative-spelling(s)) AND (stroke OR isch(a)emia OR isch(a)emic OR cerebrovascular accident OR encephalic vascular accident)*. It is important to be consistent with and document your keywords since it is a requirement to state these in the manuscript.

Further limits can be set on automatic searches, but care needs to be taken since inappropriately strict limits may exclude valid search results. Some authors choose to find the literature published within a certain publication time window (justified or not), which can be helpful when reviewing ‘recent’ advances in a particular field. However, this approach is not appropriate in some systematic searches and certainly not meta-analyses, since influential studies may be eliminated from consideration.

Depending on the nature or aim of the review, it may be appropriate to only consider certain types of study (such as case control, randomised controlled trial or cohort) and is



particularly useful when there are too many studies found to be considered for a qualitative review.

Where to search

Literature search engines are powerful tools. However, there are differences between these sources and care needs to be taken to ensure that all relevant data is obtained. Multiple engines should therefore be employed in a systematic search;



The PubMed, Medline/OvidSP (includes EMBase), Web-of-Science and BIOSIS search engines should be considered. Furthermore, to reduce the influence of publication bias, abstracts presented at an appropriate and justified selection of conferences should be manually searched.

An obvious, but important point to remember is that there may already be a review(s) similar to that which you are considering, and effort to find these should be made (with help from the Cochrane library and similar resources). Discovery of such may not necessarily negate the value of conducting a review, but may further hone its purpose.

Manual scoping for studies cited by articles your review turns up, but that do not appear after in the algorithmic search itself ('grey literature'), provide further studies for inclusion in your review.

Subscription to updates, according to the search string, from databases used allow the author to be alerted to the publication of new studies meeting the search criteria, allowing inclusion of studies that are published between the conducting of the search and to the writing of the report. This is particularly important since a review is strictly 'out-of-date' as soon as a new study emerges.

Managing your findings

A meticulous search must be coupled with meticulous record keeping.

Inclusion and rejection of studies found in literature researching must adhere strictly to selection criteria set out accordingly to answer the review pre-determined questions and/or aims (pre-determine to minimise selection bias).

Although it is not always possible, two independent reviewers should conduct the systematic literature search and consequent data assessment. This would further reiterate the importance of detailed rationale and a well-communicated record of the inclusion criteria. Rejected studies must be recorded and a third party must resolve any disagreement between reviewers, most appropriately by a supervisor.

Commonly reviewers report that inclusion was determined on reviewing the study abstracts alone, and that certain articles were rejected if sufficient information was not presented. However, this may be inappropriate since some journals have strict limits on abstract content and demand qualitative rather than quantitative abstracts (e.g. Nature). It may be more appropriate to acquire the full-text to determine inclusion rather than reject a study based on lack of data found in the abstract (although, of course, this is a more time consuming approach).

The full-text versions of studies should be sought out for inclusion in the review. Institutions may not offer full-text acquisition for all journals, particularly for less established/minor journals. Therefore justification for acquisition should be submitted to



the University Library services or polite communication to the original author should be made if the full-text is not available (or if data is missing).

Language continues to be a barrier in the global communication of research and it is still found that authors will variably favour to cite their nation's research. Studies should not be excluded from review due to language but rather retained and translated by a professional, if possible. Abstracts are usually published in English and should provide the reviewer with good indication and cause for translation.

Collected data from systematic searches should be documented in an appropriate format. This is conducted in a way that suits the reviewer best. An example is provided below in which the data from a systematic search are documented in Microsoft Excel and the references retained in Mendeley referencing software.

First Auth	Date	Source	Language	Funded	Animal	Sex	Model	Sample Size	Age at Treat	Comorbidity	Dose	Time of Treatment	Duration	Delivery	Anaesthetic	Control group	Measure of Outco	Time of Measurem	Result(s)	No of refe
Alba	Jan-11	Rev 14	Spanish																	
Castel	Aug-11	Transp	English																	
Caumartin	May-11	Kidney	English																	
Chamienia	Oct-11	Transp	English																	
Chauhan	Dec-11	Behav	English																	
Dhauhan	Dec-11	Behav	English																	
Dhauhan	Dec-11	Behav	English																	
Chen	Jan-12	Surg	English																	
Cicora	Jan-12	Clin Exl	English																	
Cicora	Jan-12	Medical	Spanish																	
Cimsit	Apr-11	Transp	English																	
Esposito	Feb-11	Am J N	English																	
Feng	Mar-11	Cardiol	English																	

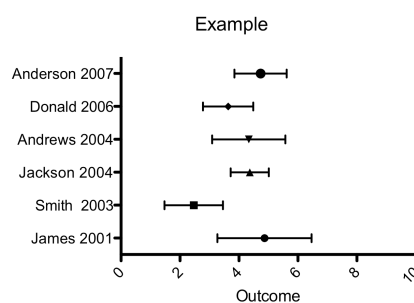
Authors	Title	Year	Published In	Added	Details	Notes
Nito, Chikako...	FK506 ameliorates oxidative damage and protects rat br...	2011	Neurological research	10:2	<p>FK506 ameliorates oxidative damage and protects rat brain following transient focal cerebral ischemia.</p> <p>Authors: C. Nito, M. Ueda, T. Inaba et al.</p> <p>View research catalog entry for this paper</p> <p>Journal: <i>Neurological research</i></p> <p>Year: 2011</p> <p>Volume: 33</p> <p>Issue: 8</p> <p>Pages: 881-9</p> <p>Abstract: The immunosuppressant FK506 (tacrolimus) is neuroprotective in experimental models of cerebral ischemia. However, the precise mechanisms underlying this neuroprotection remain unknown. In the present study, we hypothesized that FK506 treatment could protect rat brain from oxidative injuries through antioxidative and anti-inflammatory pathways after ischemia-reperfusion injury.</p>	

Interpreting your findings

If sufficient quantitative data is found, it may be appropriate to conduct a meta-analysis, using statistical methods to present and assess the data collected by primary studies. This method is of particular use in reviewing the efficacy of a therapy or diagnostic test, provided it is measured quantitatively and is comparable between studies.

Despite data handling being reliant on the sort of data collected, some forms of analysis can be anticipated.

Firstly, meta-analysis could be employed to assess the collective efficacy of a drug-x across all the studies identified. An effective method of combining different measures of outcomes is to use odds ratios calculated from each outcome with 95% confidence intervals. Analysis of statistical significance may then be employed to estimate the magnitude of effect and heterogeneity between the studies. The data can then be plotted into a forest-plot,



ranked by effect size. This is appropriate in a review situation since the individual datasets are provided and the distribution represented.

If at all unsure, the methods of statistical analysis should be consulted with a statistician (or at least a supervisor) before the review commences.

Systematic review allows the assessment of primary study quality, identifying the weaknesses in current experimental efforts and guiding the methodology of future research. Choosing the features of study design to review and critique is dependent on the subject and design of the literature identified. A list of methodological considerations in animal studies, adapted from CAMARADES, is listed in Box 1. This is just one of many resources, that are tailored to each particular paradigm, that can be employed to assess study quality. There are various methods of analysis of graphical representation, such as funnel plots (e.g. presenting publication bias) and review tables (e.g. tick-table).

Box 1. CAMARADES checklist:

1. Published in a peer-reviewed journal
2. States control of temperature
3. Randomization of treatment and/or control
4. Allocation concealment
5. Blinded assessment of outcome
6. Avoidance of anaesthetics with potential influencing properties
7. Use of animals with hypertension or diabetes (a representative study)
8. Evidence of sample-size calculation

Structuring the review

Abstract

A brief background, aims/hypothesis, summary of methods of searching, summary of quantitative results and conclusion/inference should be provided in the review abstract. An abstract derived from the earlier described demo-search may be similar to:

Decades of research and experimental study have investigated strategies for stroke treatment, but significantly efficacious neuroprotective interventions have not been developed or translated into clinical practice. This systematic review and meta-analysis will assess the latest evidence investigating FK-506/tacrolimus in experimental stroke studies published until February 2012, testing the hypothesis that this therapy provides significant neuroprotection to the brain in this particular paradigm. A systematic search of PubMed, WebofScience, BIOSIS was performed independently by two reviewers using predefined criteria. In addition, abstracts from selected conference proceedings (x and y) were screened and reference scanning of the search results was performed. X number of studies were met the selection criteria and were considered for review. The data collected shows...(results)...and may suggest...(conclusion).

Introduction

The question being asked should be emphasised, the unknowns in the literature highlighted and the aims/hypothesis stated. It is important to identify and justify the need for the review, and to state the potential implications of its completion (for example, the clinical relevance of identified conclusions). It is also considered good practice to alert the potential reader to existing reviews surrounding the subject such that, in instances where



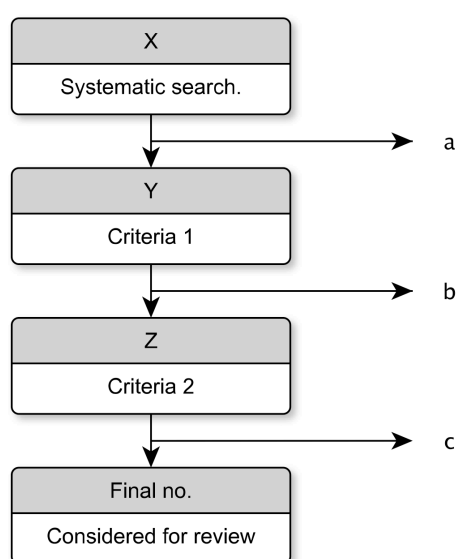
there are none, the author is able to elaborate on the potential novelty of their work.

Methods

This section of the review must be written thoroughly, giving full explanation and justification for the searching and managing steps listed earlier. In particular, justification must be stated for the source of the findings (searching strategy), search terms/string and limits used, inclusion/exclusion criteria, how studies were screened (e.g. abstract screening, and who/how many people did this), data extraction, how disagreement of inclusion was decided between reviewers and method of quality assessment. Full explanation/justification of methods of statistical analysis should be provided.

Also, if the review has adhered to a previously published review protocol then this should be declared.

Results



Firstly, thorough quantitative evidence and explanation should be given to the process of study inclusion/exclusion (start to finish) and summarised in an appropriate flow diagram.

Secondly, a summary of the study characteristics should be derived, informing the reader of the total number (sum of all studies), mean/median, age range, comorbidity and other appropriate characteristics of the subjects considered. Such information can be stored in a graph, but the 'key data' must be present in the text.

A meta-analysis of the efficacy of drug-x is likely to be the main interest of the reader and thus should be reported with rigour. The results and statistical assessment (efficacy and quality) should be appropriately graphically presented (advised in the 'interpreting' section) but also thoroughly explained in the text.

Discussion

Generally, the discussion aims to integrate rather than just list the findings by different studies, highlight the major contradictory data and give suggestions as to how these contradictions may be resolved by future research.

The opening to this section should simply state the main findings concerning the efficacy of a drug-x and the results from the meta-analysis. Next, and more importantly, the results from the review should be applied to what is already known and how this review has (or has not) generated a novel perspective on the subject.

A significant component of the discussion section should be focussed on identifying and discussing the limitations of studies included in the review.



Just like any primary study, a fully systematic review is subject to its own intrinsic limitations. Reviews can only review what is found and therefore even before the search has begun there is an element of publication bias present. Furthermore, this source of bias will be reflected in meta-analysis and may account for an overestimation of treatment efficacy. Other sources of limitations may be due to unavailable data, language barriers and these and others should be admitted in the discussion section. It is particularly important to actively search for and characterise these limitations, so as to ensure transparency and prevent them being identified by the editors following submission of the manuscript.

Conclusion

Finally, a brief and direct interpretation of the findings of the study should be made and suggestion of inference/implications for future research or clinical practice.



Key points:

- Systematic review allows rigorous, impartial and literature-wide assessment of study outcomes, quality and design.
- Poorly conducted systematic reviews can mislead just like any other experimental study.
- A vague question is likely to lead to a vague answer.
- On literature searching, care needs to be taken to ensure that all relevant data is obtained.
- A meticulous search must be coupled with meticulous record keeping.
- Be able to criticise the quality and limitations of the literature in the view to improve future study design.
- Consider what novel finding(s) your review brings to the literature.

Suggested external resources

- The Cochrane Library; <http://www.thecochranelibrary.com/view/0/index.html>
- A BMJ article on meta-analysis; <http://www.bmj.com/content/315/7121/1533#ref-1>
- Two recommended checklists for critical appraisal of study design; CAMARDADES (<http://www.camarades.info/>) and CONSORT (<http://www.consort-statement.org/>)