Evidence-Based Anaesthesia and Intensive Care

edited by
Ann Møller
and Tom Pedersen

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Evidence-Based Anaesthesia and Intensive Care

A comprehensive volume on the theories and applications of evidence-based anaesthesia and critical care. Coming from the internationally renowned Cochrane Collaboration – the global force in evidence-based medicine – this promises to be an authoritative guide for anaesthetists. The Cochrane Anaesthesia Review Group is one of the largest in the collaboration and, as Co-ordinating Editors of the group, the editors of this book have gathered a formidable set of contributions from around the world. The first half of the book provides an introduction to evidence-based medicine and applies the principles to anaesthesia and critical care, including critical appraisal, meta-analysis, interpreting results and controlling bias. The second half shows how to practise this in preoperative evaluation, regional and general anaesthesia, postoperative pain therapy, critical care and acute medicine. Medical professionals working in anaesthesia and surrounding specialties worldwide will find this book immensely useful.

Ann Møller is a specialist in Anaesthesiology and Co-ordinating Editor of the Cochrane Anaesthesia Review Group. Her specific areas of research interest are evidence-based medicine, surgery, anaesthesia and smoking intervention.

Tom Pedersen is Director of Centre of Head-Orthopaedics, Rigshospitalet, Copenhagen and Co-ordinating Editor of the Cochrane Anaesthesia Review Group. His specific areas of research interest are patient safety, quality assurance and evidence-based health economics.

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Foreword

George Hall

Evidence-based medicine has become the new religion for many in the healthcare professions. It is greeted by the believers as the answer to all their clinical problems while the sceptics view this new upstart with grave suspicion and delight in finding discrepancies between the conclusions of evidence-based medicine and large randomised controlled trials. Like many new ideas in medicine, evidence-based practice has matured over the past decade so that a more balanced view of the strengths and weaknesses of this technique is now possible. Ann Møller and Tom Pedersen are authorities in evidence-based medicine as applied to anaesthesia and in this book have assembled a group of distinguished authors.

The first part of the book describes the underlying principles used in evidence-based medicine with a critical evaluation of potential errors and pitfalls. The teaching of evidence-based medicine is a particularly important topic as it is used increasingly in undergraduate medicine. There remains fierce debate over its role in education. The second part of the book explores the use of evidence-based anaesthesia. Many key topics in the specialty are covered and the authors have published extensively in their areas of expertise. Thus this book not only covers the theoretical basis of the subject but also provides practical help for the anaesthesiologist. Unfortunately for the editors and the authors I have no doubt that a second edition will be essential in only a few years time. The "evidence" is always evolving and older studies are found to be no longer relevant to modern anaesthesia.

Ann Møller and Tom Pedersen are to be congratulated on this tome. Although I am unconvinced by all the arguments for, and analysis of, evidence-based medicine I have little doubt that the book will be a *sine qua non* for all departments of anaesthesiology and for many anaesthesiologists.

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1

Introducing evidence-based anaesthesia

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Every year, more than two million new papers are published in scientific medical journals. To keep updated even in a small field or speciality takes an ever-increasing amount of time. The main purpose of evidence-based medicine (EBM) is to aid busy clinicians in making decisions based on scientific evidence. The goal of EBM is to produce systematic reviews and clinical guidelines that summarise scientific knowledge about a topic in a single publication that preferably is updated regularly.

So why should you read (and buy) this book? Because today's clinical anaesthesiologists are faced with an ever-increasing amount of work and new challenges. We have to handle our patients in both a safe and high-quality manner and at the same time adopt new scientific developments. On top of this, we have to teach our skills to those who will succeed us: the trainees. All in all, time is short and our duties are many.

The aim of this book is to meet the needs of health professionals in anaesthesiology as medicine moves to be evidence-based. Our aim is that this book should be a tool to understand the basic and advanced use of evidence-based methodology. It should integrate the results from research articles into useful, clinically orientated summaries of diagnosis, treatment and patient management in anaesthesiology and critical care medicine. Hopefully this book will become both a resource for clinical decision-making, and for decisions concerning the implementation of new technologies or interventions. This book is aimed at practising clinicians, trainees, other health professionals, medical students, teachers in evidence-based anaesthesia and EBM and, last but not least, politicians, managers and decision-makers. The chapters make clear what we know, what we think we know and what we do not know.

The book has been organised into two parts. The first 12 chapters provide the basics of EBM. They introduce EBM, critical appraisal and meta-analysis to identify and/or minimise bias. Other chapters explore clinical and statistical heterogeneity, how papers can be read and their results interpreted. Integrating the principles of EBM into daily practice is an important but often difficult task. Although we are faced with obstacles caused by lack of knowledge, skills and resources, many tools exist to

help us teach and learn EBM. This book attempts to provide, you, the reader with the highlights of educational programmes in EBM, which have been shown to change the behaviour of clinicians; improve critical appraisal skills and the implementation of EBM in the clinical workplace.

Established educational activities, such as journal clubs, can be modified in such a manner as to place EBM at their core. Strategies to disseminate evidence, such as educational programmes, clinical decision support systems and audit, can be useful tools for changing the practice of our colleagues.

The final 14 chapters of this book detail how to practise EBM in preoperative evaluation, regional and general anaesthesia, fluid therapy and the use of antiemetics; and how to use EBM in the subspecialities in anaesthesia, postoperative pain therapy, critical care and emergency medicine. These chapters deal with a selection of topics, which currently are of practical and scientific importance to clinicians.

We hope that this book will provide an exciting agenda for research and clinical work in the field of evidence-based anaesthesia.

2

How to define the questions

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The practice of evidence-based medicine (EBM) begins with the formulation of a clinical question. Defining the clinical question forces you to think about what you really want to know. Clinical questions consist of three parts: the patient or population, the interventions to be compared and the clinically relevant outcomes. The clinical question can be about a single patient, or any group of patients. It can be narrow and thus specific, or it can be wide and sensitive. The intervention can be compared to nothing, to a placebo or to any other relevant intervention or interventions. The outcomes should be clinically relevant; all important outcomes should be considered. Spending time on the question helps the researcher focus on what is important. A well-defined question is a good starting point for finding relevant literature.

Introduction

In our practice, we come across clinical questions many times a day. These clinical questions may arise from several sources: the patient asking for information; your colleagues seeking advice; or from you, simply asking yourself what to do in a clinical situation. The question will often start off as open ended and poorly defined, such as: is propofol better than sevoflurane?

If you want to use an evidence-based approach to finding the answer to your question, your question needs to be well defined. The question can be about diagnosis, prognosis or management. The purpose of this chapter is to describe a strategy for formulating answerable clinical questions. That strategy can help you make conscientious, explicit and judicious use of the current best evidence for making decisions about the care of an individual patient, or a group of patients.

Formulating the question

A well-defined clinical question has three core elements:

1 The patient/population/problem

Key words: clinical question, systematic reviews, outcomes.

2 The interventions/exposures considered
3 The relevant outcomes

Formulating the clinical questions has several purposes. The process of formulating the question helps you consider what you really want to know; several choices have to be made within this process. Once the question has been formulated, it will be a great aid in the process of searching and evaluating the results (as described later in this book).

The formulation of the clinical question is the starting point; whether you intend to use EBM in the handling of an individual patient, if you are writing a clinical guideline for the department you work in, or you are preparing a systematic review.

The patient/population/problem

The patient population can be described from basic factors such as age, sex, race and educational status, or by the presence or absence of a clinical condition such as obesity, chronic heart disease or the need for a specific surgical procedure. Other factors used to describe the patient could be whether they are outpatients or inpatients; whether they live in urban or rural surroundings. The list is endless.

When choosing the patient population, one must be aware that a very narrow and well-defined population description will provide a very precise result (i.e. if a result can be found). An example of this could be: male patients aged between 50 and 70 years, with coronary heart disease scheduled for colorectal cancer surgery. This detailed description is likely to produce very specific results, but only for the narrow group in question. If the next patient is not like the first (i.e. is older, younger or a woman), problems may arise when trying to extrapolate the result.

On the contrary, choosing a wider group of patients will probably yield more results, and these results will cover a much larger group of patients. An example could be: all patients scheduled for knee arthroscopy. This group will include athletic, fit people in their 20s as well as older people with multiple co-existing diseases. With a broader group, there is always the risk that some subgroups of patients will react differently to the intervention. However, the results are much easier to extrapolate. The decision whether to use a narrow or broad question has to be placed within sound clinical judgement on the composition of the patient group.

When performing a systematic review, the approach could be to include a wide group of patients and if plausible, plan some subgroup analysis in advance if there is a suspicion that some groups will be different from the others (e.g. children, ASA3+, etc.).

The interventions/exposures considered

The intervention is something we consider "doing" to the patient. It could be a medication, surgical procedure or lifestyle counselling. An intervention could also be anaesthesia, intensive care, ventilatory support or fast tracking. The exposure could

be a toxin, tobacco smoke, or any other substance or incident that "happened" to the patient. The handling would be the same, except usually we find no randomised controlled trials (RCTs) dealing with exposure.

It is important when trying to focus our clinical question to consider which interventions we would offer the patient. If the hospital cannot offer a specific treatment, we may not need to look for it. On the other hand, if the literature search finds that a specific treatment does have a beneficial effect, we may after all wish to consider it to be introduced.

A treatment can be compared to another treatment (surgical versus medical treatment, or comparison of two different surgical methods), to placebo (mostly pharmaceutical trials) or to no treatment.

If feasible, more than two interventions can be compared. Again, this depends on the purpose of the search and how generalised or specific we wish the results to be.

A thorough description of the interventions will help the researcher find relevant papers and appraise their quality.

The relevant outcomes

The definition of, and dealing with, relevant outcomes are described elsewhere in this book (Chapter 6).

However, clinically relevant outcomes are outcomes that the patients feel, function or survive. Other relevant outcomes are for example: costs, length of stay in hospital or intensive care unit and ease of practice. When comparing different interventions it is important to take all relevant outcomes into consideration: even when information on these specific outcomes is likely not to be found.

As in the other part of the question, it is important to define the outcome measures carefully. This will often be a source of heterogeneity between trials. A straight definition will help overcome this problem.

Practice points

1 The formulation of the clinical question helps focus the question. It is the basis of literature search and helps the researcher appraise the papers critically.
2 A clinical question consists of three parts:
   The patient/population/problem
   The interventions/exposures considered
   The relevant outcomes
3 A narrow question yields specific results that are hard to extrapolate. A broad question yields sensitive results that are easier to extrapolate, but carries the risk of overlooking differences in subgroups.

Conclusion

Spending time and energy, formulating the clinical question before undertaking the literature search, and appraisal, is likely to improve the outcome of the process. By concentrating on the problem, one can "straighten" the search and make the critical appraisal more focused.

SUGGESTED READING

1 Sackett DL, Straus SE, Glasziou P, Richardson WS, Rosenberg W, Haynes RB. *Evidence Based Medicine*. Churchill Livingstone: London, 2005.
2 Chalmers I (ed.) et al. *Systematic Reviews*. *BMJ Publishing Group,* London 2002.
3 Higgins J, Green S. (eds). *Cochrane Handbook for Systematic Reviews of Interventions 4.2.5*. The Cochrane Library. Chichester, UK: John Wiley & Sons Ltd, 2005.

3

Developing a search strategy, locating studies and electronic databases

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This chapter shows how to conduct a comprehensive, objective and reproducible search for studies. It can be the most time-consuming and challenging task in preparing a clinical question for a project or a systematic review. Yet it is also one of the most important. Identifying all relevant studies, and documenting the search for studies with sufficient detail so that it can be reproduced, is after all, largely what distinguishes a systematic review from a traditional narrative review in evidence-based medicine. This chapter explains how, and where, the reviewers should look for studies that may be eligible for inclusion in *The Cochrane Library*, MEDLINE, EMBASE and other relevant databases that identify appropriate MeSH terms (Medical Subjects Headings). Although currently it is necessary to search multiple sources to identify relevant published studies, it is envisioned that the *Cochrane Central Register of Controlled Trials* (CENTRAL) in *The Cochrane Library* will become a comprehensive source for published studies, thus reducing the searching burden for authors. Identifying ongoing studies, however, will continue to remain a challenge until a comprehensive, searchable, ongoing trial register is produced to track, organise, and disseminate reports for ongoing studies, as CENTRAL in *The Cochrane Library* does for reports of studies that have been published.

Introduction

How do you find studies that meet your review's inclusion criteria?

You could do a very quick search of one electronic database and find a couple of relevant articles that meet your review's inclusion criteria. At the other extreme you could try to find every single study that has ever been done which addresses your review's question. As you might expect, there are problems with both these approaches. If you do not look very hard, the studies you do find are unlikely to

Key words: Search Strategy, *The Cochrane Library*, MEDLINE, EMBASE, CENTRAL.

be representative of all the studies done on the subject. The reasons for this are explained in detail in Chapter 8 (section "Publication bias"). For the moment, you just need to know that studies with dramatic results are much easier to find than studies that do not have dramatic findings. Another problem with only looking for a few studies is that you end up with less information. This can limit the precision of the results of your review, and restrict the conclusions you can make. However, is it feasible to find absolutely every relevant study that has ever been done? It is certainly not easy and might not be possible in most reviews. Many studies are never published, and those that are, may not be indexed in places, such as MEDLINE, that you would normally look. At some point, the effort required to find more studies becomes too much, but there is relatively little evidence on exactly when we need to stop searching. So, for now, most people adopt a pragmatic approach: look as far and as wide as possible, taking care to look in such a way that we take account of what we know about the biases in finding studies.

Search strategy for the identification of studies

Databases should include: *The Cochrane Library*, MEDLINE, EMBASE and all other relevant databases that identify appropriate MeSH terms and include the optimally sensitive. A common problem with search terms is inadequate indexing in MEDLINE and other databases. For example, random allocation was first introduced as a descriptor term in 1978; randomised controlled trial (RCT) was not introduced as a descriptor term until 1990 and did not appear as a publication type until 1991. All efforts should be made to search conference proceedings of important meetings and abstracts and contact experts in the field in order to identify unpublished research and trials still underway. Any speciality journals that have been hand searched should be identified and referenced. The name of the journal should be entered in full. Your search strategy must be reproducible, and not limited by language or publication status.

How to develop a search strategy?

It is always necessary to strike a balance between comprehensiveness and precision when developing a search strategy. Increasingly the comprehensiveness of a search entails reducing its precision and retrieving more non-relevant articles. Developing a search strategy is an iterative process in which the terms that are used are modified, based on what has already been retrieved. There are diminishing returns for search efforts; after a certain stage, each additional unit of time invested in searching returns fewer references that are relevant to the review. Consequently there comes a point when the rewards of further searching may not be worth the effort required to identify the additional references. The decision as to how much time and effort to invest

in the search process depends on the question the review addresses, and the resources that are available to the reviewer.

CENTRAL serves as the most comprehensive source of records related to controlled trials. As of January 2006, the register contained 463 763 citations to reports of trials and other studies potentially relevant to Cochrane Reviews. CENTRAL includes citations to reports of controlled trials that might not indexed in MEDLINE, EMBASE or other bibliographic databases; citations published in many languages; and citations that are available only in conference proceedings or other sources that are difficult to access [1].

Boolean operators: "OR" and "AND"

An electronic search strategy should generally have three sets of terms: (1) terms to search for the health condition of interest; (2) terms to search for the intervention(s) evaluated and (3) terms to search for the types of study design to be included (typically randomised trials). The exception to this is CENTRAL, which aims to contain only reports with study designs possibly relevant for inclusion in Cochrane Reviews, so searches of CENTRAL should be based on health condition and intervention only. A good approach to developing an electronic search strategy is to begin with multiple terms that describe the health condition of interest and join these together with the Boolean "OR" operator. This means you will retrieve articles containing at least one of these search terms. You can do likewise for a second set of terms related to the intervention(s) and for a third set of terms related to the appropriate study design.

These three sets of terms can then be joined together with the "AND" operator. This final step of joining the three sets with the "AND" operator limits the retrieved set to articles of the appropriate study design that address both the health condition of interest and the intervention(s) to be evaluated. A note of caution about this approach is warranted however: if an article does not contain at least one term from each of the three sets, it will not be identified. For example, if an index term has not been added to the record for the intervention or the intervention is not mentioned in the title and abstract, the article would be missed. A possible remedy is to omit one of the three sets of terms and decide which records to check on the basis of the number retrieved and the time available to check them. An example of Boolean operators is given in Table 3.1.

In the pulse oximetry review [2] the objective was to assess the effect of perioperative monitoring with pulse oximetry and to clearly identify the adverse outcomes that might be prevented or improved by the use of pulse oximetry. We searched MEDLINE (1966 to January 2005) using the following search strategy (Table 3.2).

It is helpful to approach an information specialist for help in suggesting suitable terms for the health condition and intervention. (We consulted the Cochrane Anaesthesia Review Group's Trials Search Co-ordinator.) In general, both controlled

Table 3.1. Example of search strategy for identifying reports of studies about propofol and sevoflurane in relation to postoperative nausea and vomiting (PONV) and complications in *The Cochrane Library*

Search strategy in text words
#1 propofol
#2 sevoflurane
#3 #1 OR #2
#4 PONV
#5 Complications
#6 #4 AND #5
#7 #3 AND #6

Search results: 1 Cochrane Review and 54 records in CENTRAL. For more information see: http://www.mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html

Table 3.2. Search History in MEDLINE to identify perioperative adverse outcomes using pulse oximetry

#23 #6 and #13 and #20 and #21 and #22 (184 records)
#22 #14 or #15 or #16 or #17 (16 572 records)
#21 #7 or #8 or #9 or #10 or #11 or #12 (3 063 655 records)
#20 #18 or #19 (1 584 938 records)
#19 #1 or #2 or #3 or #4 or #5 (1 582 123 records)
#18 explode "Postoperative-Complications" in MIME, MJME (94 776 records)
#17 spo2 (900 records)
#16 desaturation* (4116 records)
#15 anox?em* (6408 records)
#14 hypox?em* (9665 records)
#13 an?esth* (279 578 records)
#12 blind* (132 561 records)
#11 mask* (28 347 records)
#10 control* (1 670 827 records)
#9 trial* (306 176 records)
#8 compar* (1 583 124 records)
#7 random* (290 202 records)
#6 pulse near ox?met* (3161 records)
#5 surg* (1 484 592 records)
#4 intra?op* (60 436 records)
#3 post?op* (350 479 records)
#2 peri?op* (26 679 records)
#1 operation (133 660 records)

vocabulary terms and text words (i.e. those found in the title or abstract) should be used. You should assume that earlier articles are harder to identify. For example, abstracts are not included in MEDLINE for most articles published before 1976 and, so, text word searches will only apply to titles. In addition, few MEDLINE indexing terms relating to study design were available before the 1990s. In designing a search strategy, it may be helpful to look at published papers on the same topic and check the controlled vocabulary terms and text words. Although a research question may address particular populations, settings or outcomes, these concepts are often not well indexed with controlled vocabulary terms and generally do not lend themselves well to searching.

The Cochrane highly sensitive search strategy for MEDLINE [3] was developed specifically with the needs of Cochrane Reviews in mind. The earliest version of this search strategy was developed in 1994 and subsequent versions have been developed, each with a different syntax, specific to the version of MEDLINE being searched.

We applied the first phase of the pulse oximetry strategy to search MEDLINE for all years from 1966 to 2005. We downloaded, printed out and classified the results of our search as definite or possible randomised or quasi-randomised trials, or not using the information in the title and abstract. If no abstract was available, our decision was based on the title alone. Because identification relies solely on the titles and, where available, the abstracts, some relevant articles may not be identified. Therefore, it may still be worthwhile for authors to search MEDLINE using the Cochrane highly sensitive search strategy and to obtain and check the full reports of possibly relevant citations.

Developing a logical approach to searching

In developing your search strategy, there are a few principles. Your search should:

(i) be sensitive: trying to find as many studies as possible;
(ii) minimise bias;
(iii) be efficient.

Search strategies in the Cochrane Anaesthesia Review Group for the identification of studies

Published RCTs and clinical-controlled trials (CCTs) of interventions within the scope of the Cochrane Anaesthesia Review Group (CARG) (http://www.carg.dk) are identified by systematically handsearching specialist journals, relevant conference proceedings and abstracts, and by systematically searching electronic databases such as the Cochrane Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE. We encourage authors to design search strategies specifically for their own review. In Table 3.3 is shown the specific search strategy used for CARG's specialised register.

Table 3.3. The specific search strategy used for CARG's specialised register is quoted below

Electronic searches
MeSH terms
1 Anaesthesia
2 Anaesthetics
3 Analgesia
4 Analgesics
5 Critical care
6 Critical illness
7 Emergency treatment
8 Emergency medical services
9 Emergency medicine
10 Intensive care
11 Fluid therapy
12 Perioperative care
13 Preoperative care
14 Postoperative complications
15 Postoperative period
Key and text words
1 ANAESTHE*
2 ANALGESI*
3 Prehospital
4 Critical care
5 Intensive care
6 Emergency (treatment or medical services or medicine)
7 Recovery room
8 Fluid therapy

Locating studies

Systematic reviews of the effects of health care interventions generally focus on reports from RCTs, when such data are available, because of the general acceptance that this study design will lead to the most reliable estimates of effects. A comprehensive search for relevant RCTs, which seeks to minimise bias, is one of the essential steps in doing a systematic review, and one of the factors that distinguishes a systematic review from a traditional review.

A quick search of, for example, MEDLINE is generally not considered adequate. Studies have shown that only 30–80% of all known published RCTs were identifiable using MEDLINE (depending on the area or specific question). Even if relevant

records are in MEDLINE, it can be difficult to easily retrieve them. A comprehensive search is important not only for ensuring that as many studies as possible are identified but also to minimise selection bias for those that are found. Relying exclusively on a MEDLINE search may retrieve a set of reports unrepresentative of all reports that would have been identified through a comprehensive search of several sources. For example, the majority of the journals indexed in MEDLINE are published in English. If studies showing an intervention to be effective are more likely to be published in English, then any summary of only the English language reports retrieved through a MEDLINE search may result in an overestimate of effectiveness due to a language bias [4–7]. In addition, the results of many studies are never published, and most of these probably remain unknown. If studies showing an intervention to be effective are more likely to be published, then any summary of only the published reports may result in an overestimate of effectiveness due to a publication bias [8–15].

Electronic databases

Where to look for studies?

A search for relevant studies generally begins with health-related electronic bibliographic databases. Searches of electronic databases are generally the easiest and least time-consuming way to identify an initial set of relevant reports. Some electronic bibliographic databases, such as MEDLINE and EMBASE, include abstracts for the majority of recent records. Often a researcher can determine an article's relevance to a review based on the abstract, and can thereby avoid retrieving the full journal article, if the reported study is clearly not eligible for inclusion. Another advantage of these databases is that they can be searched electronically, for either words in the title and abstract, or using standardised subject-related indexing terms that have been assigned to the record. For example, the MEDLINE indexing term RANDOMISED-CONTROLLED-TRIAL (Publication Type) was introduced in 1991 and allows a user to search for articles describing individual randomised trials.

Hundreds of electronic bibliographic databases exist. Some databases, such as MEDLINE/PubMed and EMBASE, cover all areas of health care and index journals published from around the world. Other databases, such as the Australasian Medical Index, the Chinese Biomedical Literature Database, the Latin American Caribbean Health Sciences Literature (LILACS), and the Japan Information Centre of Science and Technology File on Science, Technology and Medicine (JICST-E) index journals published in specific regions of the world. Others, such as the Cumulative Index of Nursing and Allied Health (CINAHL) and AIDSLINE, focus on specific areas of health. The Cochrane Collaboration has been developing an electronic database of reports of

controlled trials (CENTRAL) that is now the best single source of information about records that relate to studies, which might be eligible for inclusion in Cochrane Reviews. Details of other databases that might contain eligible records are available in the Gale Directory of Online, Portable and Internet databases (http://www.dialog.com). The three electronic bibliographic databases generally considered as the richest sources of trials – CENTRAL, MEDLINE, EMBASE – are described in more detail below.

CENTRAL

This register is part of *The Cochrane Library*. The idea behind this register is that it should be a central place to put all the reports of controlled trials identified through the work of The Cochrane Collaboration. This means that it contains the results of searching MEDLINE, EMBASE, some other databases and a long list of journals, books and conference proceedings. Many of the reports of studies on the register have been included because they might be reports of trials, based on reading the title and abstract (if there was one). The content of CENTRAL changes all the time, as does the indexing of entries and retrieval methods. Guidance on searching CENTRAL has been prepared as part of the CENTRAL Management Plan (http://www.cochrane.us/central.htm). Many of the records in CENTRAL have been identified through systematic searches of MEDLINE and EMBASE.

MEDLINE and EMBASE

Index Medicus (published by the US National Library of Medicine, NLM) and Excerpta Medica (published by Elsevier) are indexes of healthcare journals that are available in electronic form as MEDLINE and EMBASE, respectively. MEDLINE indexes about 4600 journals. PubMed is a free, online MEDLINE database that also includes up-to-date citations not yet indexed (http://www.ncbi.nlm.nih.gov). EMBASE, which is often considered the European counterpart to MEDLINE, indexes nearly 4000 journals from over 70 countries.

The overlap in journals covered by MEDLINE and EMBASE has been estimated to be approximately 34% [16]. The actual degree of reference overlap depends on the topic, with reported overlap values in particular areas ranging from 10% to 75% [17–20]. Studies comparing searches of the two databases have generally concluded that a comprehensive search requires that both databases be searched. Although MEDLINE and EMBASE searches tend not to identify the same sets of references, they have been found to return similar numbers of relevant references.

MEDLINE and EMBASE can be searched using standardised subject terms assigned by indexers employed by the publishing organisation. Using the appropriate standardised subject terms, a simple search strategy can quickly identify articles pertinent to the topic of interest. This approach works well if the goal is to

identify a few good articles on a topic or to identify one particular article. However, when searching for studies for a systematic review the precision with which subject terms are applied to references should be viewed with healthy scepticism. Authors may not describe their methods or objectives well, indexers are not always expert in the subject area of the article that they are indexing, and indexers make mistakes, like all people. In addition, the available indexing terms might not correspond to the terms the searcher wishes to use. The controlled vocabulary search terms for MEDLINE and EMBASE are not identical. Search strategies need to be customised for each database. One way to begin to identify controlled vocabulary terms for a particular database is to retrieve articles from that database, which meet the inclusion criteria for the review and to note common text words and the terms the indexers had applied to the articles, which could then be used for a full search.

Assuming that search results from each database are of approximately equal value, the choice of which to search first may often be a matter of cost, with MEDLINE typically being the less costly option. As noted earlier, PubMed provides free online access to MEDLINE. Other databases, including AIDSLINE, and HealthSTAR are being phased out and their unique journal citations are migrating to PubMed. A new database, called the Gateway (http://gateway.nlm.nih.gov/gw/Cmd) searches PubMED, OLDMEDLINE, LOCATORplus, MEDLINEplus, DIRLINE, Health Services Research Meetings, and Space Life Sciences Meetings.

Sources to be searched to identify randomised trials for systematic reviews

- The Cochrane Controlled Trials Register (CENTRAL)
- MEDLINE and EMBASE
- Other databases as appropriate
- Journals
- Conference proceedings
- Reference lists
- Sources of ongoing and unpublished studies

Should we continue to handsearch?

Despite the considerable efforts described above to identify reports of controlled trials by searching electronic databases, it is still necessary to "handsearch" journals to identify additional reports. For example, MEDLINE and EMBASE only go back to 1966 and 1974, respectively and despite the efforts to extend MEDLINE back further in time; many earlier reports will never be indexed. Similarly, not all journals published in more recent years are indexed in electronic databases and even for those that are; it is not always possible to tell from the electronic record that the report is a trial.

Personal communication

People who have been working in a particular topic area may know of studies that you have not yet found. Reviewers commonly send a list of the studies they have found to the authors of those studies, asking if they are aware of any other relevant studies. Another approach is to write to the manufacturers of relevant drugs or devices and ask if they are aware of any other studies.

Document your search

It is very important to keep an accurate record of what you have searched, when you searched it and how you searched it. This record will help you avoid having to repeat searches and it will also help people using your review to appraise how well they think you have minimised bias.

Keeping it under control

Keeping track of searches can be a challenge. You may find several reports of the same study, and you will probably find the same report of a study in several databases. So you need some way of keeping track of the references you have looked at, and then some way of grouping together all the reports of a single study. You might like to keep a record of where you found each study, so that you can report how useful different sources were. Some people use reference management software to do all this, such as ProCite, Reference Manager, EndNote or IdeaList. If you like working with databases this is great, and can save time typing in references later on. Other people prefer printing out citations and writing on them. What ever system you choose to use, you will need some system for keeping track of which references you think are relevant, which ones you have ordered from the library, which ones you have received the paper for, etc. It is a good idea to keep a note of which studies you have found and rejected. You may well come across them again later and it can be very frustrating to re-read irrelevant records.

Practice points

- The main advice is simply to get some help from an expert.
- Look at the terms used to index and describe a few studies you already know are relevant to your review, and use these terms in your search strategy.
- Add new terms to your search strategy and then pilot them on part of the database to see whether you get relevant material, before you run it on the whole database.
- Use date limits for your search if appropriate. For example, if drugs, anaesthetic techniques or diseases have only been around since a certain date, there is no point searching before then.
- Other relevant material about search strategies are found in: "Systematic Reviews in Health Care" [21].

Conclusion

It is discussed in this chapter how and where the reviewers should look for studies that may be eligible for inclusion such as *The Cochrane Library*, MEDLINE, EMBASE and other relevant databases that identify appropriate MeSH terms. The inclusion of all relevant studies in projects and systematic reviews is crucial to avoid bias and maximise precision. Furthermore it is discussed which sources there should be searched to identify RCTs for systematic reviews.

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4

Retrieving the data

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In this chapter, I will discuss the methods of data retrieval and storage that help you to subsequently extract and analyse outcomes, bias and confounding factors, with particular reference to the systematic review of experimental studies.

There has been very little empirical research on how different methods of data retrieval and storage affect the results of systematic reviews. Most research has focussed on variables in the early part of the process, such as blinding data extractors to the authors, institute and publishing journal of each trial.

Because of the paucity of evidence I have written a pragmatic chapter based upon my own experience as an author and editor of Cochrane systematic reviews. Therefore you should not accord my conclusions with the same weight you would give to conclusions in other chapters that are based upon more evidence.

Introduction

Your aim is to find out what results your patient can expect from an intervention and how reliable are the effects. To do this you have to retrieve data from studies accurately without introducing bias. You determined the participants, interventions and outcomes for which you want to retrieve data when you planned your protocol (Chapter 2). Your search strategy determined the studies that you found (Chapter 3). In this chapter I will explain how best to retrieve data from those studies.

Stop

You have found studies but you have not yet retrieved data from them. Before proceeding you should review your clinical question and check that the information that you intend to retrieve will answer that question. You should avoid altering your methodology after you have started to retrieve data. The later you make changes, the more likely it is that you will be changing your question to match your results. If you do make changes later on you should make this clear, to yourself and others. One of

Key words: Electronic bibliographies, search strategies, bias, systematic review, outcome.

the tasks of The Cochrane Collaboration's editorial teams (Chapter 9) is to look for differences in the methodologies between a submitted review and the protocol.

Before you "start"

Begin by planning, piloting and redrafting your data extraction form. Read Chapter 8 in the *Cochrane Handbook for Systematic Reviews of Interventions* [1]. More than one person should retrieve data (see section "Getting the data wrong"). You are trying to develop a data extraction form that best promotes precision, accuracy and reliability so that your answer is valid.

Recording retrieved data

Why extract data?

The data you want is already recorded in the studies you have found. However it is difficult to accurately identify, remember and analyse the data you want if you do not unburden them from everything in the study that you do not need. If you do not explicitly extract the data your analyses may be inaccurate, difficult to check and you may fail to identify bias.

Why record extracted data electronically?

You can retrieve the data for each study into a separate paper record and then compare the results and integrate them, usually systematically by transferring the extracted data into a program like RevMan [2]. However if you first retrieve data from each study into software (such as Microsoft's Excel or Access programs) you can make your analyses more complete and easily verified (see below).

What data?

1 *Unique identifiers*
Most electronic bibliographies (such as MEDLINE) assign a unique identifying number to each record in that database. In addition the reference (journal, year, volume, issue, pages) is usually unique. You can take the opportunity to formulate your own unique identifier that reflects the source(s) in which you found the study. If you exclude the study you can modify the identifier to reflect the stage of exclusion. This helps you populate the QUORUM statement algorithm [3].

2 *Search strategies*
The electronic retrieval form is a convenient place to record your search strategies. You can Hyperlink the search strategy to some bibliographic databases that will update your search when you link to them. You can also annotate Figure 4.1 with the search strategy that resulted in the studies you retrieved.

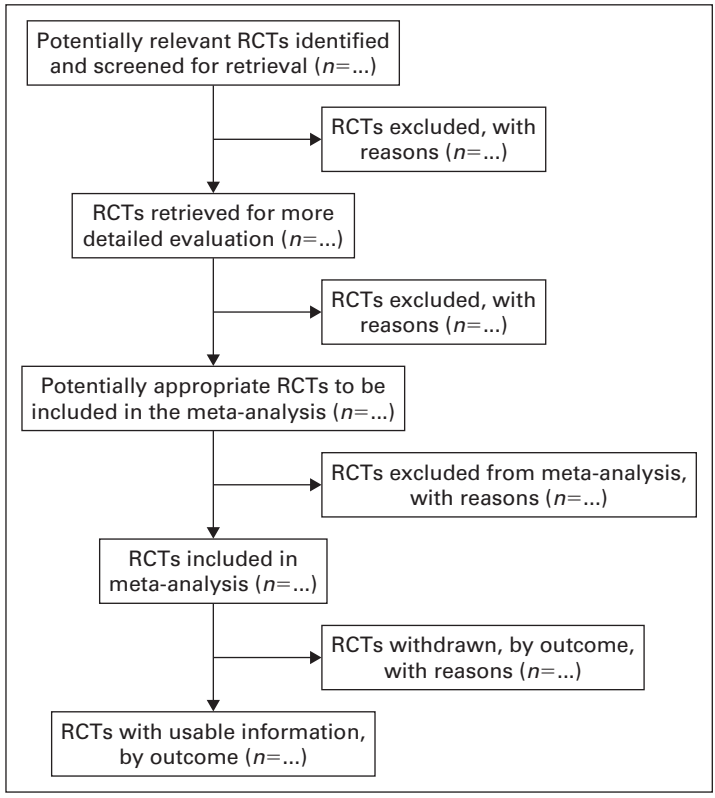

Figure 4.1 QUORUM statement algorithm. RCT: randomised controlled trial

3 *Inclusion and exclusion criteria*
You must verify that you can use the results of a study to answer your question (before you expend time extracting data). For each study you should record the presence of all your inclusion criteria and the absence of any exclusion criteria for: participants, interventions, outcomes, study methodology (e.g. randomly allocated placebo-controlled trials).

4 *Intervention*
Record the number of participants allocated to each intervention, not the number assessed (intention-to-treat analysis). Verify that the controls are adequate enough to be categorised as placebo.

5 *Outcomes*

5.1 Dichotomous outcomes – "it did or did not happen" – are recorded as proportions; the number of participants experiencing an outcome divided by the number allocated to that intervention. Ensure that the unit of analysis corresponds with the unit of allocation: this means that a participant can only be recorded as experiencing an outcome once. If you record each number in

different cells you can copy and paste as text into the comparison tables in RevMan.

5.2 Continuous data – "how much did it happen" – are recorded as the number of participants, the mean and the standard deviation (of the outcome measurement) for each of the allocated groups.

6 *Descriptive variables*

You should record the presence or value of variables even if you do not intend to use subgroup analyses to assess their association with the efficacy of the intervention. Subgroup analyses are difficult to interpret (see other chapters).

7 *Bias within studies*

7.1 Selection bias depends on two features of a study's methodology: the success of concealing the allocation sequence (for instance telephone allocation) and the unpredictability of the allocation sequence (random sequence).

7.2 Performance bias depends on both selection bias and blinding of **everyone** who could alter the incidence of the outcomes, including the patient and the anaesthetist.

7.3 Attrition bias depends on the previous biases and upon unintended consequences of the interventions (thus the preference for intention-to-treat analyses).

7.4 Detection bias depends on the preceding biases.

Record separately the quality of each study's attempts to reduce each bias. Then you can assess the impact of each independently of the other biases.

Recording retrieved data electronically

Size

- I included 763 randomised controlled trials in my systematic review. The paper pile of single data retrieval sheets would weigh nearly 4 kg and occupy a volume of 5 litres. My flash drive weighs a few grams and fits on a key ring. I extracted data from each study into between 40 and 100 columns in Excel (see below) – my writing would have to be very small to fit this information on one side of A4. I also needed to share the data retrieval forms with colleagues who verified the extracted data: it is expensive to transport 4 kg by post to another country.

Backup

It is both easy to copy and to (accidentally) erase electronic files. A simple solution to keeping track of multiple versions of your file on various media is to name each saved file with the date and place that it is stored.

- My systematic review kept me occupied for over 2 years. I must have spent thousands of hours and nearly £6000 sterling (retrieving studies that were not free).

This sort of investment disciplined me to habitually copy my files. I even e-mailed the latest version to colleagues when I went on holiday in case of drowning or burial in an avalanche!

Program

- I chose to extract data to Microsoft Excel [4] because:
  - 1.1 I was familiar with it.
  - 1.2 Most computers I access have it installed (as an anaesthetist I work in many different places – it is time-consuming to arrange installation of novel software on hospital computers).
  - 1.3 Export of data to other programs is usually easy although occasionally laborious (there are instructions in Excel, RevMan, STATA [5] and other programs).
  - 1.4 Many programs have been devised to work with data in Excel, including programs that allow you to compare two Excel sheets (see section "Getting the data wrong").

Manipulating retrieved electronic records

If you have found only a few studies you will probably be able to manipulate the data that you have extracted as easily with paper sheets as with an electronic format. But you will find it very difficult to perform the same tasks manually if you have lots of studies to assess.

Counting

Each row is numbered sequentially in Excel, so you know how many studies there are. Excel tells you how many studies you select (or "filter") from the total. If the program does not tell you how many you have selected (it will display the words "filter mode" Figure 4.2).

Go into "Tools" "Options" "Calculation" and mark "Manual" (instead of "Automatic")

Calculations

You can add subgroups (see Filter and PivotTable) and you can do other calculations in many software programs. Most of the meta-analytic calculations will be

Figure 4.2 Counting: filter mode

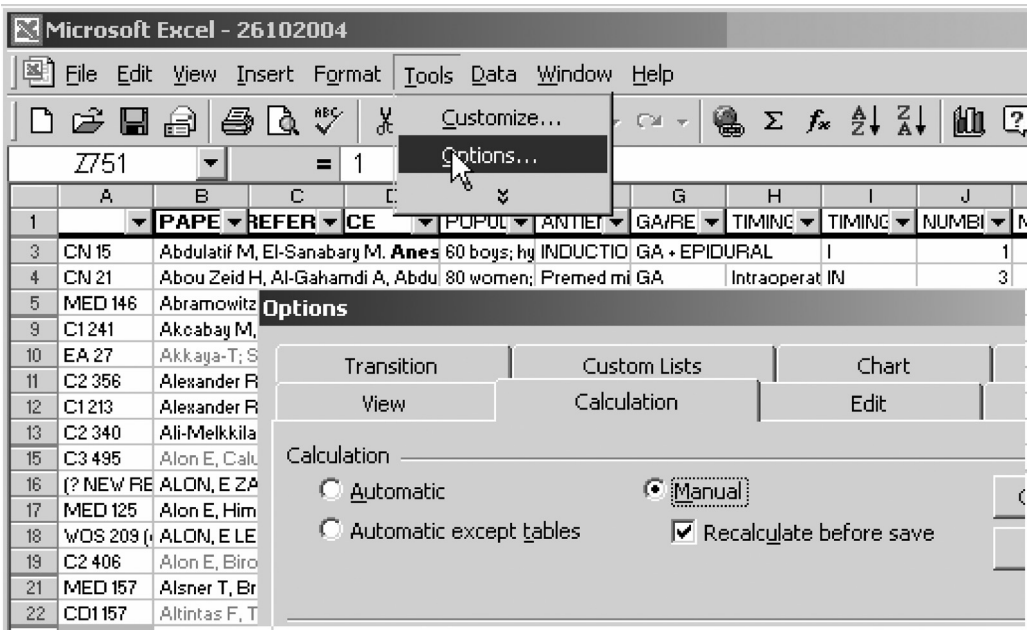

Figure 4.3 Tool option

performed after you have entered your extracted data into RevMan, STATA or another program.

Annotating and linking

You can mark certain records by changing font or by inserting a Comment. You can insert a Hyperlink to another sheet in Excel, to another file (perhaps Word or pdf [6]), or to a web page (perhaps the full text or abstract of the study).

Filter and PivotTable

These two functions allow you to rapidly count how many participants are in a subgroup in one column or in a combination of columns. In this case I had one column "age" with each study categorised as "adult", "child" and "both", and another column "sex" categorised as "male" and "female".

Other factors that affect the validity of your answer

Duplication

Your answer will be skewed if you include the same data more than once. Sometimes duplicate publication is easy to identify because the same authors publish the same

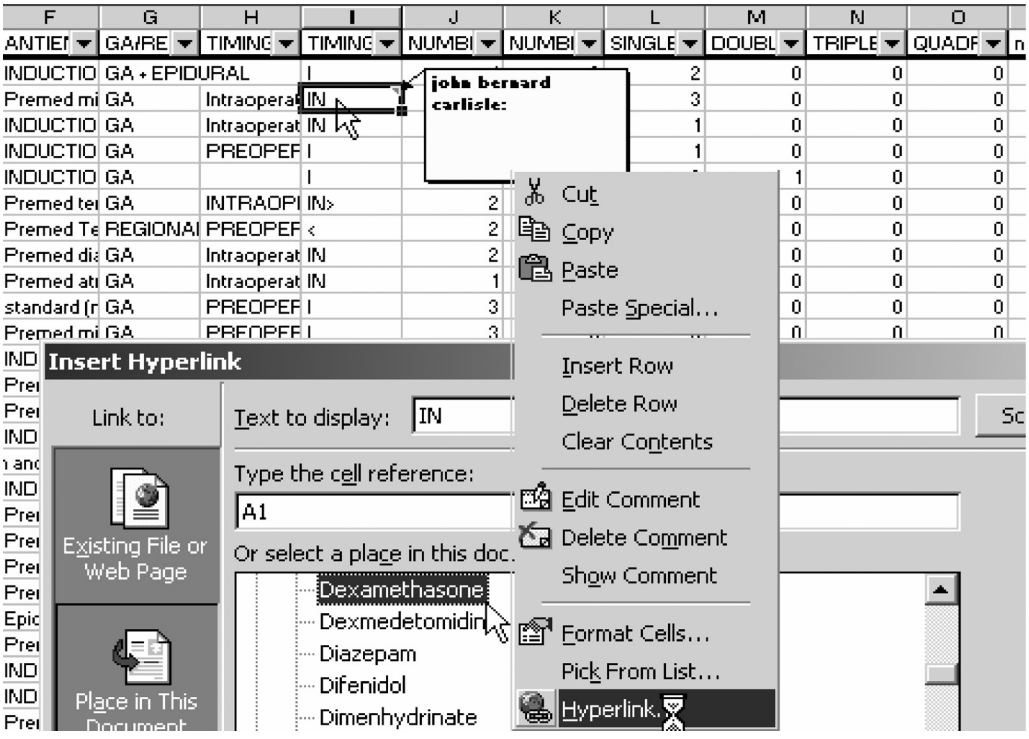

Figure 4.4 Annotating and linking

study (participants, interventions, outcomes) with small variations in the text. Sometimes data are common to multiple studies yet details will be different and the authors will be completely different. This is most likely to occur during or following multicentre studies when authors report results from their own hospitals. It can also occur when results are published during and after completion of a study. You can use Filter, PivotTable and Find to identify authors of more than one paper. If you use 26 columns for surnames beginning with each letter of the alphabet you can use these functions to identify authors who have published together. You can then look for patterns in results.

Author networks and hubs or nodes

You can also start to identify "networks". A network of authors may indirectly connect two other authors who have not published together. Networks analysis allows you to:

- Identify duplicated data when studies have no authors in common.
- Identify possible "hubs" of influence that may affect the methodology and results of studies.

You can measure the degree of "relatedness" between different studies. You can use this measure to order a set of studies and see whether the result (for instance the antiemetic effect of dexamethasone) correlates with the strength of association between studies (in RevMan or in STATA).

If you want to assess network influences on your answer you may need to use social network mapping software. There is freeware available on the web [7].

Getting the data wrong

You will make some errors, both when you retrieve data from studies, and when you transfer it to your record. You can repeat data retrieval on a separate record and then compare the data with the original record. In addition someone else should extract data for two reasons:

1 They are likely to make different errors to you.
2 There is a subjective element to qualitative categorisation of studies.

You can then compare retrieval records manually or if they are electronic, automatically. If you analyse your results, you find extreme (outlying) values, go back to the original papers and check the data retrieval form for extraction errors, such as transposing the placebo results with the intervention results.

Difficult data

Outcome summaries but no details

You are most likely to have problems retrieving outcomes when a study does not present the raw outcome data. For instance there may only be odds ratios, relative risks, differences, standard errors, 95% confidence intervals and so on. Sometimes you can derive the original outcome values or incidences from these data but you are likely to require the assistance of a statistician (see the *Cochrane Handbook for Systematic Reviews of Interventions 4.2*, Chapter 8).

Percentages

A percentage makes the result look more impressive if it exceeds the incidence. It is very easy to make the mistake of retrieving the percentage rather than the incidence. A percentage incidence may be reported that makes no sense, for instance "22% of 34 patients experienced PONV". This equals 7.48 participants! You may only have a graph labelled "%" on the Y-axis from which to estimate the incidences.

Solutions

You should decide before retrieving data what you will do when confronted with such problems to avoid your solution favouring a result towards which you are biased. You

should be conservative if you have to estimate the value of a result that you include. This means that you should use the value that reduces any difference between the intervention and control groups.

Summary and practice points

- Logical reasoning, in the absence of contradictory empirical evidence, suggests that you should plan, prepare and pilot your data extraction form. As a minimum this includes all your inclusion and exclusion criteria, methodological variables, outcomes (and their values), subgroup variables and a unique identifier.
- You will makes assumptions. Spend time identifying these assumptions and question whether they are valid (supported by reliable empirical evidence). Your assumptions will bias your results and how you handle issues of dispute.
- Are you sure that electronic data extraction and storage will not help you? Unless you are confident that you will only find a few simple studies you should spend time learning to use an electronic format.
- Consider exporting your electronic data to programs that could help you detect subtle biases and data duplication, perhaps through network analyses.

Research agenda

- The sensitivity of your results and the answer of your clinical question, may depend on how data is extracted and stored.
- There has not been much research into this aspect of systematic reviews.
- Would you like to begin?

RESOURCES

1 http://www.cochrane.dk/cochrane/handbook/hbook.htm
2 http://www.cc-ims.net/RevMan
3 http://www.consort-statement.org/QUOROM.pdf
4 http://office.microsoft.com
5 http://www.stata.com
6 http://www.adobe.com/products/acrobat/readstep2.html
7 http://www.insna.org

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5

Critical appraisal and presentation of study details

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The critical appraisal of studies and the succinct presentation of study details are essential aspects of evidence-based anaesthesia. Their primary role is to guide the interpretation of evidence from studies in terms of its validity and applicability. It is necessary to be aware of potential sources of bias that may impact on the reliability of study findings. Similarly, it is important to consider key study characteristics that may affect the relevance of study findings to clinical practice. Formal procedures, such as the use of forms itemising criteria to judge study quality and for the collection of study details, are important to make the process objective and repeatable. There is an underlying need for transparency in methods and reporting.

Introduction

The critical appraisal of studies and the systematic presentation of study details are key components of an evidence-based approach. Both require methodical processes, which should be pre-specified and, where appropriate, piloted. The importance of a written protocol, which includes details of these, cannot be overstated. The preparation and piloting of forms to assess study quality and to gather study details and results are of immense help (see Chapter 4). Similarly of benefit is an outline, which may include draft tables, of what you want to report.

This chapter focuses mainly on the critical appraisal of randomised controlled trials of treatment or preventive interventions and the presentation of study details from these in systematic reviews. Some mention will be made of the similar processes for systematic reviews of tests of diagnostic accuracy.

Critical appraisal

In the context of evidence-based medicine, critical appraisal is the systematic evaluation of the aims, design, conduct, analysis and interpretation of a study in order to