International Child Health Review Collaboration

Reviewer's Toolkit

[Last updated 23/03/06]

Defining the Search Question

Before starting, it is important to establish a search question. The PICO check list can help formulate a question:

Patient population or problem
Intervention or exposure
Comparison
Outcome

By using this checklist, an appropriate query can be drawn up, such as those supplied by the WHO. For example, '*Should zinc be used in the treatment of acute gastroenteritis in children in developing countries?'*. The population is children in developing countries with acute gastroenteritis, the intervention is zinc, the comparison is with those not treated with zinc and the outcome would be clinical improvement. It is instructive to underline the essential words and phrases of the query. In this example, *zinc*, *treatment, acute gastroenteritis, children* and *developing countries*.

Keywords, MeSH terms, synonyms and spelling

Keywords and synonyms

Keywords are often those established by underlining key components of your search query. They are essentially free-text searches that search that **exact** term and thus can retrieve articles in which the term is incidental. PubMed attempts to assign a MeSH (Medical Subject Heading) term to your keyword, though will not search for other more-specific terms that may be more appropriate. Consequently many useful papers may be missed if MeSH terms are not considered as well as keywords.

It is useful to keyword search when the term you are searching for does not appear in the MeSH database, or the term is new or highly specific. New literature may not yet have been assigned a MeSH term and hence would only be found by keyword search. With keywords, there is a requirement to think of all synonyms or use a broad enough term to cover the topic. Brainstorm (or use a thesaurus) for alternative terms. Synonyms can be included in the search query using the Boolean operator 'OR' (explained later).

Truncations

If the keyword should have variant endings – singular, plural, adjective – truncation can side-step the need to combine them all with 'OR'.

With truncation, use the common 'stem' of the word – for example, child - followed by the truncation symbol ($ * ? # - varies depending on the database being searched). Thus child* could retrieve child, children, childs, childrens etc. There is a risk that truncation may yield false 'hits'.

MeSH terms

Every article entered into PubMed / Medline is assigned a MeSH term by a third party – essentially allocating the article a topic heading. MeSH contains almost 17,000 terms. Each of these terms represents a single concept appearing in the medical literature. As important new concepts appear, a new MeSH keyword is created. When a new reference is added to MEDLINE, indexers review the article and then choose/add the appropriate MeSH keywords (usually 10 to 20) to represent the contents of the article. Using MeSH terms in the search means that articles can be retrieved by topic and bypasses the problem of whether the right term has been chosen with keywords. A useful technique is to search the database of MeSH terms available here: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=mesh. Establish the correct MeSH term by looking at the definition, and then look at the MeSH tree of Subheadings to see where this term fits in. By looking up and down the Subheadings tree, it is possible to make your search term more or less specific. Using the example of

gastroenteritis, gastrointestinal diseases offer a far broader search, whereas dysentery or gastritis would restrict the yield of papers.

Using the MeSH terms means the most recognised form of the term is used and enables greater control over your search. However, as mentioned above, newer articles or new terms may not yet be allocated a MeSH term.

For completeness, both MeSH terms and keywords should be used in the search strategy. The importance of this is illustrated in the example below.

Most databases have a section for advanced search techniques (e.g. OVID: http://gateway.uk.ovid.com/.). Though not addressed here, they may be utilised to refine the search strategy.

Remember:

- ***Keywords and MeSH terms***
- ***Related terms***
- ***Alternative spellings* (particularly between UK and US English)**
- ***Synonyms***
- ***Truncations***

Some advocate the use of a mind-map / spider diagram or columns to expand on these major topics. This is a matter for personal preference.

MeSH vs. keywords: an example

There will be vastly different results achieved depending on whether or not keywords or MeSH terms are used. Below is an example where MeSH terms do not entrain crucial articles to answer a question.

Take the question *"What is the evidence behind dexamethasone therapy in bacterial meningitis in developing countries?"*

Most authors will use keywords but these often do not match up with the MeSH terms. Using only one set will not produce the same results. The red example below uses the MeSH terms in the clinical filter and yet even with broader terms does not entrain a number of important articles. The keyword search is in blue and one can see that once put through the filter it entrains 6 further articles, (including the seminal work by Liz Molyneux.)

This of course occurs if the author when using the keyword search thinks of all synonyms or uses a broad enough term to cover the topic. They also have to take into account all truncations (hence "countr*").

#1 Search "Meningitis, Bacterial"[MeSH] AND "Developing Countries"[MeSH] **105** articles

This is then put through the Clinical Queries filter:

#2 Search (#1) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])) **4** articles

#3 Search bacterial meningitis AND developing countr* **216** articles

This is then put through the Clinical Queries filter:

#4 Search (#3) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])) **10** articles

So why not use keywords alone? The answer lies that in the example above it is relatively easy to work out the terms that will get the correct relevant articles. This is obviously not always the case. Running a search for ***skin grafting and burns*** the MeSH terms turned up a number of extra articles compared with keywords….61 Vs. 24. This is because the MeSH term is "skin transplantation" whilst with keywords the reviewer has to include a number of terms other than skin graft, such as ;

- Dermatoplasty
- Dermatoplasties
- Grafting, Skin
- Graftings, Skin
- Skin Grafting
- Skin Graftings
- Transplantation, Skin
- Skin Transplantations
- Transplantations, Skin

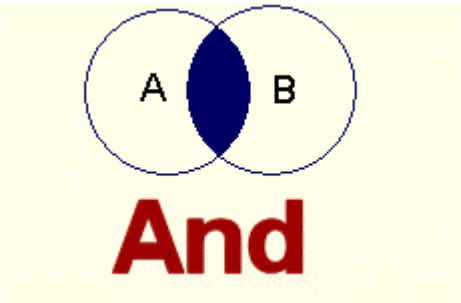
"Transplantations. skin [MeSH]" picks them all up.

Another reason not to use keywords alone is that for broader topics then a number of irrelevant articles are captured which defeats the purpose of the clinical filter somewhat.

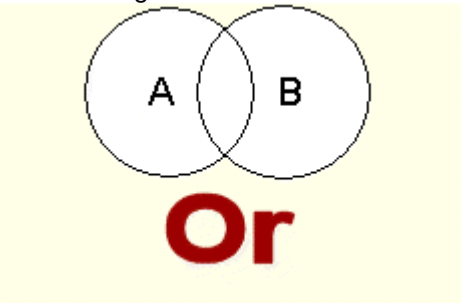
Combining the search terms

The keywords identified in the last section should be combined to search the databases. This refines the search. Use of the Boolean operators 'AND', 'OR, and 'NOT' achieves this.

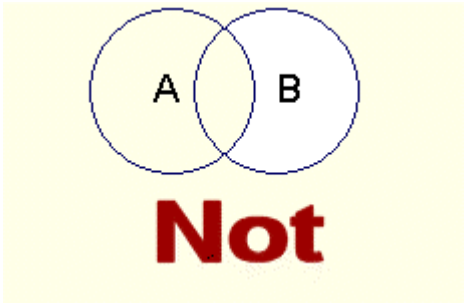
AND retrieves records containing both / all of the combined terms. In the figure below, the shaded area represents the papers found when A (e.g. gastroenteritis) AND B (e.g. zinc) are combined.



OR retrieves records containing either term. This is useful when synonymous terms exist. In this example, A represents gastroenteritis and B acute diarrhoea. For this search the terms are interchangeable so can be combined with OR.



NOT is a term of exclusion, retrieving records that use one term but not another. In the figure below, B could represent gastritis but NOT A, appendicitis. This risks excluding records that could be useful, shown in the overlap.



In this example then, a final search strategy could be:
Zinc AND (acute diarrhoea OR gastroenteritis OR infectious diarrhoea OR acute gastroenteritis OR diarrhea). Further examples can be found in the 'example search strategies' below.

As the search strategy is for the WHO review, it should focus on children in developing countries. At this stage however, it is preferable not to restrict the findings.

Inclusion and Exclusion Criteria – Setting Parameters

Before searching, set out on paper what you would and would not like to include. Obviously, the key terms should be included. Decide what sort of papers you need – systematic reviews and randomised controlled trials are the order of the day for the WHO review, but would you consider cohort studies or retrospective reviews? Humans only? Paper age? Paper language? Certain journals? Treatment versus prophylaxis? How will you select your papers?

Setting this out at the start avoids ambiguity later.

It is possible to specify these parameters on some databases (e.g. OVID) with check boxes for English language and children for example.

Limiting or Expanding Search Results

Your strategy will almost invariably retrieve too many, too few or irrelevant hits at first try.

If too few hits:
- Use truncation
- Use a thesaurus – ensure all relevant synonyms are included
- Spelling – check, or try an alternative
- Check terminology
- Combine keywords with the Boolean operative 'OR'
- Select 'All Subheadings' if presented with the option
- Free-text searches – for terms too new or not widely used enough to be Subject Headings
- Use the 'broad, sensitive search' checkbox with PubMed Clinical Queries

If too many hits:
- Use Boolean operators – particularly 'AND' or 'NOT'
- Use specific Subheadings
- Use filters – this will be done by using the Clinical Queries tool on PubMed to restrict to randomised controlled trials
- Focus – available on many databases to focus on Subject Heading terms, retrieving articles with the Subject Heading as a main subject.
- Use thesaurus terms
- Use the 'narrow, specific search' checkbox with PubMed Clinical Queries

- **Note – the goal of evidence based medicine is to elucidate the evidence behind interventions. Arbitrarily excluding papers due to a large volume of research risks excluding key findings**

If too many irrelevant hits:
- Use Subject Headings rather than free-text alternatives
- Use the subject tree (see MeSH) to find more precise Subject Headings
- Use the Boolean operator 'NOT' – use with caution!

For thoroughness:
- **Avoid limits**
- **Search reference lists**
- **Use Cited Reference Tool : Web Of Science (http://isiknowledge.com)**
- **Specify inclusion and exclusion criteria**
- **Include ALL relevant data**
- **Should be reproducible**

What if no relevant papers can be found?

Having searched the Cochrane Library and PubMed Clinical Queries for systematic reviews and randomised controlled trials, the final stage would be to include a good quality review. This only really refers to a small subset of questions not easily answered by randomised controlled trials.

It may simply be that the current recommendations are based on institutional traditions, hence the importance of evidence-based medicine.

With thanks to Marshall Dozier and the University of Edinburgh Library Staff for their advice on literature searching. The Edinburgh Medical Library website is very useful for tips on searching, and they have produced a useful pdf paper on how to systematically search the literature, accessible here.

Literature Search

First, make sure the work hasn't already been done! By looking for previous reviews on your subject you can save a lot of time and frustration in the long run.

The Cochrane Library has a large database of independent high quality systematic reviews. From here, you can search for both completed and proposed reviews as well as the The Cochrane Central Register of Controlled Trials (CENTRAL) database of randomised controlled trials which had 470,000 registered randomised controlled trials, and other databases.

If there are no systematic reviews on your subject, you will now need to start searching the literature for relevant articles for your project. Should the work be done already, a link to the appropriate website or a short summary would be welcomed.

The aim of the literature search is to theoretically get ALL the articles relevant to your subject area. The most important thing is to find all the *relevant* articles without being too sensitive so that you have to wade through hundreds of irrelevant articles to find them.

PubMed is a free medical database of over 16 million articles. It incorporates Medline and OldMedline.

For the purposes of the WHO reviews, the search strategy utilises the 'Clinical Queries' (http://www.ncbi.nlm.nih.gov/entrez/query/static/clinical.shtml) framework available in PubMed. This enables systematic searches of therapeutic, diagnostic, etiologic or prognostic questions on disease state or condition. This technique has been well validated, is reproducible, and is generally available in developing countries. It is possible to use broad or narrow (sensitive or specific) sub-searches.

Accessing Relevant Articles

Having formulated a search strategy, the next stage is to retrieve the articles.

Abstracts **must** be read. This minimises the risk of missing a relevant article.

Some papers can be accessed directly from the database, such as PubMed, by a link to the appropriate journal. It may be possible to retrieve others by searching for the journal online and retrieving the electronic article from the archive. Otherwise, the paper copy should be sought in the library or by inter-library loan where such facilities exist.

Students at institutions with access to library facilities should use these. For those in developing countries that may not have such access, HINARI may help (Health InterNetwork Access to Research Initiative (http://www.who.int/hinari/en/). This has been set up by the WHO and major publishers to enable developing countries to gain access to over 3100 journal titles. Currently this resource is available to 113 countries, and may help authors in developing countries contribute to this project.

Extracting Data From Articles

The WHO reviews should be concise yet contain all the pertinent points. Read the collected articles to understand the background and key points, and highlight the relevant findings that answer your query.

Establish:

- Paper type – systematic review, randomised controlled trial etc.
- Does the paper meet your inclusion / exclusion strategy? – for example, dated information, adults not children
- What is the clinical question the paper addresses?
- Patient numbers

- Key results and outcomes – actual figures are useful here
- P values and confidence intervals – what statistical tests have been performed?
- Assess the methodology (see below)
- Grade the level of evidence (to follow)

Tabulate this data using the table templates provided.

Assessing the Methodology

The methodology of the paper must be considered before papers are included. The strategies differ slightly between systematic reviews and randomised controlled trials.

Quality criteria for systematic studies

- Were the questions and methods clearly stated?
- Was the search method comprehensive and the methodology described?
- Were explicit methods used to determine which studies were included in the review?
- Was the methodological quality of primary studies assessed?
- Was the selection and assessment of primary studies reproducible and free from bias?
- Were differences in individual study results adequately explained?
- Were the results of primary studies combined appropriately?
- Were the reviewers' conclusions supported by data cited?

Quality criteria for randomised controlled trials

- Were the setting and study patients clearly described?
- Was assignment randomised and similarity between groups documented?
- Was allocation to study groups adequately concealed from patients and investigators, including blind assessment of outcome?
- Were all clinically relevant outcomes reported?
- Were > 80% of patients who entered the study accounted for at its conclusion?
- Were they analysed in the groups to which they were randomised (intention to treat)?
- Were both statistical and clinical significance considered?

Quality for cohort studies / retrospective studies

- Were the recruitment setting, diagnostic criteria, disease severity, co-morbidity and demographic details documented?
- Was the referral pattern described?
- Referral or diagnostics access bias avoided?
- Was an adequate follow up rate achieved?
- Were > 80% patients entered accounted for in results and clinical status known?
- Were objective outcome criteria developed and used?
- Was outcome assessment blind?
- Was adjustment for extraneous prognostic factors carried out?

Methodology sound – include
Methodology suboptimal – site reservations if included
Methodology unsound – exclude

BMJ Publishing Group Limited. Critical appraisal criteria. Clinical Evidence. © 2006 [cited 2006 February 18]. Available from:
URL: http://www.clinicalevidence.org/ceweb/about/appraisal.jsp

Evaluating the Evidence

Each paper eligible for inclusion should be analysed using the criteria from the Oxford Centre for Evidence-Based Medicine Levels of Evidence reproduced below.

Level	*Therapy/Prevention, Aetiology/Harm*
1a	Systematic review (with homogeneity*) of randomised controlled trials
1b	Individual randomised controlled trial (with narrow confidence interval)
1c	All or none §
2a	Systematic review (with homogeneity*) of cohort studies
2b	Individual cohort study (including low quality randomised controlled trial; e.g., <80% follow-up)
2c	"Outcomes" research; ecological studies
3a	Systematic review (with homogeneity*) of case-control studies
3b	Individual case-control study
4	Case-series (and poor quality cohort and case-control studies §§)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

* By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. Studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.

§ Met when all patients died before the treatment became available, but some now survive on it; or when some patients died before the treatment became available, but none now die on it.

§§ By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.

Grades of Recommendation	
A	consistent level 1 studies
B	consistent level 2 or 3 studies or extrapolations from level 1 studies
C	level 4 studies or extrapolations from level 2 or 3 studies
D	level 5 evidence or troublingly inconsistent or inconclusive studies of any level

"Extrapolations" are where data is used in a situation which has potentially clinically important differences than the original study situation.

From http://www.cebm.net/levels_of_evidence.asp#notes. Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998.

Preparing and Writing the Review

Having formulated a search strategy, retrieved papers, evaluated the evidence and tabulated key results, the final stage is to bring this together into the WHO report.

Though this process has much in common with Cochrane Reviews, there is a very clearly defined scope in terms of topic and target settings. **The WHO reports will be short but clear summaries rather than extensive reviews.**

The basic template should be as follows:

Title

INTRODUCTION

This should be short and snappy. The people using the reviews will understand the background to the topic, though a brief explanation of any controversy is welcome. It should conclude with:
'This review intends to answer the question: *e.g. Should zinc be used in the treatment of acute gastroenteritis?*'

METHODS

This will be very similar between reviews. Explain the search strategy, e.g. zinc AND (acute diarrhoea OR gastroenteritis OR infectious diarrhoea OR acute gastroenteritis OR diarrhea) and that the PubMed Clinical Queries framework was used. Mention if other databases were searched, how articles were selected and graded. Also state the number of papers identified.

RESULTS

It is helpful to consider the results in terms of outcomes and include the relevant data. P values, confidence intervals and other statistical tests are valued. Systematic reviews and randomised controlled trials should really be the source of your data. Discuss any methodological points, and dosage information if relevant.

Ideally, only good data should be included. Aim to transmit the information in as clear a form as possible.

DISCUSSION

This should briefly put into context the findings. The main conclusions should be stated. Disclaimers on the quality of the relevant literature may be mentioned, and options for future work discussed.

SUMMARY

A concise statement of the evidence.

REFERENCES

The final report should be no more than a few pages long. These should be sent to Dr Trevor Duke or Dr Julian Kelly. From here they will be sent to secondary reviewers, and returned to you in order to make any changes. Eventually, these reviews will be published on the WHO website. These reports will be updated every few years to reflect the changing evidence base.

Example Search Strategies

Should zinc be used in the treatment of acute gastroenteritis?

Zinc AND (acute diarrhoea OR gastroenteritis OR infectious diarrhoea OR acute gastroenteritis OR diarrhea)

When should antibiotics be used in diarrhoeal illness?

(acute diarrhoea OR gastroenteritis OR infectious diarrhoea OR acute gastroenteritis) AND (antibiotics or antimicrobials)

What antibiotics are appropriate in acute dysentery?

(Dysentery OR bloody diarrhoea OR shigella) AND antibiotics

What is the evidence behind continued oral / breastfeeding as a co-intervention in acute infectious diarrhoea?

(feeding OR breastfeeding OR breastmilk) AND (acute diarrhoea OR gastroenteritis OR infectious diarrhoea OR acute gastroenteritis OR diarrhea)

What is the optimal feeding regime in persistent diarrhoea?

(feeding OR refeeding OR nutrition OR diet OR supplemental feeds OR supplemental feeding OR caloric intake OR lactose reduced OR lactose free) AND (persistent diarrhoea OR chronic diarrhoea OR intestinal infection)

In children with diarrhoea and dehydration without shock, is rehydration by the nasogastric route as effective as fluid given intravenously?

(Intravenous fluids OR intravenous rehydration OR parenteral rehydration OR fluid therapy OR infusions OR nasogastric fluids OR enteral fluids OR NG fluids) AND (acute diarrhoea OR gastroenteritis OR infectious diarrhoea OR acute gastroenteritis OR diarrhea OR dehydration OR acute dehydration)

What antimalarials are appropriate for the management of uncomplicated malaria in areas of falciparum resistance?

Malaria AND (therapy OR antimalarials OR falciparum OR chloroquine resistance OR multi-drug resistant malaria)

What adjuvant therapies are beneficial in malaria?

(malaria OR severe malaria) AND adjuvant therapy OR adjunctive therapy OR heparin OR steroids OR dextran OR mannitol)

When should a blood transfusion be given to children with severe malaria?

(severe malaria OR malaria) AND (blood transfusion OR transfusion OR whole blood OR packed cells)

What are appropriate fluids to use in the management of severe malaria?

(severe malaria OR malaria) AND (fluid therapy OR i.v. fluids OR cerebral oedema OR coma OR maintenance fluids)