

Chapter 6: Searching for studies

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Key points

- Review authors should work closely from the start with the Trials Search Co-ordinator (TSC) of their Cochrane Review Group (CRG).
- Studies (not reports of studies) are included in Cochrane reviews but identifying reports of studies is currently the most convenient approach to identifying the majority of studies and obtaining information about them and their results.
- Trials registers and trials results registers are an increasingly important source of information.
- The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE (if access is available to either the review author or TSC) should be searched for all Cochrane reviews, either directly or via the CRG’s Specialized Register.
- Searches should seek high sensitivity, which may result in relatively low precision.
- Too many *different* search concepts should be avoided, but a wide variety of search terms should be combined with OR within *each* concept.
- Both free-text and subject headings should be used (for example Medical Subject Headings (MeSH) and Emtree).
- Existing highly sensitive search strategies (filters) to identify randomized trials should be used, such as the newly revised Cochrane Highly Sensitive Search Strategies for identifying randomized trials in MEDLINE (but do not apply these filters in CENTRAL).

6.1 Introduction

Cochrane Review Groups (CRGs) are responsible for providing review authors with references to studies that are possibly relevant to their review. The majority of CRGs employ a dedicated Trials Search Co-ordinator to provide this service (see Section 6.1.1.1). The information in this chapter is designed to assist authors wishing to undertake supplementary searches for studies and to provide background information so that they can better understand the search process. In all cases review authors should contact the Trials Search Co-ordinator of their CRG before starting to search, in order to find out the level of support they provide.

This chapter will also be useful to Trials Search Co-ordinators who are new to their post, as well those who are more experienced, who may wish to consult this chapter as a reference source.

This chapter outlines some general issues in searching for studies; describes the main sources of potential studies; and discusses how to plan the search process, design and carry out search strategies, manage references found during the search process and correctly document and report the search process.

This chapter concentrates on searching for randomized trials. Many of the search principles discussed, however, will also apply to other study designs as discussed elsewhere. For some review topics, for example complex interventions, it may be necessary to adopt other approaches and to include studies other than randomized trials. Review authors are recommended to seek specific guidance from their CRG and refer also to the relevant chapters of this *Handbook*, such as Chapter 13 for non-randomized studies, Chapter 14 for adverse effects, Chapter 15 for economics data, Chapter 17 for patient-reported outcomes, Chapter 20 for qualitative research and Chapter 21 for reviews in health promotion and public health. Review authors searching for studies for inclusion in Cochrane reviews of diagnostic test accuracy should refer to the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy*.

The numerous web sites listed in this chapter were checked in June 2008.

6.1.1 General issues

6.1.1.1 Role of the Trials Search Co-ordinator

The Trials Search Co-ordinator for each CRG is responsible for providing assistance to authors with searching for studies for inclusion in their reviews. The range of assistance varies according to the resources available to individual CRGs but may include some or all of the following: providing relevant studies from the CRG's Specialized Register (see Section 6.3.2.4 for more detail), designing search strategies for the main bibliographic databases, running these searches in databases available to the CRG, saving search results and sending them to authors, advising authors on how to run searches in other databases and how to download results into their reference management software (see Section 6.5). Contact your Trials Search Co-ordinator before you start searching to find out the level of assistance offered.

If a CRG is currently without a Trials Search Co-ordinator authors should seek the guidance of a local healthcare librarian or information specialist, where possible one with experience of conducting searches for systematic reviews.

6.1.1.2 Minimizing bias

Systematic reviews of interventions require a thorough, objective and reproducible search of a range of sources to identify as many relevant studies as possible (within resource limits). This is a major factor in distinguishing systematic reviews from traditional narrative reviews and helps to minimize bias and therefore assist in achieving reliable estimates of effects.

A search of MEDLINE alone is not considered adequate. A systematic review showed that only 30% - 80% of all known published randomized trials were identifiable using MEDLINE (depending on the area or specific question) (Dickersin 1994). Even if relevant records are in MEDLINE, it can be difficult to retrieve them (Golder 2006, Whiting 2008). Going beyond MEDLINE is important not only for ensuring that as many relevant studies as possible are identified but also to minimize 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.

Time and budget restraints require the review author to balance the thoroughness of the search with efficiency in use of time and funds and the best way of achieving this balance is to be aware of, and try to minimize, the biases such as publication bias and language bias that can result from restricting searches in different ways (see Chapter 10, Section 10.2).

6.1.1.3 Studies versus reports of studies

Systematic reviews have studies as the primary units of interest and analysis. However, a single study may have more than one report about it and each of these reports may contribute useful information for the review (see Chapter 7, Section 7.2). For most of the sources listed in Section 6.2, the search process will retrieve individual reports of studies, however there are some study-based resources, such as trials registers and trials results databases (see Sections 6.2.3.1 to 6.2.3.4).

6.1.1.4 Copyright and licensing

It is Cochrane Collaboration policy that all review authors and others involved in the Collaboration should adhere to copyright legislation and the terms of database licensing agreements. With respect to searching for studies, this refers in particular to adhering to the terms and conditions of use when searching databases and downloading records and adhering to copyright legislation when obtaining copies of articles. Review authors should seek guidance on this from their Trials Search Co-ordinator or local healthcare librarian, as copyright legislation varies across jurisdictions and licensing agreements across institutions.

6.1.2 Summary points

- Cochrane review authors should seek advice from the Trials Search Co-ordinator of their Cochrane Review Group (CRG) *before* starting a search.
- If the CRG is currently without a Trials Search Co-ordinator, seek the guidance of a local healthcare librarian or information specialist, where possible one with experience of searching for systematic reviews.
- Use the Table of Contents to navigate to specific sections of this chapter.
- A search of MEDLINE alone is not considered adequate.
- It is Cochrane Collaboration policy that all review authors and others involved in the Collaboration should adhere to database licensing terms and conditions of use and copyright legislation.

6.2 Sources to search

6.2.1 Bibliographic databases

6.2.1.1 Bibliographic databases – general introduction

Searches of health-related bibliographic databases are generally the easiest and least time-consuming way to identify an initial set of relevant reports of studies. Some bibliographic databases, such as MEDLINE and EMBASE, include abstracts for the majority of recent records. A key advantage of these databases is that they can be searched electronically both for words in the title or abstract and by using the standardized indexing terms, or controlled vocabulary, assigned to each record (see Section 6.4.5).

The Cochrane Collaboration has been developing a database or register of reports of controlled trials called The Cochrane Central Register of Controlled Trials (CENTRAL). This is considered to be the

best single source of reports of trials that might be eligible for inclusion in Cochrane reviews. The three bibliographic databases generally considered to be the most important sources to search for reports of trials – CENTRAL, MEDLINE and EMBASE – are described in more detail in subsequent sections.

Databases are available to individuals for a fee, on a subscription or on a ‘pay-as-you-go’ basis. They can also be available free at the point of use through national provisions, site-wide licences at institutions such as universities or hospitals, through professional organizations as part of their membership packages or free of charge on the internet.

There are also a number of international initiatives to provide free or low-cost online access to databases (and full-text journals) over the internet. The Health InterNetwork Access to Research Initiative (HINARI) provides access to a wide range of databases including *The Cochrane Library* and nearly 4000 major journals from a wide range of publishers in biomedical and related social sciences, for healthcare professionals in local, not-for-profit institutions in over 100 low-income countries.

- www.who.int/hinari/en/

The International Network for the Availability of Scientific Publications (INASP) also provides access to a wide range of databases including *The Cochrane Library* and journals. Journal titles available vary by country. For further details see:

- www.inasp.info/file/68/about-inasp.html

Electronic Information for Libraries (eIFL) is a similar initiative based on library consortia to support affordable licensing of journals in 50 low-income and transition countries in central, eastern and south-east Europe, the former Soviet Union, Africa, the Middle-East and south-east Asia.

- www.eifl.net/cps/sections/about

For more detailed information about how to search these and other databases refer to Sections 6.3.3 and 6.4.

6.2.1.2 The Cochrane Central Register of Controlled Trials (CENTRAL)

The Cochrane Central Register of Controlled Trials (CENTRAL) serves as the most comprehensive source of reports of controlled trials. CENTRAL is published as part of *The Cochrane Library* and is updated quarterly. As of January 2008 (Issue 1, 2008), CENTRAL contains nearly 530,000 citations to reports of trials and other studies potentially eligible for inclusion in Cochrane reviews, of which 310,000 trial reports are from MEDLINE, 50,000 additional trial reports are from EMBASE and the remaining 170,000 are from other sources such as other databases and handsearching.

Many of the records in CENTRAL have been identified through systematic searches of MEDLINE and EMBASE, as described in Sections 6.3.2.1 and 6.3.2.2. CENTRAL, however, includes citations to reports of controlled trials that are 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 (Dickersin 2002). It also includes records from trials registers and trials results registers (see Section 6.2.3).

CENTRAL is available free of charge to all CRGs through access to *The Cochrane Library*. The web address for *The Cochrane Library* is: <http://www.thecochranelibrary.com>. Many health and academic institutions and organizations provide access to their members, and in many countries there is free

access for the whole population (for example through funded national licences or arrangements for low-income countries). Information about access to *The Cochrane Library* for specific countries can be found under 'Access to Cochrane' at the top of *The Cochrane Library* home page.

6.2.1.3 MEDLINE and EMBASE

MEDLINE currently contains over 16 million references to journal articles from the 1950s onwards. Currently 5,200 journals in 37 languages are indexed for MEDLINE:

- www.nlm.nih.gov/pubs/factsheets/medline.html

PubMed provides access to a free version of MEDLINE that also includes up-to-date citations not yet indexed for MEDLINE:

- www.nlm.nih.gov/pubs/factsheets/pubmed.html

Additionally, PubMed includes records from journals that are not indexed for MEDLINE and records considered 'out-of-scope' from journals that are partially indexed for MEDLINE. For further information about the differences between MEDLINE and PubMed see:

- www.nlm.nih.gov/pubs/factsheets/dif_med_pub.html

MEDLINE is also available on subscription from a number of online database vendors, such as Ovid. Access is usually free to members of the institutions paying the subscriptions (e.g. hospitals and universities).

The US National Library of Medicine (NLM) has developed the NLM Gateway, which allows users to search MEDLINE or PubMed together with other NLM resources simultaneously such as the Health Services Research Projects database (HSRProj), Meeting Abstracts and the TOXLINE Subset for toxicology citations.

- gateway.nlm.nih.gov/gw/Cmd

EMBASE currently contains over 12 million records from 1974 onwards. Currently 4,800 journals are indexed for EMBASE in 30 languages.

- www.info.embase.com/embase_suite/about/brochures/embase_fs.pdf

EMBASE.com is Elsevier's own version of EMBASE that, in addition to the 12 million EMBASE records from 1974 onwards, also includes over 7 million unique records from MEDLINE from 1966 to date, thus allowing both databases to be searched simultaneously.

- www.info.embase.com/embase_com/about/index.shtml

In 2007, Elsevier launched EMBASE Classic which now provides access to records digitized from the *Excerpta Medica* print journals (the original print indexes from which EMBASE was created) from 1947 to 1973.

- www.info.embaseclassic.com/pdfs/factsheet.pdf

EMBASE is only available by subscription. Authors should check if their CRG has access and, if not, whether it is available through their local institution's library.

For guidance on how to search MEDLINE and EMBASE for reports of trials, see Sections [6.3.3.2](#), [6.4.11.1](#) and [6.4.11.2](#) respectively.

Database overlap

Of the 4,800 journals indexed in EMBASE, 1,800 are not indexed in MEDLINE. Similarly, of the 5,200 journals indexed in MEDLINE, 1,800 are not indexed in EMBASE.

- www.info.embase.com/embase_suite/about/brochures/embase_fs.pdf

The actual degree of reference overlap varies widely according to the topic but studies comparing searches of the two databases have generally concluded that a comprehensive search requires that both databases be searched (Suarez-Almazor 2000). 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.

6.2.1.4 National and regional databases

In addition to MEDLINE and EMBASE, which are generally considered to be the key international general healthcare databases, many countries and regions produce electronic bibliographic databases that concentrate on the literature produced in those regions, and which often include journals and other literature not indexed elsewhere. Access to many of these databases is available free of charge on the internet. Others are only available by subscription or on a 'pay-as-you-go' basis. Indexing complexity and consistency varies, as does the sophistication of the search interface, but they can be an important source of additional studies from journals not indexed in other international databases such as MEDLINE or EMBASE. Some examples are included in [Box 6.2.a](#).

Box 6.2.a: Examples of regional electronic bibliographic databases

Africa: African Index Medicus

- indexmedicus.afro.who.int/

Australia: Australasian Medical Index (fee-based)

- www.nla.gov.au/ami/

China: Chinese Biomedical Literature Database (CBM) (in Chinese)

- www.imicams.ac.cn/cbm/index.asp

Eastern Mediterranean: Index Medicus for the Eastern Mediterranean Region

- www.emro.who.int/his/vhsl/

Europe: PASCAL (fee-based)

- international.inist.fr/article21.html

India: IndMED

- indmed.nic.in/

Korea: KoreaMed

- www.koreamed.org/SearchBasic.php

Latin America and the Caribbean: LILACS

- bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i&Form=F

South-East Asia: Index Medicus for the South-East Asia Region (IMSEAR)

- library.searo.who.int/modules.php?op=modload&name=websis&file=imsear

Ukraine and the Russian Federation: Panteleimon

- www.panteleimon.org/maine.php3

Western Pacific: Western Pacific Region Index Medicus (WPRIM)

- wprim.wpro.who.int/SearchBasic.php

6.2.1.5 Subject-specific databases

Which subject-specific databases to search in addition to CENTRAL, MEDLINE and EMBASE will be influenced by the topic of the review, access to specific databases and budget considerations. Most of the main subject-specific databases are available only on a subscription or 'pay-as-you-go' basis. Access to databases is therefore likely to be limited to those databases that are available to the Trials Search Co-ordinator at the CRG editorial base and those that are available at the institutions of the review authors. A selection of the main subject-specific databases that are more likely to be available through institutional subscriptions (and therefore 'free at the point of use') or are available free of charge on the internet are listed in **Box 6.2.b**, together with web addresses for further information. Access details vary according to institution. Review authors should seek advice from their local healthcare librarian for access at their institution.

In addition to subject-specific databases, general search engines include:

- Google Scholar (free on the internet):
 - scholar.google.com/advanced_scholar_search?hl=en&lr=
- Intute (free on the internet):
 - www.intute.ac.uk/
- Turning Research into Practice (TRIP) database (evidence-based healthcare resource) (free on the internet):
 - www.tripdatabase.com/

Box 6.2.b: Examples of subject-specific electronic bibliographic databases

Biology and pharmacology

- Biological Abstracts / BIOSIS Previews:
 - biosis.org/
- Derwent Drug File:
 - scientific.thomson.com/support/products/drugfile/
- International Pharmaceutical Abstracts:
 - scientific.thomson.com/products/ipa/

Health promotion

- BiblioMap – EPPI-Centre database of health promotion research (free on the internet):
 - eppi.ioe.ac.uk/webdatabases/Intro.aspx?ID=7
- Database of Promoting Health Effectiveness Reviews (DoPHER) (free on the internet):
 - eppi.ioe.ac.uk/webdatabases/Intro.aspx?ID=2

International health

- Global Health:
 - www.cabi.org/datapage.asp?iDocID=169

- POPLINE (reproductive health) (free on the internet):
 - db.jhuccp.org/ics-wpd/popweb/

Nursing and allied health

- Allied and Complementary Medicine (AMED):
 - www.bl.uk/collections/health/amed.html
- British Nursing Index (BNI):
 - www.bnipius.co.uk/
- Cumulative Index to Nursing and Allied Health (CINAHL):
 - www.cinahl.com/
- EMCare:
 - www.elsevier.com/wps/find/bibliographicdatabasedescription.cws_home/708272/description#description
- MANTIS (osteopathy and chiropractic):
 - www.healthindex.com/
- OTseeker (systematic reviews and appraised randomized trials in occupational therapy) (free on the internet):
 - www.otseeker.com/
- Physiotherapy Evidence Database (PEDro) (systematic reviews and appraised randomized trials in physiotherapy) (free on the internet):
 - www.pedro.fhs.usyd.edu.au/

Social and community health and welfare

- AgeLine (free on the internet):
 - www.aarp.org/research/ageline/
- Childdata:
 - www.childdata.org.uk/
- CommunityWISE:
 - www.oxmill.com/communitywise/
- Social Care Online (free on the internet):
 - www.scie-socialcareonline.org.uk/
- Social Services Abstracts:
 - www.csa.com/factsheets/ssa-set-c.php

Social science, education, psychology and psychiatry

- Applied Social Sciences Index and Abstracts (ASSIA):
 - www.csa.com/factsheets/assia-set-c.php
- Campbell Collaboration's Social, Psychological, Educational and Criminological Trials Register (C2-SPECTR) (free on the internet):
 - geb9101.gse.upenn.edu/
- Education Resources Information Center (ERIC) (free on the internet)
 - www.eric.ed.gov/

- PsycINFO:
 - www.apa.org/psycinfo/
- Social Policy and Practice (evidence-based social science research):
 - www.ovid.com/site/catalog/DataBase/1859.pdf
- Sociological Abstracts:
 - www.csa.com/factsheets/socioabs-set-c.php

6.2.1.6 Citation indexes

Science Citation Index / Science Citation Index Expanded is a database that lists published articles from approximately 6,000 major scientific, technical and medical journals and links them to the articles in which they have been cited (a feature known as cited reference searching). It is available online as SciSearch and on the internet as Web of Science. Web of Science is also incorporated in Web of Knowledge. It can be searched as a source database like MEDLINE. It can also be used to identify studies for a review by identifying a known relevant source article, and checking each of the articles citing the source article, to see if they are also relevant to the review. It is a way of searching forward in time from the publication of an important relevant article to identify additional relevant articles published since then. Records also include the listed references from the original record, which in turn are another possible source of relevant trial reports. Citation searching is an important adjunct to database searching and handsearching (Greenhalgh 2005). Information about these products is available at:

- scientific.thomson.com/products/sci/
- scientific.thomson.com/products/wos/
- isiwebofknowledge.com/

A similar database exists for the social sciences known as Social Sciences Citation Index:

- scientific.thomson.com/products/ssci/

In 2004, Elsevier launched an abstract and citation database – Scopus. Scopus covers 15,000 journals (of which over 1,200 are open access journals) and 500 conference proceedings. It contains over 33 million abstracts, and results from nearly 400 million scientific web pages:

- info.scopus.com/overview/what/

6.2.1.7 Dissertations and theses databases

Dissertations and theses are not normally indexed in general bibliographic databases such as MEDLINE or EMBASE but there are exceptions, such as CINAHL, which indexes nursing dissertations. To identify relevant studies published in dissertations or theses it is advisable to search specific dissertation sources: see [Box 6.2.c](#).

Box 6.2.c: Examples of dissertations and theses databases

- ProQuest Dissertations & Theses Database: indexes more than 2 million doctoral dissertations and masters' theses:
 - www.proquest.co.uk/products_pq/descriptions/pqdt.shtml
- Index to Theses in Great Britain and Ireland: lists over 500,000 theses:
 - www.theses.com/

- DissOnline: indexes 50,000 German dissertations:
 - www.dissonline.de/

6.2.1.8 Grey literature databases

There are many definitions of grey literature, but it is usually understood to mean literature that is not formally published in sources such as books or journal articles. Conference abstracts and other grey literature have been shown to be sources of approximately 10% of the studies referenced in Cochrane reviews (Mallett 2002). In a recently updated Cochrane methodology review, all five studies reviewed showed that published trials showed an overall greater treatment effect than grey literature trials (Hopewell 2007b). Thus, failure to identify trials reported in conference proceedings and other grey literature might affect the results of a systematic review.

Conference abstracts are a particularly important source of grey literature and are covered in Section [6.2.2.4](#).

EAGLE (the European Association for Grey Literature Exploitation), has closed the SIGLE (System for Information on Grey Literature) database, which was one of the most widely-used databases of grey literature. INIST in France (Institute for Scientific and Technical) has launched OpenSIGLE, which provides access to all the former SIGLE records, new data added by EAGLE members and information from Greynet.

- opensigle.inist.fr

The Healthcare Management Information Consortium (HMIC) database contains records from the Library & Information Services department of the Department of Health (DH) in England and the King's Fund Information & Library Service. It includes all DH publications including circulars and press releases. The King's Fund is an independent health charity that works to develop and improve management of health and social care services. The database is considered to be a good source of grey literature on topics such as health and community care management, organizational development, inequalities in health, user involvement, and race and health.

- www.ovid.com/site/catalog/DataBase/99.jsp?top=2&mid=3&bottom=7&subsection=10

The National Technical Information Service (NTIS) provides access to the results of both US and non-US government-sponsored research and can provide the full text of the technical report for most of the results retrieved. NTIS from 1964 is free on the internet.

- www.ntis.gov/

PsycEXTRA is a companion database to PsycINFO in psychology, behavioural science and health. It includes references from newsletters, magazines, newspapers, technical and annual reports, government reports and consumer brochures. PsycEXTRA is different from PsycINFO in its format, because it includes abstracts and citations plus full text for a major portion of the records. There is no coverage overlap with PsycINFO.

- www.apa.org/psycextra/

6.2.2 Journals and other non-bibliographic database sources

6.2.2.1 Handsearching

Handsearching involves a manual page-by-page examination of the entire contents of a journal issue or conference proceedings to identify all eligible reports of trials. In journals, reports of trials may appear in articles, abstracts, news columns, editorials, letters or other text. Handsearching healthcare journals and conference proceedings can be a useful adjunct to searching electronic databases for at least two reasons: 1) not all trial reports are included in electronic bibliographic databases, and 2) even when they are included, they may not contain relevant search terms in the titles or abstracts or be indexed with terms that allow them to be easily identified as trials (Dickersin 1994). Each journal year or conference proceeding should be handsearched thoroughly and competently by a well-trained handsearcher for all reports of trials, irrespective of topic, so that once it has been handsearched it will not need to be searched again. A Cochrane Methodology Review has found that a combination of handsearching and electronic searching is necessary for full identification of relevant reports published in journals, even for those that are indexed in MEDLINE (Hopewell 2007a). This was especially the case for articles published before 1991 when there was no indexing term for randomized trials in MEDLINE and for those articles that are in parts of journals (such as supplements and conference abstracts) which are not routinely indexed in databases such as MEDLINE.

To facilitate the identification of all published trials The Cochrane Collaboration has organized extensive handsearching efforts, predominantly through CRGs, Fields and Cochrane Centres. The US Cochrane Center oversees prospective registration of all potential handsearching and maintains files of handsearching activity in the Master List (Journals) and the Master List (Conference Proceedings) (see apps1.jhsph.edu/cochrane/masterlist.asp). Over 3,000 journals have been, or are being, searched within the Collaboration. The Master Lists enable search progress to be recorded and monitored for each title and also prevent duplication of effort which might occur if the same journal or conference proceeding were to be searched by more than one group or individual.

Cochrane entities and authors can prioritize handsearching based on where they expect to identify the most trial reports. This prioritization can be informed by searching CENTRAL, MEDLINE and EMBASE in a topic area and identifying which journals appear to be associated with the most retrieved citations. Preliminary evidence suggests that most of the journals with a high yield of trial reports are indexed in MEDLINE (Dickersin 2002) but this may reflect the fact that Cochrane contributors have concentrated early efforts on searching these journals. Therefore, journals not indexed in MEDLINE or EMBASE should also be considered for handsearching.

Authors are not routinely expected to handsearch journals for their reviews but they should discuss with their Trials Search Co-ordinator whether in their particular case handsearching of any journals or conference proceedings might be beneficial. Authors who wish to handsearch journals or conference proceedings should consult their Trials Search Co-ordinator who can determine whether the journal or conference proceedings has already been searched, and, if it has not, they can register the search on the relevant Master List and provide training in handsearching. Training material is available on the US Cochrane Center web site (apps1.jhsph.edu/cochrane/handsearcher_res.htm).

All correspondence regarding the initiation, progress and status of a journal or conference proceeding search should be between the CRG Trials Search Co-ordinator and staff at the US Cochrane Center.

6.2.2.2 Full text journals available electronically

The full text of an increasing number of journals is available electronically on a subscription basis or free of charge on the internet. In addition to providing a convenient method for retrieving the full article of already identified records, full-text journals can also be searched electronically, depending

on the search interface, in a similar way to the way database records can be searched in a bibliographic database.

It is important to specify if the full text of a journal has been searched electronically. Some journals omit sections of the print version, for example letters, from the electronic version and some include extra articles in electronic format only.

Most academic institutions subscribe to a wide range of electronic journals and these are therefore available free of charge at the point of use to members of those institutions. Review authors should seek advice about electronic journal access from the library service at their local institution. Some professional organizations provide access to a range of journals as part of their membership package. In some countries similar arrangements exist for health service employees through national licences. There are also a number of international initiatives to provide free or low-cost online access to full-text journals (and databases) over the internet, including the Health InterNetwork Access to Research Initiative (HINARI), the International Network for the Availability of Scientific Publications (INASP) and Electronic Information for Libraries (eIFL). For further information on these initiatives see Section 6.2.1.1.

Examples of some full-text journal sources that are available worldwide free of charge without subscription are given in [Box 6.2.d](#).

It is recommended that a local electronic copy or print copy be taken and filed of any possibly relevant article found electronically for subscription journals, as the subscription to that journal may not be in perpetuity. The journal may cease publication or change publishers and access to previously available articles may cease. The same applies to journals available free of charge on the internet, as the circumstances around availability of specific journals might change.

Box 6.2.d: Examples of full-text journal sources available worldwide without charge

- BioMed Central:
 - www.biomedcentral.com/browse/journals/
- Public Library of Science (PLOS):
 - www.plos.org/journals/
- PubMed Central (PMC):
 - www.pubmedcentral.nih.gov/

Web sites listing journals offering free full-text access include:

- Free Medical Journals:
 - freemedicaljournals.com/
- HighWire Press:
 - highwire.stanford.edu/lists/freeart.dtl

6.2.2.3 Tables of contents

Many journals, even those that are available by subscription only, offer Table of Contents (TOC) services free of charge, normally through e-mail alerts or RSS feeds. In addition a number of organizations offer TOC services: see [Box 6.2.e](#).

Box 6.2.e: Examples of organizations offering Table of Contents (TOC) services

- British Library Direct (free):
 - direct.bl.uk/bld/Home.do
- British Library Direct Plus (subscription):
 - www.bl.uk/reshelp/atyourdesk/docsupply/productsservices/bldplus/
- British Library Inside (to be replaced by British Library Direct Plus) (subscription):
 - www.bl.uk/inside
- Current Contents Conntect (subscription):
 - scientific.thomson.com/products/ccc/
- Scientific Electronic Library Online (SciELO) – Brazil (free):
 - www.scielo.br/
- Zetoc (Z39.50 Table Of Contents) (free as specified below):

Zetoc provides access to the British Library's Electronic Table of Contents. It is free of charge for members of the Joint Information Systems Committee (JISC)-sponsored higher and further education institutions in the UK and all of NHS Scotland and Northern Ireland:

 - zetoc.mimas.ac.uk/

6.2.2.4 Conference abstracts or proceedings

Although conference proceedings are not indexed in MEDLINE and a number of major databases, they are indexed in the BIOSIS databases (<http://www.biosis.org/>). Over one-half of trials reported in conference abstracts never reach full publication, and those that are eventually published in full have been shown to be systematically different from those that are never published in full (Scherer 2007). It is, therefore, important to try to identify possibly relevant studies reported in conference abstracts through specialist database sources and by handsearching or electronically searching those abstracts that are made available in print form, on CD-ROM or on the internet. Many conference proceedings are published as journal supplements. Specialist conference abstract sources are listed in [Box 6.2.f](#).

Many conference abstracts are published free of charge on the internet, such as those of the American Society of Clinical Oncology (ASCO):

- www.asco.org/ASCO/Meetings

Box 6.2.f: Examples of specialist conference abstract sources

- Biological Abstracts/RRM (Reports, Reviews, Meetings):
 - scientific.thomson.com/products/barrm/
- British Library Inside (to be replaced by British Library Direct Plus):
 - www.bl.uk/inside
- British Library Direct Plus:
 - www.bl.uk/reshelp/atyourdesk/docsupply/productsservices/bldplus/
- ISI Proceedings:
 - scientific.thomson.com/products/proceedings/

6.2.2.5 Other reviews, guidelines and reference lists as sources of studies

Some of the most convenient and obvious sources of references to potentially relevant studies are existing reviews. Copies of previously published reviews on, or relevant to, the topic of interest should be obtained and checked for references to the included (and excluded) studies. As well as the *Cochrane Database of Systematic Reviews (CDSR)*, *The Cochrane Library* includes *The Database of Abstracts of Reviews of Effects (DARE)* and the *Health Technology Assessment Database (HTA Database)*, both produced by the Centre for Reviews and Dissemination (CRD) at the University of York in the UK. Both databases provide information on published reviews of the effects of health care. As well as being published and updated quarterly in *The Cochrane Library*, more up-to-date versions of these databases are available free of charge on the CRD web site, where they are updated more frequently. For example, for the issue of *The Cochrane Library* published in January 2007, the DARE and HTA records were supplied by CRD staff in November 2006. The January 2007 publication of *The Cochrane Library* was the current issue until April 2007, so the DARE and HTA records in *The Cochrane Library* range between being two months to five months out of date.

- www.crd.york.ac.uk/crdweb

CRD used to produce the CRD Ongoing Reviews Database which was searchable through the UK National Research Register (NRR) but since that was archived in September 2007, records of ongoing reviews have been transferred to the HTA Database.

Reviews and guidelines may also provide useful information about the search strategies used in their development: see [Box 6.2.g](#). Specific evidence-based search services such as Turning Research into Practice (TRIP) can be used to identify reviews and guidelines. For the range of systematic review sources searched by TRIP see:

- www.tripdatabase.com/Aboutus/Publications/index.html?catid=11
- www.guideline.gov

MEDLINE, EMBASE and other bibliographic databases can also be used to identify review articles and guidelines. In MEDLINE, the most appropriate review articles should be indexed under the Publication Type term 'Meta-analysis', which was introduced in 1993, or 'Review', which was introduced in 1966. Guidelines should be indexed under the Publication Type term 'Practice Guideline', which was introduced in 1991. EMBASE also has a thesaurus term 'Systematic Review', which was introduced in 2003, and 'Practice Guideline', which was introduced in 1994.

There is a so-called 'Systematic Review' search strategy or filter on PubMed under the Clinical Queries link:

- www.ncbi.nlm.nih.gov/entrez/query/static/clinical.shtml

It is very broad in its scope and retrieves many references that are not systematic reviews. The strategy is described as follows: "This strategy is intended to retrieve citations identified as systematic reviews, meta-analyses, reviews of clinical trials, evidence-based medicine, consensus development conferences, guidelines, and citations to articles from journals specializing in review studies of value to clinicians."

- www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_strategy.html

Search strategies or filters have been developed to identify systematic reviews in MEDLINE (White 2001, Montori 2005) and EMBASE (Wilczynski 2007). Search strategies for identifying systematic reviews in other databases and for identifying guidelines are listed on the InterTASC Information Specialists' Subgroup Search Filter Resource web site.

- www.york.ac.uk/inst/crd/intertasc/sr.htm

As well as searching the references cited in existing systematic reviews and meta-analyses, reference lists of identified studies may also be searched for additional studies (Greenhalgh 2005). Since investigators may selectively cite studies with positive results, reference lists should be used with caution as an adjunct to other search methods (see Chapter 10, Section 10.2.2.3).

Box 6.2.g: Examples of evidence-based guidelines

- Australian National Health and Medical Research Council: Clinical Practice Guidelines:
 - nhmrc.gov.au/publications/subjects/clinical.htm
- Canadian Medical Association – Infobase: Clinical Practice Guidelines:
 - mdm.ca/cpgsnew/cpgs/index.asp
- National Guideline Clearinghouse (US):
 - www.guideline.gov/
- National Library of Guidelines (UK):
 - www.library.nhs.uk/guidelinesFinder/
- New Zealand Guidelines Group:
 - www.nzgg.org.nz
- NICE Clinical Guidelines (UK):
 - www.nice.org.uk/aboutnice/whatwedo/aboutclinicalguidelines/about_clinical_guidelines.jsp

6.2.2.6 Web searching

There is little empirical evidence as to the value of using general internet search engines such as Google to identify potential studies (Eysenbach 2001). Searching research funders' and device manufacturers' web sites might be fruitful. Searching pharmaceutical industry web sites may be useful, in particular their trials registers, covered in Section 6.2.3.3. If internet searches are conducted, it is recommended that review authors should file a print copy or save locally an electronic copy of details of information about any possibly relevant study found on the internet, rather than simply 'book-marking' the site, in case the record of the trial is removed or altered at a later stage. It is important to keep a record of the date the web site was accessed for citation purposes.

6.2.3 Unpublished and ongoing studies

Some completed studies are never published. An association between 'significant' results and publication has been documented across a number of studies, as summarized in Chapter 10 (Section 10.2). Finding out about unpublished studies, and including them in a systematic review when eligible and appropriate, is important for minimizing bias. There is no easy and reliable way to obtain information about studies that have been completed but never published. This situation is improving as a result of a number of initiatives:

- The International Standard Randomised Controlled Trial Number Register scheme launched as the first online service that provided unique numbers to randomized controlled trials in all areas of health care and from all countries around the world and subsequently ClinicalTrials.gov (see Section 6.2.3.1);

- The increasing acceptance on behalf of investigators of the importance of registering trials at inception;
- The support of registration at inception by the leading medical journal publishers and their refusal to subsequently publish reports of trials not properly registered (De Angelis 2004, De Angelis 2005);
- The US National Institutes for Health (NIH) Public Access Policy (see publicaccess.nih.gov/), which until December 2007 was voluntary but now requires that “all investigators funded by the NIH submit or have submitted for them to the National Library of Medicine's PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication to be made publicly available no later than 12 months after the official date of publication”.
 - publicaccess.nih.gov/policy.htm

Colleagues can be an important source of information about unpublished studies, and informal channels of communication can sometimes be the only means of identifying unpublished data. Formal letters of request for information can also be used to identify completed but unpublished studies. One way of doing this is to send a comprehensive list of relevant articles along with the inclusion criteria for the review to the first author of reports of included studies, asking if they know of any additional studies (published or unpublished) that might be relevant. It may also be desirable to send the same letter to other experts and pharmaceutical companies or others with an interest in the area. It should be borne in mind that asking researchers for information about completed but never published studies has not always been found to be fruitful (Hetherington 1989, Horton 1997) though some researchers have reported that this is an important method for retrieving studies for systematic reviews (Royle 2003, Greenhalgh 2005). Some organizations set up web sites for systematic review projects listing the studies identified to date and inviting submission of information on studies not already listed. It has also been suggested that legislation such as the Freedom of Information Acts in countries such as the UK and the US might be used to gain access to information about unpublished trials (Bennett 2003, MacLean 2003).

It is also important to identify ongoing studies, so that when a review is later updated these can be assessed for possible inclusion. Information about possibly relevant ongoing studies should be included in the review in the ‘Characteristics of ongoing studies’ table (see Chapter 4, Section 4.6.5). Awareness of the existence of a possibly relevant ongoing study might also affect decisions with respect to when to update a specific review. Unfortunately, no single, comprehensive, centralized register of ongoing trials exists (Manheimer 2002). Efforts have, however, been made by a number of organizations, including organizations representing the pharmaceutical industry and pharmaceutical companies themselves, to begin to provide central access to ongoing trials and in some cases trial results on completion, either on a national or international basis. In an effort to improve this situation, the World Health Organization (WHO) launched the International Clinical Trials Registry Platform Search Portal in May 2007 to search across a range of trials registers, similar to the initiative launched some years earlier by Current Controlled Trials with their so-called *metaRegister*. Currently (as at June 2008) the WHO portal only searches across three primary registers (the Australian and New Zealand Clinical Trials Registry, ClinicalTrials.gov and the Current Controlled Trials International Standard Randomised Controlled Trial Number Register) but it is anticipated that other registers will be included as the project progresses.

6.2.3.1 National and international trials registers

[Box 6.2.h](#) lists national and international trials registers.

In addition, Drugs@FDA provides information about most of the drugs approved in the US since 1939. For those approved more recently (from 1998), there is often a 'review', which contains the scientific analyses that provided the basis for approval of the new drug.

- www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Other national and regional drug approval agencies may also be useful sources of trial information.

Box 6.2.h: Examples of national and international trials registers

- The Association of the British Pharmaceutical Industry (ABPI) – Pharmaceutical Industry Clinical Trials database:
 - www.cmrinteract.com/clintrial/
- The Australian New Zealand Clinical Trials Registry:
 - www.anzctr.org.au/
- CenterWatch Clinical Trials Listing Service:
 - www.centerwatch.com/
- Chinese Clinical Trial Register:
 - www.chictr.org/Default.aspx
- ClinicalTrials.gov register:
 - clinicaltrials.gov/
- Community Research & Development Information Service (of the European Union) (trials and other research):
 - cordis.europa.eu/en/home.html
- Current Controlled Trials *meta*Register of Controlled Trials (*mRCT*) – active registers:
 - www.controlled-trials.com/mrct/
- Current Controlled Trials *meta*Register of Controlled Trials (*mRCT*) – archived registers:
 - www.controlled-trials.com/mrct/archived
- European Medicines Agency (EMA):
 - www.emea.europa.eu/index/indexh1.htm
- German trials register – not yet launched. Final agreement reached 30 August 2007 – will be included under the WHO International Clinical Trials Registry Platform Search Portal – for further details as and when available see:
 - www.who.int/trialsearch
- Hong Kong clinical trials register – HKClinicalTrials.com:
 - www.hkclinicaltrials.com/
- Indian clinical trials registry – Clinical Trials Registry – India (CTRI):
 - www.ctri.in
- International Clinical Trials Registry Platform Search Portal:
 - www.who.int/trialsearch
- International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) Clinical Trials Portal:
 - www.ifpma.org/clinicaltrials.html
- International Standard Randomised Controlled Trial Number Register:

- www.controlled-trials.com/isrctn/
- Netherlands trial register (Nederlands Trialregister – in Dutch):
 - www.trialregister.nl/trialreg/index.asp
- South African National Clinical Trial Register:
 - www.sanctr.gov.za/
- UK Clinical Research Network Portfolio Database:
 - portal.nihr.ac.uk/Pages/Portfolio.aspx
- UK Clinical Trials Gateway:
 - www.controlled-trials.com/ukctr/
- UK National Research Register (NRR) (trials and other research – archived September 2007 – see UK Clinical Trials Gateway):
 - portal.nihr.ac.uk/Pages/NRRArchive.aspx
- University hospital Medical Information Network (UMIN) Clinical Trials Registry (for Japan) – UMIN CTR:
 - www.umin.ac.jp/ctr/

6.2.3.2 Subject-specific trials registers

There are many condition-specific trials registers, especially in the field of cancer – which are too numerous to list. They can be identified by searching the internet and by searching within some of the resources listed above such as the Current Controlled Trials *meta*Register of Controlled Trials (*mRCT*).

6.2.3.3 Pharmaceutical industry trials registers

Some pharmaceutical companies make available information about their clinical trials through their own web sites, either instead of or in addition to the information they make available through national or international web sites such as those listed above. Some examples are included in [Box 6.2.i](#).

Box 6.2.i: Examples of pharmaceutical industry trials registers

- AstraZeneca Clinical Trials web site:
 - www.astrazenecaclinicaltrials.com/
- Bristol-Myers Squibb Clinical Trial Registry:
 - ctr.bms.com/ctd/registry.do
- Eli Lilly and Company Clinical Trial Registry (also includes trial results)
 - www.lillytrials.com/
- GlaxoSmithKline clinical trial register:
 - ctr.gsk.co.uk/medicinelist.asp
- NovartisClinicalTrials.com:
 - www.novartisclinicaltrials.com/webapp/etrial/home.do
- Roche Clinical Trial Protocol Registry:
 - www.roche-trials.com/registry.html

- Wyeth Clinical Trial Listings:
 - www.wyeth.com/ClinicalTrialListings

6.2.3.4 Trials results registers and other sources

Registers of the results of completed trials are a more recent phenomenon, following on from ongoing trials registers that simply list details of the trial. They are of particular value because trial results are not always published, and even if published are not always published in full. Recent legislation in the US known as Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA 801), enacted in September 2007, called for expanding ClinicalTrials.gov and adding a clinical trial results database. Examples of trials results registers are provided in [Box 6.2.j](#).

In addition, Clinical Trial Results is a web site that hosts slide presentations from clinical trialists reporting the results of clinical trials:

- www.clinicaltrialresults.org/

Box 6.2.j: Examples of trials results registers

- International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) Clinical Trials Portal:
 - www.ifpma.org/clinicaltrials.html
- PhRMA Clinical Study Results Database:
 - www.clinicalstudyresults.org/about
- Bristol-Myers Squibb Clinical Trial Results:
 - ctr.bms.com/ctd/results.do
- Eli Lilly and Company Clinical Trial Registry:
 - www.lillytrials.com/
- Roche Clinical Trials Results Database:
 - www.roche-trials.com/results.html
- Wyeth Clinical Trial Results:
 - www.wyeth.com/ClinicalTrialResults

6.2.4 Summary points

- Cochrane review authors should seek advice from their Trials Search Co-ordinator on sources to search.
- CENTRAL is considered to be the best single source of reports of trials for inclusion in Cochrane reviews.
- The three bibliographic databases generally considered to be the most important sources to search for studies for inclusion in Cochrane reviews are CENTRAL, MEDLINE and EMBASE.
- National, regional and subject-specific databases should be selected for searching according to the topic of the review.
- Conference abstracts and other grey literature can be an important source of studies for inclusion in reviews.

- Reference lists in other reviews, guidelines, included (and excluded) studies and other related articles should be searched for additional studies.
- Efforts should be made to identify unpublished studies.
- Ongoing trials should be identified and tracked for possible inclusion in reviews on completion.
- Trials registers and trials results registers are an important source of ongoing and unregistered trials.

6.3 Planning the search process

6.3.1 Involving Trials Search Co-ordinators and healthcare librarians in the search process

It is the responsibility of each CRG to support review authors in identifying reports of studies for inclusion in their reviews, and most CRGs employ a Trials Search Co-ordinator to fulfil this role (see Section 6.1.1.1). Most CRGs offer support to authors in study identification from the early planning stage to the final write-up of the review for publication in the *CDSR*. This support might include designing search strategies or advising on their design, running searches, in particular in databases not available to the review author at their institution, and providing review authors with lists of references to studies from the CRG's Specialized Register and possibly from other databases. The range of services offered varies across CRGs according to the resources available. Review authors are, therefore, encouraged to contact the Trials Search Co-ordinator of their CRG at the earliest stage for advice and support.

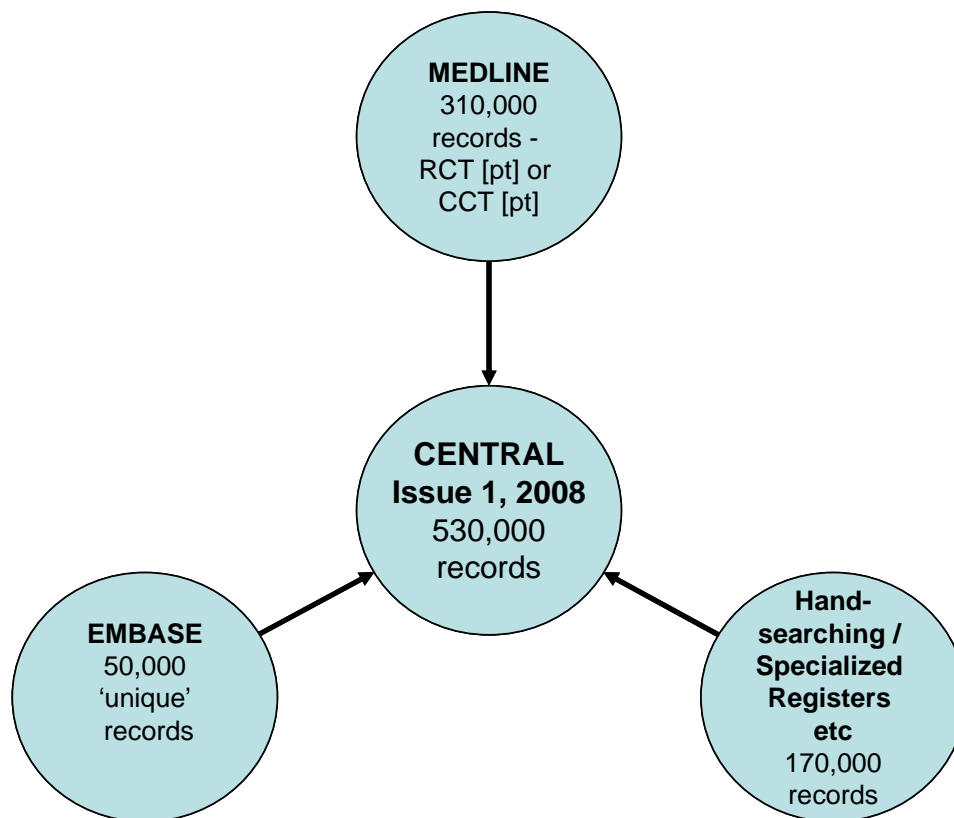
If authors are conducting their own searches, they should seek advice from their Trials Search Co-ordinator with respect to which database(s) to search and the exact strategies to be run. It should also be borne in mind that the search process needs to be documented in enough detail throughout to ensure that it can be reported correctly in the review, to the extent that all the searches of all the databases are reproducible. The full search strategies for each database should be included in the review in an Appendix. It is, therefore, important that review authors should save all search strategies and take notes at the time to enable the completion of that section at the appropriate time. For further guidance on this, authors should contact their Trials Search Co-ordinator, and see Section 6.6.

If the CRG is currently without a Trials Search Co-ordinator it is recommended that review authors seek guidance from a healthcare librarian or information specialist, where possible with experience of supporting systematic reviews.

6.3.2 Collaboration-wide search initiatives

In planning the search process it is necessary to take into account what other searching has already been undertaken to avoid unnecessary duplication of effort. For example, considerable efforts over the years have gone into searching MEDLINE and EMBASE and incorporating reports of trials from these two major international databases into the Cochrane Central Register of Controlled Trials (CENTRAL). It is necessary, therefore, that any additional searching for a specific review should take into account what has gone before. [Figure 6.3.a](#) illustrates the contents of CENTRAL.

Figure 6.3.a: Illustration of the contents of CENTRAL



6.3.2.1 What is in The Cochrane Central Register of Controlled Trials (CENTRAL) from MEDLINE?

CENTRAL contains all records from MEDLINE indexed with the Publication Type term 'Randomized Controlled Trial' or 'Controlled Clinical Trial' that are indexed as human studies. These records are downloaded quarterly from MEDLINE by Wiley-Blackwell as part of the build of CENTRAL for publication in *The Cochrane Library*. For further details see:

- www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/CENTRALHelpFile.html

A substantial proportion of the MEDLINE records coded 'Randomized Controlled Trial' or 'Controlled Clinical Trial' in the Publication Type field have been coded as a result of the work of The Cochrane Collaboration (Dickersin 2002). Handsearch results from Cochrane entities, for journals indexed in MEDLINE, have been sent to the US National Library of Medicine (NLM), where the MEDLINE records have been re-tagged with the publication types 'Randomized Controlled Trial' or 'Controlled Clinical Trial' as appropriate. In addition, the US Cochrane Center (formerly the New England Cochrane Center, Providence Office and the Baltimore Cochrane Center) and the UK Cochrane Centre have conducted an electronic search of MEDLINE from 1966–2004 to identify reports of randomized controlled trials, identifiable from the MEDLINE titles and/or abstracts, not already indexed as such, using the first two phases of the Cochrane Highly Sensitive Search Strategy first published in 1994 (Dickersin 1994) and subsequently updated and included in the *Handbook*. The free text terms used were: clinical trial; (singl\$ OR doubl\$ OR trebl\$ OR tripl\$) AND (mask\$ OR blind\$); placebo\$; random\$. The \$ sign indicates the use of a truncation symbol. The following subject index terms (MeSH) used were exploded: randomized controlled trials; random allocation; double-blind method; single-blind method; clinical trials; placebos. The following subject heading

(MeSH) was used unexploded: research design. The Publication Type terms used were: randomized controlled trial; controlled clinical trial; clinical trial.

A test was carried out using the terms in phase three of the 1994 Cochrane Highly Sensitive Search Strategy but the precision of those terms, having already searched on all the terms in phases one and two as listed above, was considered to be too low to warrant using these terms for the above project (Lefebvre 2001). It was, however, recognized that some of these terms might be useful when combined with subject terms to identify studies for some specific reviews (Eisinga 2007).

The above search was limited to humans. The following years were completed by the US Cochrane Center (1966–1984; 1998–2004) and by the UK Cochrane Centre (1985–1997). The results have been forwarded to the NLM and re-tagged in MEDLINE and are thus included in CENTRAL. This project is currently on hold. If the US Cochrane Center can attract funding for this project they will continue the electronic search of records entered into MEDLINE in 2005 and beyond. Any updates to this situation will be described in the CENTRAL Creation Details file in *The Cochrane Library*:

- www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/CENTRALHelpFile.html

CENTRAL includes from MEDLINE not only reports of trials that meet the more restrictive Cochrane definition for a controlled clinical trial (Box 6.3.a) but also trial reports that meet the less restrictive original NLM definition (Box 6.3.b), which used to include historical comparisons. There is currently no method of distinguishing, either in CENTRAL or in MEDLINE, which of these records meet the more restrictive Cochrane definition, as they are all indexed with the Publication Type term ‘Controlled Clinical Trial’.

Box 6.3.a: Cochrane definitions and criteria for randomized controlled trials (RCTs) and controlled clinical trials (CCTs)

Records identified for inclusion should meet the eligibility criteria devised and agreed in November 1992, which were first published, in 1994, in the first version of the *Handbook* (see Chapter 1, Section 1.4). According to these eligibility criteria:

A trial is eligible if, on the basis of the best available information (usually from one or more published reports), it is judged that:

- the individuals (or other units) followed in the trial were definitely or possibly assigned prospectively to one of two (or more) alternative forms of health care using
 - random allocation or
 - some quasi-random method of allocation (such as alternation, date of birth, or case record number).

Trials eligible for inclusion are classified according to the reader’s degree of certainty that random allocation was used to form the comparison groups in the trial. If the author(s) state explicitly (usually by some variant of the term ‘random’ to describe the allocation procedure used) that the groups compared in the trial were established by random allocation, then the trial is classified as a RCT (randomized controlled trial). If the author(s) do not state explicitly that the trial was randomized, but randomization cannot be ruled out, the report is classified as a CCT (controlled clinical trial). The classification CCT is also applied to quasi-randomized studies, where the method of allocation is known but is not considered strictly random, and possibly quasi-randomized trials. Examples of quasi-random methods of assignment include alternation, date of birth, and medical record number.

The classification as RCT or CCT is based solely on what the author has written, not on the reader’s

interpretation; thus, it is not meant to reflect an assessment of the true nature or quality of the allocation procedure. For example, although ‘double-blind’ trials are nearly always randomized, many trial reports fail to mention random allocation explicitly and should therefore be classified as CCT.

Relevant reports are reports published in any year, of studies comparing at least two forms of health care (healthcare treatment, healthcare education, diagnostic tests or techniques, a preventive intervention, etc.) where the study is on either living humans or parts of their body or human parts that will be replaced in living humans (e.g., donor kidneys). Studies on cadavers, extracted teeth, cell lines, etc. are not relevant. *Searchers should identify all controlled trials meeting these criteria regardless of relevance to the entity with which they are affiliated.*

The highest possible proportion of all reports of controlled trials of health care should be included in CENTRAL. Thus, those searching the literature to identify trials should give reports the benefit of any doubts. Review authors will decide whether to include a particular report in a review.

Box 6.3.b: US National Library of Medicine 2008 definitions for the Publication Type terms ‘Randomized Controlled Trial’ and ‘Controlled Clinical Trial’

Randomized Controlled Trial

Work consisting of a clinical trial that involves at least one test treatment and one control treatment, concurrent enrolment and follow-up of the test- and control-treated groups, and in which the treatments to be administered are selected by a random process, such as the use of a random-numbers table.

Controlled Clinical Trial

Work consisting of a clinical trial involving one or more test treatments, at least one control treatment, specified outcome measures for evaluating the studied intervention, and a bias-free method for assigning patients to the test treatment. The treatment may be drugs, devices, or procedures studied for diagnostic, therapeutic, or prophylactic effectiveness. Control measures include placebos, active medicine, no-treatment, dosage forms and regimens, historical comparisons, etc. When randomization using mathematical techniques, such as the use of a random-numbers table, is employed to assign patients to test or control treatments, the trial is characterized as a ‘Randomized Controlled Trial’.

6.3.2.2 What is in The Cochrane Central Register of Controlled Trials (CENTRAL) from EMBASE?

In a study similar to that described above for MEDLINE, a search of EMBASE has been carried out by the UK Cochrane Centre for reports of trials not indexed as trials in MEDLINE (Lefebvre 2008). (Trials indexed as such in MEDLINE are already included in CENTRAL as described in Section 6.3.2.1, and are therefore de-duplicated against the EMBASE records as part of the search process.) The following terms are those currently used for the project and have been searched for the years 1980 to 2006: free-text terms: random\$; factorial\$; crossover\$; cross over\$; cross-over\$; placebo\$; doubl\$ adj blind\$; singl\$ adj blind\$; assign\$; allocat\$; volunteer\$; and index terms, known as EMTREE terms: crossover-procedure; double-blind procedure; randomized controlled trial; single-blind procedure. A search for the years 1974 to 1979 inclusive has also been completed for the free-text terms: random\$; factorial\$; crossover\$ and placebo\$. The \$ sign indicates the use of a truncation symbol.

These searches have yielded a total of 80,000 reports of trials not, at the time of the search, indexed as reports of trials in MEDLINE. All of these records are now published in CENTRAL, under contract between Elsevier, the publishers of EMBASE, and The Cochrane Collaboration. Of these 80,000 records, 50,000 are ‘unique’ to CENTRAL, that is they are not already included in CENTRAL with the records sourced from MEDLINE. This search is updated annually. Updates are described in the CENTRAL Creation Details file in *The Cochrane Library*:

- www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/CENTRALHelpFile.html

and the What’s New section on *The Cochrane Library* home page:

- www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME

6.3.2.3 What is in The Cochrane Central Register of Controlled Trials (CENTRAL) from other databases and handsearching?

Other general healthcare databases such as those published in Australia and China have undergone similar systematic searches to identify reports of trials for CENTRAL. The Australasian Cochrane Centre co-ordinated a search of the National Library of Australia’s Australasian Medical Index from 1966 (McDonald 2002). This search has recently been updated to include records added up to 2007. The Chinese Cochrane Center, with support from the Australasian Cochrane Centre, co-ordinated a search of the Chinese Biomedical Literature Database from 1999 to 2001. In an ongoing project, the Chinese Cochrane Center, with support from the UK Cochrane Centre, is searching a number of Chinese sources with a view to including these records in CENTRAL. Similarly, the Brazilian Cochrane Centre in collaboration with the Regional Library of Medicine in Brazil (Biblioteca REgional de MEDicina – BIREME) is planning to co-ordinate a search of the Pan American Health Organization’s database LILACS (Latin American Caribbean Health Sciences Literature).

Each of the Cochrane Centres has the responsibility for searching the general healthcare literature of its country or region. The CRGs and Fields are responsible for co-ordinating searching of the specialist healthcare literature in their areas of interest. More than 3000 journals have been, or are being, handsearched. Identified trial reports that are not relevant to a CRG’s scope and thus are not appropriate for their Specialized Register (see below) are forwarded to Wiley-Blackwell as handsearch results. Handsearch records can be identified in CENTRAL as they are assigned the tag HS-HANDSRCH or HS-PRECENTRL.

- www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/CENTRALHelpFile.html

6.3.2.4 What is in The Cochrane Central Register of Controlled Trials (CENTRAL) from Specialized Registers of Cochrane Review Groups and Fields?

It is an ‘essential core function’ of CRGs that their “editorial bases develop and maintain a Specialized Register, containing all relevant studies in their area of interest, and submit this to CENTRAL on a quarterly basis”, as outlined in Section 3.2.1.5 ‘Core functions of Cochrane Review Groups’ in *The Cochrane Manual* (www.cochrane.org/admin/manual.htm).

The Specialized Register serves to ensure that individual review authors within the CRG have easy and reliable access to trials relevant to their review topic, normally through their Trials Search Co-ordinator. CRGs use the methods described in this Chapter of the *Handbook* to identify trials for their Specialized Registers. Most CRGs also have systems in place to ensure that any additional eligible reports identified by authors for their review(s) are contributed to the CRG’s Specialized Register. The registers are, in turn, submitted for inclusion in CENTRAL on a quarterly basis. Thus, records included in the Specialized Register of one CRG become accessible to all other CRGs through CENTRAL. Many Fields also develop subject-specific Specialized Registers and submit them for

inclusion in CENTRAL as described above. To identify records in CENTRAL from within a specific Specialized Register it is possible to search on the Specialized Register tag, such as SR-STROKE. A list of all the Specialized Register tags can be found in the ‘Appendix: Review Group or Field/Network Specialized Register Codes’ in the ‘CENTRAL Creation Details’ Help File in *The Cochrane Library*:

- www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/CENTRALHelpFile.html

Records in a CRG’s Specialized Register will often contain coding and other information not included in CENTRAL, so the Trials Search Co-ordinator will often be able to identify additional records in their Specialized Register, which could not be identified by searching in CENTRAL, by searching for these codes in the Specialized Register. Conversely, the search functionality of the bibliographic or other software used to manage Specialized Registers is usually less sophisticated than the search functionality available in *The Cochrane Library* so a search of CENTRAL will retrieve records from the Specialized Register that may not be easily retrievable from within the Specialized Register itself. It is therefore recommended that both CENTRAL and the Specialized Register itself are searched separately to maximize retrieval.

6.3.3 Searching CENTRAL, MEDLINE and EMBASE: specific issues

It is recommended that for all Cochrane reviews, CENTRAL and MEDLINE should be searched, as a minimum, together with EMBASE if it is available to either the CRG or the review author.

6.3.3.1 Searching The Cochrane Central Register of Controlled Trials (CENTRAL): specific issues

CENTRAL is comprised of records from a wide range of sources (see Section 6.2.1.2 and 6.3.2 and subsections), so there is no consistency in the format or content of the records.

The 310,000 records sourced from MEDLINE are best retrieved by a combination of Medical Subject Heading (MeSH) and free-text terms. The other records, including the 50,000 records sourced from EMBASE, are best retrieved using free-text searches across all fields.

Most of the records that do not come from MEDLINE or EMBASE (about 170,000 in *The Cochrane Library* Issue 1, 2008) do not have abstracts or any indexing terms. To retrieve these records, which consist predominantly of titles only, it is necessary to carry out a very broad search consisting of a wide range of free-text terms, which may be considered too broad to run across the whole of CENTRAL.

It is possible to identify the records that have been sourced from MEDLINE and EMBASE by searching in CENTRAL for those records that have PubMed or EMBASE accession numbers. It is possible then to exclude these records from a broad search of CENTRAL, as illustrated in the example in [Box 6.3.c](#).

For general information about searching, which is relevant to searching CENTRAL, see Section 6.4.

Box 6.3.c: Example of exclusion of MEDLINE and EMBASE records when searching CENTRAL

Note: the example is for illustrative purposes only. A search of CENTRAL for a systematic review on this topic would require a wide range of alternative terms for both tamoxifen and breast cancer.

#1	"accession number" near pubmed
#2	"accession number" near2 embase
#3	#1 or #2
#4	tamoxifen
#5	(breast near cancer)
#6	#4 and #5
#7	#6 not #3

6.3.3.2 Searching MEDLINE and EMBASE: specific issues

Despite the fact that both MEDLINE and EMBASE have been searched systematically for reports of trials and that these reports of trials have been included in CENTRAL, as described in Sections 6.3.2.1 and 6.3.2.2, supplementary searches of both MEDLINE and EMBASE are recommended. Any such searches, however, should be undertaken in the knowledge of what searching has already been conducted to avoid duplication of effort.

Searching MEDLINE

There is a delay of some months between records being indexed in MEDLINE and appearing indexed as reports of trials in CENTRAL, since CENTRAL is only updated quarterly. For example, for the issue of *The Cochrane Library* published in January 2007, the MEDLINE records were downloaded by Wiley-Blackwell staff in November 2006. The January 2007 publication of *The Cochrane Library* was the current issue until April 2007, so the MEDLINE records range between being two to five months out of date. The most recent months of MEDLINE should, therefore, be searched, at least for records indexed as either 'Randomized Controlled Trial' or 'Controlled Clinical Trial' in the Publication Type, to identify those records recently indexed as RCTs or CCTs in MEDLINE.

Additionally, the most recent year to be searched under the project to identify reports of trials in MEDLINE and send them back to the US National Library of Medicine for re-tagging was 2004, so records added to MEDLINE during and since 2005 should be searched using one of the search strategies described in Section 6.4.11.1.

Finally, for extra sensitivity, or where the use of a randomized trial 'filter' is not appropriate, review authors should search MEDLINE for all years using subject terms only.

It should be remembered that the MEDLINE re-tagging project described in Section 6.3.2.1 assessed whether the records identified were reports of trials on the basis of the title and abstract only, so any supplementary search of MEDLINE that is followed up by accessing the full text of the articles will identify additional reports of trials, most likely through the methods sections, that were not identified through the titles or abstracts alone.

For guidance on running separate search strategies in the MEDLINE-indexed versions of MEDLINE and the versions of MEDLINE containing 'in process' and other non-indexed records please refer to Section 6.4.11.1.

Any reports of trials identified by the review author can be submitted to the Trials Search Co-ordinator who can ensure that they are added to CENTRAL. Any errors, in respect of records indexed as trials in MEDLINE that on the basis of the full article are definitely not reports of trials according to the definitions used by the National Library of Medicine (NLM) (see Section 6.3.2.1), should also be reported to the Trials Search Co-ordinator, so they can be referred to the NLM and corrected.

For general information about searching, which is relevant to searching MEDLINE, see Section 6.4.

Searching EMBASE

The project to identify reports of trials in EMBASE for inclusion in CENTRAL, described in Section 6.3.2.2, is carried out on an annual basis, so there is a time lag of approximately one to two years with respect to EMBASE records appearing in CENTRAL. The last two years of EMBASE should, therefore, be searched to cover work still in progress. Some suggested search terms are listed in Section 6.3.2.2. A search filter designed by the McMaster Hedges Team is also available (Wong 2006).

Finally, for extra sensitivity, or where the use of a randomized trial ‘filter’ is not appropriate, review authors should search EMBASE for all years using subject terms only, as described under similar circumstances for MEDLINE above. It should be remembered that the EMBASE project described above assessed whether the records identified were reports of trials on the basis of the title and abstract only, in the same way as the MEDLINE project described above. Therefore, any supplementary search of EMBASE that is followed up by accessing the full text of the articles will identify additional reports of trials, most likely through the methods sections, that were not identified through the titles or abstracts alone.

For general information about searching, which is relevant to searching EMBASE, see Section 6.4.

6.3.4 Summary points

- Cochrane review authors should seek advice from their Trials Search Co-ordinator throughout the search process.
- It is recommended that for all Cochrane reviews CENTRAL and MEDLINE should be searched, as a minimum, together with EMBASE if it is available to either the CRG or the review author.
- The full search strategies for each database searched will need to be included in an Appendix of the review, so all search strategies should be saved, and notes taken of the number of records retrieved for each database searched.
- CENTRAL contains over 350,000 records from MEDLINE and EMBASE, so care should be taken when searching MEDLINE and EMBASE to avoid unnecessary duplication of effort.
- MEDLINE should be searched from 2005 onwards inclusive using one of the revised and updated Cochrane Highly Sensitive Search Strategies for identifying randomized trials in MEDLINE as outlined in Section 6.4.11.1.
- EMBASE should be searched for the most recent two years as outlined in Section 6.4.11.2.
- Additional studies can be identified in MEDLINE and EMBASE by searching across the years already searched for CENTRAL, by obtaining the full article and by reading, in particular, the methods section.

6.4 Designing search strategies

6.4.1 Designing search strategies – an introduction

This section highlights some of the issues to consider when designing search strategies, but does not adequately address the many complexities in this area. It is in particular in this aspect of searching for studies that the skills of a Trials Search Co-ordinator or healthcare librarian are highly recommended. Many of the issues highlighted below relate to both the methodological aspect of the search (such as identifying reports of randomized trials) and the subject of the search. For a search to be robust both aspects require equal attention to be sure that relevant records are not missed.

The eligibility criteria for studies to be included in the review will inform how the search is conducted (see Chapter 5). The eligibility criteria will specify the types of designs, types of participants, types of intervention (experimental and comparator) and, in some cases, the types of outcomes to be addressed. Issues to consider in planning a search include the following:

- whether the review is limited to randomized trials or whether other study designs will be included (see also Chapter 13);
- the requirement to identify adverse effects data (see also Chapter 14);
- the nature of the intervention(s) being assessed;
- any geographic considerations such as the need to search the Chinese literature for studies in Chinese herbal medicine;
- the time period when any evaluations of these interventions may have taken place; and
- whether data from unpublished studies are to be included.

6.4.2 Structure of a search strategy

The structure of a search strategy should be based on the main concepts being examined in a review. For a Cochrane review, the review title should provide these concepts and the eligibility criteria for studies to be included will further assist in the selection of appropriate subject headings and text words for the search strategy.

It is usually unnecessary, and even undesirable, to search on every aspect of the review's clinical question (often referred to as PICO – that is Patient (or Participant or Population), Intervention, Comparison and Outcome). Although a research question may address particular populations, settings or outcomes, these concepts may not be well described in the title or abstract of an article and are often not well indexed with controlled vocabulary terms. They generally, therefore, do not lend themselves well to searching. In general databases, such as MEDLINE, a search strategy to identify studies for a Cochrane review will typically have three sets of terms: 1) terms to search for the health condition of interest, i.e. the population; 2) terms to search for the intervention(s) evaluated; and 3) terms to search for the types of study design to be included (typically a 'filter' for randomized trials). CENTRAL, however, aims to contain only reports with study designs possibly relevant for inclusion in Cochrane reviews, so searches of CENTRAL should not use a trials 'filter'. Filters to identify randomized trials and controlled trials have been developed specifically for MEDLINE and guidance is also given for searching EMBASE: see Section 6.4.1.1 and sub-sections. For reviews of complex interventions, it may be necessary to adopt a different approach, for example by searching only for the population or the intervention (Khan 2001).

6.4.3 Service providers and search interfaces

Both MEDLINE and EMBASE are offered by a number of service providers, via a range of search interfaces; for example Dialog offers both Dialog and DataStar. In addition the US National Library of

Medicine and Elsevier both offer access to their own versions of MEDLINE and EMBASE respectively: MEDLINE through PubMed, which is available free of charge on the internet, and EMBASE through EMBASE.com which is available on subscription only. Search syntax varies across interfaces. For example, to search for the Publication Type term 'Randomized Controlled Trial' in the various search interfaces it is necessary to enter the term as:

randomized controlled trial.pt. (in Ovid)

randomized controlled trial [pt] (in PubMed)

randomized controlled trial in pt (in SilverPlatter)

Many service providers offer links to full-text versions of articles on other publishers' web sites, such as the PubMed 'Links / LinkOut' feature.

6.4.4 Sensitivity versus precision

Searches for systematic reviews aim to be as extensive as possible in order to ensure that as many as possible of the necessary and relevant studies are included in the review. It is, however, necessary to strike a balance between striving for comprehensiveness and maintaining relevance when developing a search strategy. Increasing the comprehensiveness (or sensitivity) of a search will reduce its precision and will retrieve more non-relevant articles.

Sensitivity is defined as the number of relevant reports identified divided by the total number of relevant reports in existence. Precision is defined as the number of relevant reports identified divided by the total number of reports identified.

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 where the rewards of further searching may not be worth the effort required to identify the additional references. The decision as to how much to invest in the search process depends on the question a review addresses, the extent to which the CRG's Specialized Register is developed, and the resources that are available. It should be noted, however, that article abstracts identified through a literature search can be 'scan-read' very quickly to ascertain potential relevance. At a conservatively-estimated reading rate of two abstracts per minute, the results of a database search can be 'scan-read' at the rate of 120 per hour (or approximately 1000 over an 8-hour period), so the high yield and low precision associated with systematic review searching is not as daunting as it might at first appear in comparison with the total time to be invested in the review.

6.4.5 Controlled vocabulary and text words

MEDLINE and EMBASE (and many other databases) can be searched using standardized subject terms assigned by indexers. Standardized subject terms (as part of a controlled vocabulary or thesaurus) are useful because they provide a way of retrieving articles that may use different words to describe the same concept and because they can provide information beyond that which is simply contained in the words of the title and abstract. When searching for studies for a systematic review, however, the extent to which subject terms are applied to references should be viewed with caution. Authors may not describe their methods or objectives well and indexers are not always experts in the subject areas or methodological aspects of the articles that they are indexing. In addition, the available indexing terms might not correspond to the terms the searcher wishes to use.

The controlled vocabulary search terms for MEDLINE (MeSH) and EMBASE (EMTREE) are not identical, and neither is the approach to indexing. For example, the pharmaceutical or pharmacological aspects of an EMBASE record are generally indexed in greater depth than the equivalent MEDLINE record, and in recent years Elsevier has increased the number of index terms assigned to each EMBASE record. Searches of EMBASE may, therefore, retrieve additional articles that were not retrieved by a MEDLINE search, even if the records were present in both databases. Search strategies need to be customized for each database.

One way to begin to identify controlled vocabulary terms for a particular database is to retrieve articles from that database that meet the inclusion criteria for the review, and to note common text words and the subject terms the indexers have applied to the articles, which can then be used for a full search. Having identified a key article, additional relevant articles can be located, for example by using the 'Find Similar' option in Ovid or the 'Related Articles' option in PubMed. Additional controlled vocabulary terms should be identified using the search tools provided with the database, such as the Permuted Index under Search Tools in Ovid and the MeSH Database option in PubMed.

Many database thesauri offer the facility to 'explode' subject terms to include more specific terms automatically in the search. For example, a MEDLINE search using the MeSH term BRAIN INJURIES, if exploded, will automatically search not only for the term BRAIN INJURIES but also for the more specific term SHAKEN BABY SYNDROME. As articles in MEDLINE on the subject of shaken baby syndrome should only be indexed with the more specific term SHAKEN BABY SYNDROME and not also with the more general term BRAIN INJURIES it is important that MeSH terms are 'exploded' wherever appropriate, in order not to miss relevant articles. The same principle applies to EMTREE when searching EMBASE and also to a number of other databases. For further guidance on this topic, review authors should consult their Trials Search Co-ordinator or healthcare librarian.

It is particularly important in MEDLINE to distinguish between Publication Type terms and other related MeSH terms. For example, a report of a randomized trial would be indexed in MEDLINE with the Publication Type term 'Randomized Controlled Trial' whereas an article about randomized controlled trials would be indexed with the MeSH term RANDOMIZED CONTROLLED TRIALS AS TOPIC (note the latter is plural). The same applies to other indexing terms for trials, reviews and meta-analyses.

Review authors should assume that earlier articles are even harder to identify than recent articles. For example, abstracts are not included in MEDLINE for most articles published before 1976 and, therefore, text word searches will only apply to titles. In addition, few MEDLINE indexing terms relating to study design were available before the 1990s, so text word searches are necessary to retrieve older records.

In order to identify as many relevant records as possible searches should comprise a combination of subject terms selected from the controlled vocabulary or thesaurus ('exploded' where appropriate) with a wide range of free-text terms.

6.4.6 Synonyms, related terms, variant spellings, truncation and wildcards

When designing a search strategy, in order to be as comprehensive as possible, it is necessary to include a wide range of free-text terms for each of the concepts selected. For example:

- synonyms: 'pressure sore' OR 'decubitus ulcer', etc;

- related terms: ‘brain’ OR ‘head’, etc; and
- variant spellings: ‘tumour’ OR ‘tumor’.

Service providers offer facilities to capture these variations through truncation and wildcards:

- truncation: random* (for random or randomised or randomized or randomly, etc); and
- wildcard: wom?n (for woman or women).

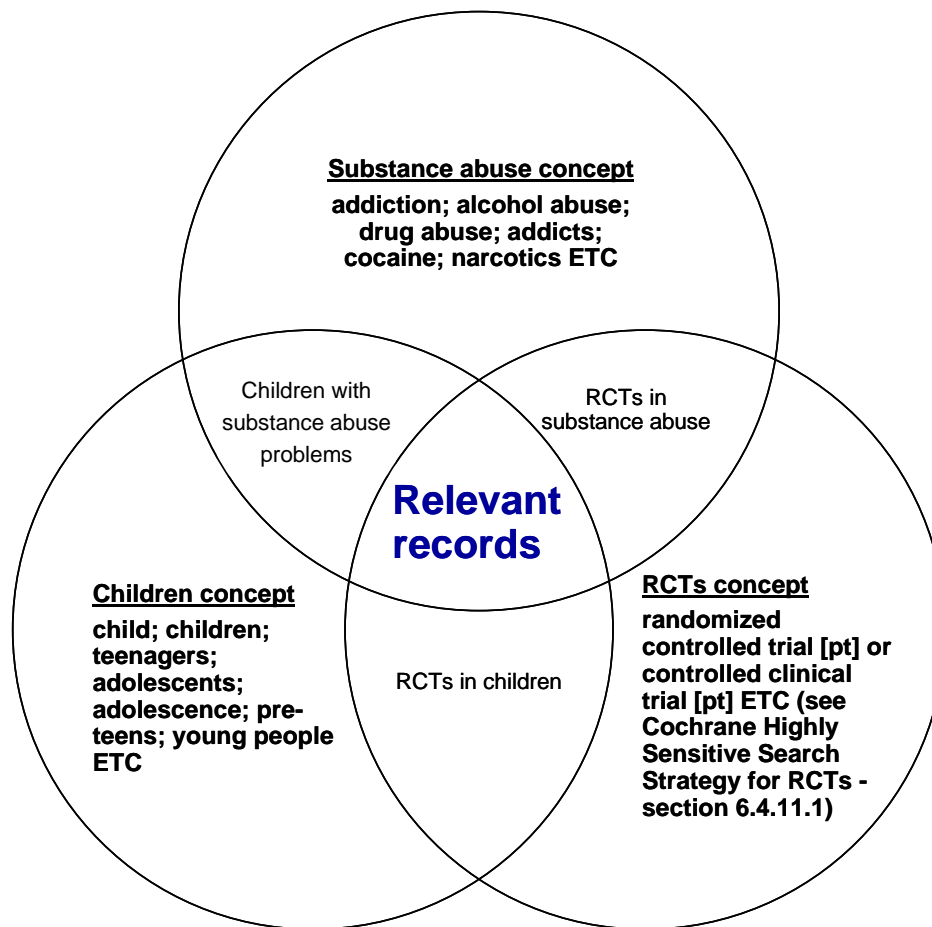
These features vary across service providers. For further details refer to the service provider help files for the database in question.

6.4.7 Boolean operators (AND, OR and NOT)

A search strategy should build up the controlled vocabulary terms, text words, synonyms and related terms for each concept at a time, joining together each of the terms within each concept with the Boolean ‘OR’ operator: see demonstration search strategy [Box 6.4.f](#)). This means articles will be retrieved that contain at least one of these search terms. Sets of terms should usually be developed for the healthcare condition, intervention(s) and 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 and 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. The ‘NOT’ operator should be avoided where possible to avoid the danger of inadvertently removing from the search set records that are relevant. For example, when searching for records indexed as female, ‘NOT male’ would remove any record that was about both males and females.

Searches for Cochrane reviews can be extremely long, often including over 100 search statements. It can be tedious to type in the combinations of these search sets, for example as ‘#1 OR #2 OR #3 OR #4 OR #100’. Some service providers offer alternatives to this. For example, in Ovid it is possible to combine sets using the syntax ‘or/1-100’. For those service providers where this is not possible, including *The Cochrane Library* for searches of CENTRAL, it has been recommended that the search string above could be typed in full and saved, for example, as a Word document and the requisite number of combinations copied and pasted into the search as required. Having typed the string with the # symbols as above, a second string can be generated by globally replacing the # symbol with nothing to create the string ‘1 OR 2 OR 3 OR 4 OR 100’ to be used for those service providers where the search interface does not use the # symbol.

Figure 6.4.a: Combining concepts as search sets



6.4.8 Proximity operators (NEAR, NEXT and ADJ)

In some search interfaces it is necessary to specify, for example by using the 'NEXT' or 'ADJ' operator, that two search terms should be adjacent to each other, as the search might simply default to finding both words in the document as if the 'AND' operator had been used. It should be noted that the 'NEXT' operator in *The Cochrane Library* is more sensitive (i.e. retrieves more hits) than the alternative method of phrase searching using quotation marks, since quotation marks specify that exact phrase whereas the 'NEXT' operator incorporates auto-pluralization and auto-singularization as well as other variant word endings.

In addition, it is possible in many search interfaces to specify that the words should be within a specific number of words of each other. For example, the 'NEAR' operator in *The Cochrane Library* will find the search terms within six words of each other. This results in higher sensitivity than simple phrase searching or use of the 'NEXT' operator but greater precision than use of the 'AND' operator. It is, therefore, desirable to use this operator where available and relevant.

6.4.9 Language, date and document format restrictions

Research related to identifying trials has recently focused on the effect of excluding versus including from meta-analyses trials reported in languages other than English. This question is particularly important because the identification and translation of, or at least data extraction from, trials reported in languages other than English can substantially add to the costs of a review and the time taken to complete it. For further discussion of these issues, see Chapter 10 (Section 10.2.2.4). Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant

reports of trials irrespective of language of publication. No language restrictions should be included in the search strategy. Date restrictions should be applied only if it is known that relevant studies could only have been reported during a specific time period, for example if the intervention was only available after a certain time point. Format restrictions such as excluding letters are not recommended because letters may contain important additional information relating to an earlier trial report or new information about a trial not reported elsewhere.

6.4.10 Identifying fraudulent studies, other retracted publications, errata and comments

When considering the eligibility of studies for inclusion in a Cochrane review, it is important to be aware that some studies may have been found to be fraudulent or may for other reasons have been retracted since publication. Reports of studies indexed in MEDLINE that have been retracted (as fraudulent or for other reasons) will have the Publication Type term ‘Retracted Publication’ added to the record. The article giving notice of the retraction will have the Publication Type term ‘Retraction of Publication’ assigned. Prior to any decision being taken to retract an article, articles may be published that refer to an original article and raise concerns of this sort. Such articles would be classified as a Comment. The US National Library of Medicine’s (NLM’s) policy on this is that “Among the types of articles that will be considered comments are: announcements or notices that report questionable science or investigations of scientific misconduct (sometimes published as ‘Expression of concern’)”.

- www.nlm.nih.gov/pubs/factsheets/errata.html

In addition, articles may have been partially retracted, corrected through a published erratum or may have been corrected and re-published in full. When updating a review, it is important to search MEDLINE for the latest version of the citations to the records for the included studies. In some display formats of some versions of MEDLINE the retracted publication, erratum and comment statements are included in the citation data immediately after the title and are, therefore, highly visible. This is not, however, always the case so care should be taken to ensure that this information is always retrieved in all searches by downloading the appropriate fields together with the citation data (see Section 6.5.2). For further details of NLM’s policy and practice in this area see:

- www.nlm.nih.gov/pubs/factsheets/errata.html

6.4.11 Search filters

Search filters are search strategies that are designed to retrieve specific types of records, such as those of a particular methodological design. They may be subjectively derived strategies such as the original Cochrane Highly Sensitive Search Strategy for identifying reports of randomized trials in MEDLINE (Dickersin 1994) or they may be objectively derived by word frequency analysis and tested on data sets of relevant records to assess their sensitivity and precision, such as the search strategies below for identifying randomized trials in MEDLINE (Glanville 2006). Recently a search filters web site has been developed by the UK InterTASC Information Specialists Subgroup (ISSG), which is the group of information professionals supporting research groups within England and Scotland providing technology assessments to the National Institute for Health and Clinical Excellence (NICE) (Glanville 2008). The purpose of the web site is to list methodological search filters and to provide critical appraisals of the various filters. The site includes, amongst others, filters for identifying systematic reviews, randomized and non-randomized studies and qualitative research in a range of databases and across a range of service providers.

- www.york.ac.uk/inst/crd/intertasc/

Search filters should be used with caution. They should be assessed not only for the reliability of their development and reported performance but also for their current accuracy, relevance and effectiveness given the frequent interface and indexing changes affecting databases.

The ISSG offer a search filter appraisal tool to assist with assessing search filters and examples can be seen on the website.

- www.york.ac.uk/inst/crd/intertasc/qualitat.htm

6.4.11.1 The Cochrane Highly Sensitive Search Strategies for identifying randomized trials in MEDLINE

The first Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE was designed by Carol Lefebvre and published in 1994 (Dickersin 1994). This strategy was subsequently published in the *Handbook* and has been adapted and updated as necessary over time. The Cochrane Highly Sensitive Search Strategies for MEDLINE in subsequent sections are adapted from strategies first published in 2006 as a result of a frequency analysis of MeSH terms and free-text terms occurring in the titles and abstracts of MEDLINE-indexed records of reports of randomized controlled trials (Glanville 2006), using methods of search strategy design first developed by the authors to identify systematic reviews in MEDLINE (White 2001).

Two strategies are offered: a sensitivity-maximizing version and a sensitivity- and precision-maximizing version. It is recommended that searches for trials for inclusion in Cochrane reviews begin with the sensitivity-maximizing version in combination with a highly sensitive subject search. If this retrieves an unmanageable number of references the sensitivity- and precision-maximizing version should be used instead. It should be borne in mind that MEDLINE abstracts can be read quite quickly as they are relatively short and, at a conservative estimate of 30 seconds per abstract, 1000 abstracts can be read in approximately 8 hours.

The strategies have been updated, after re-analysis of the data used to derive those strategies, to reflect changes in indexing policy introduced by the US National Library of Medicine since the original analysis and changes in search syntax. These changes include:

- no longer assigning ‘Clinical Trial’ as a Publication Type to all records indexed with ‘Randomized Controlled Trial’ or ‘Controlled Clinical Trial’ as a Publication Type; and
- the change of the MeSH term CLINICAL TRIALS to CLINICAL TRIALS AS TOPIC.

The strategies are given in [Box 6.4.a](#) and [Box 6.4.b](#) for PubMed, and in [Box 6.4.c](#) and [Box 6.4.d](#) for Ovid.

It must be borne in mind that the strategies below are based on data derived from MEDLINE-indexed records and were designed to be run in MEDLINE. These strategies are not designed to retrieve ‘in process’ and other records not indexed with MeSH. It is, therefore, recommended that these strategies are run in the MEDLINE-indexed versions of MEDLINE and separate searches for non-indexed records are run in the database containing the ‘in process’ and non-indexed records. For example, in Ovid the strategies below should be run and updated in databases such as ‘Ovid MEDLINE(R) 1950 to Month Week X 200X’ and non-indexed records should be searched for in ‘Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations Month X, 200X’. For identifying non-indexed records a range of truncated free-text terms would be required, such as random, placebo, trial, etc, and the search must not be limited to humans (as the records are not yet indexed as humans).

As discussed in Section [6.3.2.1](#), MEDLINE has been searched from 1966 to 2004 inclusive, using previous versions of the Cochrane Highly Sensitive Search Strategy for identifying randomized trials, and records of reports of trials (on the basis of the titles and abstracts only) have been re-indexed in

MEDLINE and included in CENTRAL. Refer to Section [6.3.2.1](#) and [6.3.3.2](#) for further guidance as to the appropriate use of these Highly Sensitive Search Strategies.

Box 6.4.a: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); PubMed format

- | | |
|-----|---|
| #1 | randomized controlled trial [pt] |
| #2 | controlled clinical trial [pt] |
| #3 | randomized [tiab] |
| #4 | placebo [tiab] |
| #5 | drug therapy [sh] |
| #6 | randomly [tiab] |
| #7 | trial [tiab] |
| #8 | groups [tiab] |
| #9 | #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 |
| #10 | animals [mh] not (humans [mh] and animals [mh]) |
| #11 | #9 not #10 |

PubMed search syntax

[pt] denotes a Publication Type term;

[tiab] denotes a word in the title or abstract;

[sh] denotes a subheading;

[mh] denotes a Medical Subject Heading (MeSH) term ('exploded');

[mesh: noexp] denotes a Medical Subject Heading (MeSH) term (not 'exploded');

[ti] denotes a word in the title.

Box 6.4.b: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); PubMed format

- | | |
|-----|---|
| #1 | randomized controlled trial [pt] |
| #2 | controlled clinical trial [pt] |
| #3 | randomized [tiab] |
| #4 | placebo [tiab] |
| #5 | clinical trials as topic [mesh: noexp] |
| #6 | randomly [tiab] |
| #7 | trial [ti] |
| #8 | #1 or #2 or #3 or #4 or #5 or #6 or #7 |
| #9 | animals [mh] not (humans [mh] and animals [mh]) |
| #10 | #8 not #9 |

The search syntax is explained in [Box 6.4.a](#).

Box 6.4.c: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format

1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomized.ab.
4	placebo.ab.
5	drug therapy.fs.
6	randomly.ab.
7	trial.ab.
8	groups.ab.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	animals.sh. not (humans.sh. and animals.sh.)
11	9 not 10

Ovid search syntax

.pt. denotes a Publication Type term;

.ab. denotes a word in the abstract;

.fs. denotes a 'floating' subheading;

.sh. denotes a Medical Subject Heading (MeSH) term;

.ti. denotes a word in the title.

Box 6.4.d: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format

1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomized.ab.
4	placebo.ab.
5	clinical trials as topic.sh.
6	randomly.ab.
7	trial.ti.
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	animals.sh. not (humans.sh. and animals.sh.)
10	9 not 10

The search syntax is explained in [Box 6.4.c](#).

6.4.11.2 Search filters for identifying randomized trials in EMBASE

The UK Cochrane Centre is working on designing an objectively derived highly sensitive search strategy for identifying reports of randomized trials in EMBASE, using word frequency analysis methods similar to those used to design the highly sensitive search strategies for identifying randomized trials in MEDLINE described in Section 6.4.11.1 (Glanville 2006). Review authors wishing to conduct their own searches of EMBASE in the meanwhile might wish to consider using the search terms listed in Section 6.3.2.2 that are currently used by the UK Cochrane Centre to identify

EMBASE reports of randomized trials for inclusion in CENTRAL (Lefebvre 2008). Alternatively, the search filter designed by Wong and colleagues for identifying what they define as “clinically sound treatment studies” in EMBASE may be used (Wong 2006).

As discussed in Section 6.3.2.2, EMBASE has been searched from 1980 to 2006 inclusive, using the terms listed in that section, and records of reports of trials (on the basis of the titles and abstracts only) have been included in CENTRAL.

6.4.12 Updating searches

When a Cochrane review is updated, the search process (i.e. deciding which databases and other sources to search for which years) will have to be reviewed. Those databases that were previously searched and are considered relevant for the update will need to be searched again. The previous search strategies will need to be updated to reflect issues such as: changes in indexing such as the addition or removal of controlled vocabulary terms (MeSH, Emtree etc); changes in search syntax; comments or criticisms of the previous search strategies. If any of the databases originally searched are not to be searched for the update this should be explained and justified. New databases or other sources may have been produced or become available to the review author or Trials Search Co-ordinator and these should also be considered.

Caution should be exercised with the use of update limits when searching across MEDLINE-indexed and un-indexed records simultaneously such as in PubMed or in the Ovid MEDLINE ‘In-Process & Other Non-Indexed Citations and Ovid MEDLINE 1950 to Present’ file. Where possible, separate files should be selected and searched separately, such as the Ovid MEDLINE ‘1950 to Month Week X 200X’, and the non-indexed records should be searched for in the Ovid MEDLINE ‘In-Process & Other Non-Indexed Citations Month X, 200X’ file. For further guidance on this issue, contact a Trials Search Co-ordinator.

6.4.13 Demonstration search strategies

[Box 6.4.e](#) provides a demonstration search strategy for CENTRAL for the topic ‘Tamoxifen for breast cancer’. Note that it includes topic terms only (a randomized trial filter is not appropriate for CENTRAL). There is no limiting to humans only. The strategy is provided for illustrative purposes only: searches of CENTRAL for studies to include in a systematic review would have many more search terms for each of the concepts.

[Box 6.4.f](#) provides a demonstration search strategy for MEDLINE (Ovid format) for the topic ‘Tamoxifen for breast cancer’. Note that both topic terms and a randomized trial filter are used for MEDLINE. The search is limited to humans. The strategy is provided for illustrative purposes only: searches of MEDLINE for systematic reviews would have many more search terms for each of the concepts

Box 6.4.e: Demonstration search strategy for CENTRAL, for the topic ‘Tamoxifen for breast cancer’

- | | |
|----|--|
| #1 | MeSH descriptor Breast Neoplasms explode all trees |
| #2 | breast near cancer* |
| #3 | breast near neoplasm* |
| #4 | breast near carcinoma* |

#5	breast near tumour*
#6	breast near tumor*
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	MeSH descriptor Tamoxifen explode all trees
#9	tamoxifen
#10	#8 OR #9
#11	#7 AND #10

The 'near' operator defaults to within six words;

'*' indicates truncation.

Box 6.4.f: Demonstration search strategy for MEDLINE (Ovid format), for the topic 'Tamoxifen for breast cancer'

1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomized.ab.
4	placebo.ab.
5	drug therapy.fs.
6	randomly.ab.
7	trial.ab.
8	groups.ab.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	animals.sh. not (humans.sh. and animals.sh.)
11.	9 not 10
12.	exp Breast Neoplasms/
13.	(breast adj6 cancer\$).mp.
14.	(breast adj6 neoplasm\$).mp.
15.	(breast adj6 carcinoma\$).mp.
16.	(breast adj6 tumour\$).mp.
17.	(breast adj6 tumor\$).mp.
18.	12 or 13 or 14 or 15 or 16 or 17
19.	exp Tamoxifen/
20.	tamoxifen.mp.
21.	19 or 20
22.	11 and 18 and 21

The 'adj6' operator indicates within six words;

'\$' indicates truncation;

.mp. indicates a search of title, original title, abstract, name of substance word and subject heading word.

6.4.14 Summary points

- Cochrane review authors should contact their Trials Search Co-ordinator *before* starting a search.
- For most Cochrane reviews, the search structure in most databases will be comprised of a subject search for population or condition and intervention together with a methodological filter for the study design, such as randomized trials.
- For searches of CENTRAL, do not apply a randomized trial filter and do not limit to human.
- Avoid too many *different* search concepts but use a wide variety of synonyms and related terms (both free text and controlled vocabulary terms) combined with ‘OR’ within *each* concept.
- Combine different concepts with ‘AND’.
- Avoid use of the ‘NOT’ operator in combining search sets.
- Aim for high sensitivity and be prepared to accept low precision.
- Do not apply language restrictions to the search strategy.
- Searches designed for a specific database and service provider will need to be ‘translated’ for use in another database or service provider.
- Ensure awareness of any retracted publications (e.g. fraudulent publications), errata and comments.
- For identifying randomized trials in MEDLINE, begin with the sensitivity-maximizing version of the Cochrane Highly Sensitive Search Strategy. If this retrieves an unmanageable number of references, use the sensitivity- and precision-maximizing version instead.
- For update searches, where possible, separate database files should be selected and searched separately for the MEDLINE-indexed records and the non-indexed in-process records.

6.5 Managing references

6.5.1 Bibliographic software

Specially designed bibliographic or reference management software such as EndNote, ProCite, Reference Manager and RefWorks is useful and relatively easy to use to keep track of references to and reports of studies. The choice of which software to use is likely to be influenced by what is available and thus supported at the review author’s institution. For a comparison of the above products and links to reviews of other bibliographic software packages see:

- www.burioni.it/forum/dellorso/bms-dasp/text/

Of the packages listed above, ProCite is generally considered to be very efficient for identifying duplicate references but is no longer updated by the suppliers. It does not support the wider range of character sets allowing references to be entered correctly in languages other than English, whereas EndNote does. Bibliographic software also facilitates storage of information about the methods and process of a search. For example, separate unused fields can be used to store information such as 1) the name of the database or other source details from which a trial report was identified, 2) when and from where an article was ordered and the date of article receipt and 3) whether the study associated with an article was included in or excluded from a review and, if excluded, the reasons for exclusion.

Files for importing references from CENTRAL into bibliographic software are available from the Cochrane Information Retrieval Methods Group web site at:

- www.cochrane.org/docs/import.htm

6.5.2 Which fields to download

In addition to the full record citation a number of key fields should be considered for downloading from databases where they are available. Further detailed guidance on which fields to download has been compiled by the Trials Search Co-ordinators' Working Group and is available in a document entitled 'TSC User Guide to Managing Specialized Registers and Handsearch Records' at:

- www.cochrane.org/resources/hsearch.htm

Abstract: abstracts can be used to eliminate clearly irrelevant reports, obviating the need to obtain the full text of those reports or to return to the bibliographic database at a later time.

Accession number / unique identifier: it is advisable to set aside an unused field for storing the unique identifier / accession number of records downloaded, such as the PubMed ID number (PMID). This allows subsequent linkage to the full database record and also facilitates information management such as duplicate detection and removal.

Affiliation / address: may include the institutional affiliation and / or e-mail address of the author(s).

Article identifier / digital object identifier (DOI): can be used to cite and link to the full record.

Clinical trial number: if the record contains a clinical trial number such as those assigned by the ClinicalTrials.gov or ISRCTN schemes or a number allocated by the sponsor of the trial, these should be downloaded to aid linking of trial reports to the original studies. An example of this is the Clinical Trial Number (CN) field recently introduced in EMBASE.

Index terms / thesaurus terms / keywords: see Section 6.4.5. These help indicate why records were retrieved if the title and abstract lack detail.

Language: language of publication of the original article.

Comments, corrections, errata, retractions and updates: it is important to ensure that any fields that relate to subsequently published comments, corrections, errata, retractions and updates are selected for inclusion in the download, so that any impact of these subsequent publications can be taken into account. The most important fields to consider, together with their field labels in PubMed, are provided in [Box 6.5.a](#).

- www.nlm.nih.gov/bsd/mms/medlineelements.html#cc

Box 6.5.a: Important field labels in PubMed

CIN: 'Comment in'
CON: 'Comment on'
CRI: 'Corrected and republished in'
CRF: "'Corrected and republished from'
EIN: 'Erratum in'
EFR: 'Erratum for'
PRIN: 'Partial retraction in'
PROF: 'Partial retraction of'
RIN: 'Retraction in'
ROF: 'Retraction of'
RPI: 'Republished in'
RPF: "'Republished from'
UIN: 'Update in'
UOF: 'Update of'

6.5.3 Summary points

- Use bibliographic software to manage references.

- Ensure that all the necessary fields are downloaded.

6.6 Documenting and reporting the search process

6.6.1 Documenting the search process

The search process needs to be documented in enough detail throughout the process to ensure that it can be reported correctly in the review, to the extent that all the searches of all the databases are reproducible. It should be borne in mind at the outset that the full search strategies for each database will need to be included in an Appendix of the review. The search strategies will need to be copied and pasted exactly as run and included in full, together with the search set numbers and the number of records retrieved. The number of records retrieved will need to be recorded in the Results section of the review, under the heading 'Results of the search' (see Chapter 4, Section 4.5). The search strategies should not be re-typed as this can introduce errors. A recent study has shown lack of compliance with guidance in the *Handbook* with respect to search strategy description in Cochrane reviews (Sampson 2006). In the majority of CRGs, the Trials Search Co-ordinators are now asked to comment on the search strategy sections of a review as part of the sign-off process prior to a review being considered ready for publication in the *CDSR*. It is, therefore, recommended that review authors should seek guidance from their Trials Search Co-ordinator at the earliest opportunity with respect to documenting the process to facilitate writing up this section of the review. As mentioned elsewhere in this chapter, it is particularly important to save locally or file print copies of any information found on the internet, such as information about ongoing trials, as this information may no longer be accessible at the time the review is written up.

6.6.2 Reporting the search process

6.6.2.1 Reporting the search process in the protocol

The inclusion of any search strategies in the protocol for a Cochrane review is optional. Where searches have already been undertaken at the protocol stage it is considered useful to include them in the protocol so that they can be commented upon in the same way as other aspects of the protocol. Some CRGs are of the view that no searches should be undertaken until the protocol is finalized for publication as knowledge of the available studies might influence aspects of the protocol such as inclusion criteria.

6.6.2.2 Reporting the search process in the review

Reporting the search process in the review abstract

- List all databases searched.
- Note the dates of the last search for each database or the period searched.
- Note any language or publication status restrictions (but refer to Section 6.4.9).
- List individuals or organizations contacted.

For further guidance on how this information should be listed see Chapter 11 (Section 11.8).

Reporting the search process in the Methods section

In the 'Search methods for identification of studies' section(s):

- List all databases searched.
- Note the dates of the last search for each database AND the period searched.
- Note any language or publication status restrictions (but refer to Section 6.4.9).

- List grey literature sources.
- List individuals or organizations contacted.
- List any journals and conference proceedings specifically handsearched for the review.
- List any other sources searched (e.g. reference lists, the internet).

The full search strategies for each database should be included in an Appendix of the review to avoid interrupting the flow of the text of the review. The search strategies should be copied and pasted exactly as run and included in full together with the line numbers for each search set. They should not be re-typed as this can introduce errors. For further detailed guidance on this contact the Trials Search Co-ordinator.

Reporting the search process in the Results section

The number of hits retrieved by the electronic searches should be included in the Results section.

Reporting date of the search

A single date should be specified in the 'Date of search' field, to indicate when the most recent comprehensive search was started. For more information on specifying this date, see Chapter 3 (Section 3.3.3).

6.6.3 Summary points

- Seek guidance on documenting the search process from a Trials Search Co-ordinator before starting searching.
- The full strategy for each search of each database should be copied and pasted into an Appendix of the review.
- The total number of hits retrieved by each search strategy should be included in the Results section.
- Save locally or file print copies of any information found on the internet, such as information about ongoing trials.
- Refer to Chapter 4 (Section 4.5) and Chapter 11 (Section 11.8) for more information on what to report in the review and the abstract, respectively.

6.7 Chapter information

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Box 6.7.a: The Cochrane Information Retrieval Methods Group

The Information Retrieval Methods Group (IRMG) aims to provide advice and support, to conduct research and to facilitate information exchange regarding methods to support the information retrieval activities of The Cochrane Collaboration. The group was officially registered with the Collaboration in November 2004. Members concentrate on providing practical support for the development of information retrieval techniques and facilities for information searchers. The group's aims are realized by the following activities:

- Offering advice on information retrieval policy and practice;
- Providing training and support;
- Conducting empirical research (including systematic reviews) into information retrieval methods;
- Helping to monitor the quality of searching techniques employed in systematic reviews;
- Liaising with members of the Campbell Collaboration to avoid duplication of effort in areas of information retrieval of interest to both the Cochrane and Campbell Collaborations;
- Serving as a forum for discussion.

Web site: www.cochrane.org/docs/irmg.htm

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