

## Annotated bibliography of published studies addressing searching for unpublished studies and obtaining access to unpublished data

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# Section 1: Introduction

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## 1.1 INTRODUCTION

This work is a sub-project of a larger project entitled “Searching for unpublished trials using trials registers and trials web sites and obtaining unpublished trial data and corresponding trial protocols from regulatory agencies”. Other outputs of this project include reviews conducted by Wolfe<sup>1</sup> and Bennekou Schroll<sup>2</sup>.

The project is a collaboration between the San Francisco Branch of the United States Cochrane Center, Nordic Cochrane Centre, Cochrane Acute Respiratory Infections Group, York Health Economics Consortium and the Cochrane Information Retrieval Methods Group. This sub-project has been undertaken by staff of York Health Economics Consortium and Carol Lefebvre of Lefebvre Associates Ltd, for which some funding was provided by the Cochrane Collaboration under the Methods Innovation Funding initiative.

## 1.2 OBJECTIVES

To prepare an annotated bibliography of published studies addressing searching for and obtaining access to unpublished studies.

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<sup>1</sup> Wolfe N, Gotzsche PC, Bero L. Strategies for obtaining unpublished drug trial data: a qualitative interview study. *Systematic Reviews*. 2013;2:31.

<sup>2</sup> Bennekou Schroll J, Bero L, Gotzsche PC. Searching for unpublished data for Cochrane reviews: cross sectional study. *BMJ*. 2013;346:f2231.

## Section 2: Methods

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### 2.1 CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

The following types of study were eligible for inclusion:

- Studies assessing methods of searching for / accessing unpublished trial information in healthcare settings;
- Reports discussing methods of searching for / accessing unpublished trial information in healthcare settings, even if no assessment of the methods' utility was made.

No date, language or study design restrictions were applied. Unpublished studies were defined as those not published in any of the following:

- The 'mainstream' (e.g. journal) literature
- Conference abstracts
- Bibliographic databases recording journal publications.

Examples of methods of interest included:

- Use of regulatory agencies (for example for access to regulatory information such as trial protocols, clinical study reports, reviewers' comments, correspondence and individual patient data);
- Use of trials registers; trials results registers; trials databases; trials web sites;
- Use of web sites of manufacturers; funders / sponsors;
- Contact with investigators; funders / sponsors.

Documents reporting the following issues were not eligible for inclusion:

- Reports of initiatives around trial registration and progress in trial registration;
- Reports of details of individual trial registries;
- Reports on methods of searching bibliographic databases of journal articles;
- Reports on methods such as citation searching / pearl growing;
- Reports of the results of a systematic review on healthcare interventions;
- Reports of single trials;
- Reports of the development, population and results of cohort studies/registers of patients with a specific condition (patient registries);
- Reports of trial methods and conduct which do not relate to prospective registration or reporting of the trial;
- Reports of clinical trial legislation unrelated to registration;
- Reports of trial recruitment activity/methods;

- Reports on hand-searching the journal literature;
- Reports on publication rate of conference abstracts;
- News stories;
- Animal studies, animal trials.

## 2.2 SEARCH METHODS FOR IDENTIFICATION OF STUDIES

The search strategy shown in Figure 2.1 shows the MEDLINE strategy used to identify studies. The other strategies are provided in Appendix A.

**Figure 2 1: MEDLINE strategy to identify studies**

1	((request\$ or obtain\$ or identify\$ or locat\$ or find\$ or detect\$ or search\$ or ask\$ or access\$) adj3 (unpublished or "un published" or "not published") adj3 (data or information or evidence or study or studies or trial\$1 or paper\$1 or article\$1 or report\$1 or literature or work)).ti,ab.
2	(Randomized Controlled Trials as Topic/ or Clinical Trials as Topic/) and Registries/
3	((search or identify\$ or retriev\$ or locat\$ or find\$ or detect\$ or access) adj6 (trial\$1 register or trial\$1 registers or trial\$1 registry or trial\$1 registries)).ti,ab.
4	clinicaltrial\$.ti,ab. not (clinicaltrial\$ or ISRCTN).si.
5	current controlled trials.ti,ab.
6	(ictrp or mrct).ti,ab.
7	WHO portal.ti,ab.
8	or/1-7
Key:	
\$	Truncation symbol; words beginning with the specified stem
adj	Proximity operator: words must appear together, within a specified number of words
ti,ab.	Search terms in the title or abstract
si.	Search terms in the Secondary Source ID field
/	Subject heading

MEDLINE and MEDLINE in process, Embase and the Cochrane Methodology Register were searched for relevant studies (Table 2.1).

**Table 2 1: Databases searched to identify studies**

Database / information source	Interface / URL
MEDLINE and MEDLINE In-Process	OvidSP
Embase	OvidSP
Cochrane Methodology Register	Cochrane Library/Wiley Interscience

The search approach was limited by the funding available for this part of the project. This meant that no attempts were made to check the references listed in the included studies. Features such as 'related articles' were not used and no citation searching to identify references citing the included studies was undertaken. A number of the studies we abstracted provided limited data and would benefit from being followed up with the authors / investigators. This is particularly the case with studies reported in conference abstracts, letters or other brief communications. No systematic approach was made to link references

reporting the same study. Where related references were identified by the abstractor or the reviewer / editor, links were made to other relevant citations.

Searching a number of databases produces a degree of duplication in the results. To manage this issue, the titles and abstracts of bibliographic records were downloaded and imported into EndNote bibliographic management software. Duplicate records were removed using several algorithms. Results in the EndNote library were then exported into the Mendeley reference management software, where further de-duplication and selection of studies took place.

### **2.2.1 Selection of studies**

Two of three reviewers (MA, HW, JG) independently assessed each of the titles and abstracts (where available) of records to identify and exclude clearly irrelevant studies. Where there was disagreement between reviewers, the records were passed to the second stage of assessment. The full text of documents was retrieved where possible for the remaining records. The full-text reports were examined by a single reviewer for compliance of the studies with eligibility criteria. Where inclusion was not clear-cut the document was classed as a query. Inclusion decisions and queries were checked by a second reviewer (JG). Where appropriate, authors were contacted to clarify study eligibility and to provide papers which we were unable to source elsewhere.

### **2.2.2 Study abstraction**

A structured abstract was completed for each included study. The abstract content was structured as follows:

- Study reference;
- Study objectives;
- Study methods;
- Study results;
- Study limitations as noted by study authors;
- Study limitations noted by abstractor;
- Key messages.

MC and JG wrote the structured abstracts which comprise the Annotated Bibliography. CL reviewed and edited the structured abstracts. The documents which could not be obtained and/or assessed for relevance within the resources of the project are listed in Appendix B.

## Section 3: Results

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### 3.1 SEARCH RESULTS

The searches retrieved 13366 records (Table 3.1). After deduplication 9577 records were assessed for relevance from title and abstract.

1761 records were selected to be assessed from the full text. We erred on the side of inclusion on the assumption that reports of searching for unpublished trials might not be explicitly indicated in abstracts. 80/1761 documents were not accessible to the research team (Appendix B) or could not be read by us because they were in a language other than English. 1522/1761 documents were excluded because they did not prove to be relevant based on an assessment of the full text. The majority of excluded documents reported on the issues around trial registration, described trial registers, or explored publication bias in various ways including exploring the publication fate of conference abstracts, trials approved by ethics committees and papers submitted to journals.

159 documents received structured abstracts and these are presented in Section 3.2.

**Table 3.1: Number of records retrieved by the searches**

<b>Database</b>	<b>Number of records retrieved</b>
MEDLINE	5320
Embase	5148
Cochrane Methodology Register	2898
Total number of records retrieved	13366
Number of records remaining after deduplication	9577



## 3.2 STRUCTURED ABSTRACTS

### **Study reference:**

Abrams, A., & Pienaar, E. Threading the needle we found in the haystack: identifying ongoing trials with the Pan African Clinical Trials Registry. Poster presentation at the 19th Cochrane Colloquium; 2011 Oct 19-22; Madrid, Spain [abstract].

### **Study objectives:**

This abstract is based on an abstract of a conference presentation. The study objective was to assess the value of the Pan African Clinical Trials Registry ([www.pactr.org](http://www.pactr.org)) in conducting systematic reviews.

### **Study methods:**

Details of registered trials were downloaded from the Registry on 11 April 2011. The Cochrane Database of Systematic Reviews (CDSR) 2011, Issue 3, was then searched for published reviews or protocols evaluating the interventions reported in these registered trials.

### **Study results:**

Forty-six trials were registered on [www.pactr.org](http://www.pactr.org), of which 30 were randomized controlled trials of efficacy. Twenty of these ongoing trials would be eligible for inclusion in the thirteen reviews and two protocols identified in the CDSR. None of the reviews reported any of the ongoing trials.

### **Study limitations as noted by study authors:**

The abstract does not note any limitations.

### **Study limitations noted by abstractor:**

There was no breakdown of the topics covered by the Cochrane reviews and protocols, to enable comparison with the Registry trials.

### **Key messages:**

The Pan African Clinical Trials Registry is a free, useful tool for identifying ongoing African trials.

**Study reference:**

Atkinson N L, Saperstein S L, Massett H A, Leonard C R, Grama L, Manrow R. Using the Internet to search for cancer clinical trials: a comparative audit of clinical trial search tools. *Contemporary Clinical Trials*, 2008;29:555-564.

**Study objectives:**

To examine the potential of online clinical trial search tools in helping people locate and enrol in cancer clinical trials.

**Study methods:**

An initial list of eight expert-recommended websites that offered an online tool to search for clinical trials was expanded by searching Google for clinical trials. Only weblinks which featured on the first two pages of search results were considered. Sites were included if they contained an English language tool that allowed people to search for cancer clinical trials. Sites were excluded if the tool only searched one establishment for trials, if the exact same tool was available elsewhere, or if the links to the search tool were broken, did not function properly, or were not currently maintained. Informational sites were also reviewed. The characteristics of the websites were reviewed, initially in April 2006 and then again to assess any changes.

**Study results:**

Google retrieved 11 websites, including six of those recommended. An additional site was identified from informational sites. Thus, 14 sites, not all specific to cancer trials, were reviewed. These included government, non-profit and commercial sites.

The majority of search interfaces required users to be proficient users of the Internet, have a reasonable knowledge of their medical condition, and understand complex terminology. There was significant variation in the usability, features, functionality and content of the different search tools. The sites differed in the descriptions of the trials, and how the user should proceed; not all sites provided trial contact information, advised the user to contact their physician, or discussed participation.

**Study limitations as noted by study authors:**

The website audit was limited by the use of researcher-generated search terms to locate clinical trial websites; should the general public use different search terminology then their results may differ. Some of the reviewed websites may have been modified since this review.

**Study limitations noted by abstractor:**

The general public would most likely not apply exclusion criteria, as the researchers did, when searching for and selecting websites with online clinical trial search tools. The retrieval rate of the different search tools was not evaluated in this study.

**Key messages:**

Online clinical trial search tools are easy to identify, but their use is more complex. Potential trial participants may lack the skills and perseverance necessary to identify clinical trials that match their needs, given the variation in use, functionality, content and language of the different tools.

**Study reference:**

Avenell A, Handoll H H, Grant A M. Lessons for search strategies from a systematic review, in The Cochrane Library, of nutritional supplementation trials in patients after hip fracture. American Journal of Clinical Nutrition, 2001;73:505-510.

**Study objectives:**

To evaluate the search strategy for identifying published and unpublished reports of randomized controlled trials (RCTs) in nutrition, using a variety of methods, as part of a regularly updated systematic review.

To evaluate whether the strategy could lay the foundations for search strategies for other nutrition-related reviews.

**Study methods:**

Several methods were used to identify reports of RCTs. Electronic searches of MEDLINE (1966 to Jan 2000), HEALTHSTAR (1975-Dec 1999), CINAHL (1982-Nov 1999), EMBASE (1980-Jan 2000), BIOSIS (1985-Dec 1999) and CABNAR (1973-Dec 1999) were conducted. Four journals were hand-searched: American Journal of Clinical Nutrition (1954-Jan 2000), Clinical Nutrition (1982-Dec 1999), Journal of Parenteral and Enteral Nutrition (1977-Dec 1999), and Proceedings of the Nutrition Society (1944-Aug 1999). These were chosen because they contained abstracts of conference proceedings and studies of clinical nutrition, and were available locally. The reference lists in trials included in reviews, and in epidemiologic and other trial reports were checked for additional reports of trials. The authors contacted the first authors of identified RCTs and experts in the field to identify further relevant trials.

**Study results:**

The electronic searches identified 11 RCTs from approximately 7300 citations, but failed to retrieve three trials (one each in MEDLINE, EMBASE and CABNAR). One trial was identified through hand-searches. Two unpublished trials were identified via experts in the field, while the publication of the review protocol in The Cochrane Library generated a response from the investigators of another unpublished trial.

**Study limitations as noted by study authors:**

The search plan was not exhaustive because of the need to balance the potential of further searches to influence the results against the delay to the publication of the review and subsequent update. An optimal search plan cannot be proposed because the authors did not know which trials they failed to identify and retrieval would vary for other topics given the likely variation in yields from the different sources used.

**Study limitations noted by abstractor:**

Selection of the journals to hand-search was partly influenced by the journals being available locally. The authors stated that they did not search the CCTR database of The Cochrane Library because they had entered many of the trials into the CCTR themselves.

**Key messages:**

Searching for trials is time-consuming and costly, and should incorporate both electronic and manual searches. Personal contact with investigators in the field can provide important information on unpublished, ongoing and planned trials.

**Study reference:**

Balas, E. A., Mitchell, J. A., Bopp, K., Brown, G. D., & Ewigman, B. T. The Columbia Registry of Controlled Clinical Computer Trials. Proceedings / the ... Annual Symposium on Computer Application [sic] in Medical Care. Symposium on Computer Applications in Medical Care, 1992: 220–4.

**Study objectives:**

This abstract is based on a report of the development and implementation of a registry of randomized controlled trials of computer-based interventions.

**Study methods:**

Eligible trial reports were identified using various methods: electronic searches of MEDLINE; hand-searches of the proceedings of various medical information associations which are not indexed in MEDLINE; by scrutiny of the reference lists of retrieved trial reports and review papers; and hand-searches of relevant books and monographs. Ad hoc methods such as informal contact (e.g. correspondence, meetings, E-mail) were used to gather further trials and unpublished results. Papers reporting ongoing clinical computer trials were also collected.

In the Discussion section, the authors made a request for any information leading to the capture of unpublished or unindexed trials reports.

**Study results:**

A total of 106 clinical computer trials had been registered. Falling numbers of registered reports since the 1980s suggested difficulties in retrieval. These were partly attributed to the fact that reference list analysis could not cover the most recent years. Seventeen per cent of registered reports were published in periodicals, proceedings and monographs not indexed in MEDLINE.

**Study limitations as noted by study authors:**

The authors did not note any limitations of their study.

**Study limitations noted by abstractor:**

The number of trials and amount of unpublished data retrieved by the various methods was not reported.

**Key messages:**

Searches of MEDLINE alone are insufficient to retrieve all reports of clinical computer trials. Retrieval is hampered by the variety of sources, inconsistencies in indexing and editorial policies, and a bias towards publishing only significant or positive results.

**Study reference:**

Balas E A, Stockham M G, Mitchell M A, Austin S M, West D A, Ewigman B G. The Columbia Registry of Information and Utilization Management Trials. Journal of the American Medical Informatics Association, 1995;2(5):307–315.

**Study objectives:**

This abstract is based on a report describing the expansion of the Columbia Registry of randomized controlled clinical computer trials to include trials of various information services (computerized and non-computerized) and utilization management interventions.

**Study methods:**

Eligible, published trial reports were identified through electronic searches of NLM databases (e.g. MEDLINE, HEALTH and HSTAR), manual searches of publications not indexed in MEDLINE, and by scrutiny of the reference lists of retrieved trial reports. Additional trial information was obtained from informal contact such as correspondence, telephone calls and attendance at scientific meetings. Planned and ongoing trials were not included in the registry. The sources of the trial reports were noted.

**Study results:**

Nearly 600 published trials had been registered. Most (about 95%) of the registered trial reports were indexed in the MEDLINE database, although often found only after other database searches. A time lag between publication date and appearance in the indexes meant that many potential trials published in 1994 had not been located.

**Study limitations as noted by study authors:**

The authors noted limitations in the registry in that only published trial reports were retrieved.

**Study limitations noted by abstractor:**

The success of other approaches such as reference lists and informal contact in identifying further trials, in particular those yet to be indexed in electronic databases, and obtaining additional information was not reported. There was no indication of the amount of unpublished data retrieved.

**Key messages:**

Searches of MEDLINE alone will identify the majority of trials, but supplemental methods should still be employed. Locating and registering eligible trials is an ongoing process and some trial reports will remain elusive.



**Study reference:**

Bayliss S E, Dretzke J. Health technology assessment in social care: a case study of randomized controlled trial retrieval. *International Journal of Technology Assessment in Health Care*, 2006;22:39-46.

**Study objectives:**

To examine the problems encountered when conducting literature searches in social care, in particular when focusing on a specific study design, by evaluating the success of search strategies in identifying randomized controlled trials (RCTs) for a technology assessment report on parent training programmes.

**Study methods:**

Ten core databases (MEDLINE (1966 to Sept 2003), EMBASE, the Cochrane Library, ERIC, CareData, IBSS, SSCI, Campbell Collaboration SPECTR, EPPI-Centre, NCJRS) were searched per protocol, and an additional eight searched following discussions with subject experts. Hand searching was not carried out, and citation searching was restricted to the citations from good quality systematic reviews. The review team sought advice from experts in the field. No specific attempts to identify unpublished trials were described.

**Study results:**

A combination of MEDLINE, EMBASE, the Cochrane Library and PsycINFO would have found all 32 included studies; searching PsycINFO alone would have yielded 78% of these references. A further two additional trials were retrieved through contact with experts, although they were not considered further in this case study. The authors stated that searching the four core databases combined with input from subject experts and contacts enabled most published and unpublished RCTs to be located.

**Study limitations as noted by study authors:**

The authors acknowledged that it was unlikely that all relevant RCTs were found and their conclusions on where and how extensively to search are uncertain. They considered their case study to be atypical given the large number of RCTs identified.

**Study limitations noted by abstractor:**

This case study focused on the use of electronic (database) searching. Aside from a cursory mention of input from subject experts and consultees, there were no specific details of attempts to locate unpublished studies. The number of unpublished RCTs identified was not reported.

**Key messages:**

Searches conducted across a basic core of key databases will find most relevant references. Contact with subject experts and experts in the field may not yield any additional relevant trials.

**Study reference:**

Bayliss, S., Fry-Smith, A., Yahaya, I., Ashfaq, K., & Anderson, R. The pitfalls of translating search strategies across a wide range of bibliographic databases: a case study from injury prevention/safety promotion [abstract]. HTAi 7th Annual Meeting: Maximising the Value of HTA; 2010 Jun 6-9; Dublin, Ireland.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To examine the performance of a search strategy used to locate literature on injury prevention/safety promotion topics when applied across a wide range of bibliographic databases.

**Study methods:**

Electronic databases were searched for papers for a systematic review. The search strategy was initially developed for MEDLINE then adapted for the other databases (EMBASE, CENTRAL, HMIC, SafetyLit, SPORTDiscus, SSCI, EPPI Centre). Database yield was based on 40 key papers selected by the reviewers from the initial search results. A retrospective author/title search of the databases was conducted to establish whether the search strategy failed to identify key references.

**Study results:**

A minimum combination of three databases identified all key papers; searching MEDLINE alone would have yielded 87.5% of these references. Seven databases contained studies missed by the search strategies. A further five additional trials were retrieved through grey literature, contacts or reference searching, although these were not included in this case study.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

This case study focused on the performance of a single strategy for searching a wide range of databases. There were no specific details of attempts to locate unpublished studies. It was unclear how many of the additional trials found were unpublished.

**Key messages:**

Extensive database searching may be counterproductive, even when searching for topics of a multidisciplinary nature. It may be more advantageous to search fewer databases and

spend more time on other strategies (e.g. grey literature, citation tracking and expert contact).

**Study reference:**

Beahler C C, Sundheim J J, Trapp N I. Information retrieval in systematic reviews: challenges in the public health arena. *American Journal of Preventive Medicine*, 2000;18(4S):6-10.

**Study objectives:**

To discuss the challenges and methodology associated with identifying and retrieving studies for systematic reviews in the field of occupational injury.

**Study methods:**

Several methods were used to identify studies for systematic reviews in 12 areas of occupational injury. A broad range of 16 databases covering biomedical, occupational health, social science, education, criminal justice, agriculture, government and business disciplines was searched for relevant studies (typically up to 1999). Unindexed, unpublished or difficult to obtain literature was sought through 'pearled references' (i.e. 'hidden' references within an article) and contact with professionals and experts in the field. Conference proceedings were hand-searched.

**Study results:**

The searches yielded 1356 articles potentially eligible for review. A significant proportion of these were identified through pearled references or professional contacts. There was a correlation between the proportion of total literature located through contacts or hidden references with the degree to which a topic was considered clinical, or could be concisely defined. For example, most of the referenced literature on carpal tunnel, a more clinical topic, was indexed in biomedical databases. For farm safety, a multidisciplinary topic, 37% of the documents obtained for potential review were identified from largely unindexed conference proceedings. More than half of the literature retrieved for a paper evaluating environmental interventions in workplace violence was obtained from reviewing references and through professional contacts. These methods also contributed highly to studies performed by police departments.

**Study limitations as noted by study authors:**

The authors did not report any limitations. They provided an overview of the difficulties associated with identifying and retrieving information for systematic reviews in a multidisciplinary area.

**Study limitations noted by abstractor:**

This paper collates experiences during the conduct of 12 systematic reviews in a multidisciplinary area. It did not present an overall breakdown of the yields and type of content identified through electronic database searches, 'pearled references' and

professional contacts for each systematic review. The proportion of unpublished literature retrieved was unclear.

**Key messages:**

Much of the literature on occupational injury is not well-indexed. Database searches alone are not sufficient for identifying relevant information. Conference proceedings, professional contacts and reference reviewing play a significant role in locating additional material.

**Study reference:**

Bennett D A. FDA: untapped source of unpublished trials. *Lancet*, 2003;361:1402-1403.

**Study objectives:**

This abstract is based on a commentary relating to a published study (Maclean CH, Morton SC, Ofman JJ, et al. How useful are unpublished data from the Food and Drug Administration in meta-analysis. *J Clin Epidemiol* 2003;56:44–51.). It contains additional information provided by the study authors.

The original study evaluated US Food and Drug Administration (FDA) reviews as a source of unpublished trials.

**Study methods:**

FDA reviews of new drug applications for non-steroidal anti-inflammatory drugs were searched for randomized trials on dyspepsia. Trials submitted to the FDA were compared with published trials identified through database searches in terms of methodological quality (assessed using the Jadad scale) and data presented. The Cochrane Controlled Trials Register was not searched.

**Study results:**

To summarize the original study: 11 randomized trials were identified through FDA reviews and another 15 by searching databases. Only one of the FDA-sourced trials had been published, albeit with different sets of authors for the FDA and published versions. Whilst study quality was acceptable in similar proportions of FDA-sourced and published randomized trials, the reporting in FDA reviews was less detailed.

Further information provided by the study authors revealed that more than 100 hours was spent in identifying and extracting FDA-sourced trials. In addition, there was no evidence of publication bias in their meta-analysis of the individual studies. No Cochrane Review Group includes the FDA in searches for unpublished literature.

**Study limitations as noted by study authors:**

The abstract does not note any limitations of the original study.

**Study limitations noted by abstractor:**

This commentary provided limited details and results of the original study.

**Key messages:**

The FDA is a useful source of unpublished trials. However, randomized trials remain largely unpublished, and the reporting of FDA reviews suffers from a lack of detail and needs improvement. The FDA should put all randomized trials that have been included within its drug applications into the public domain. Currently, systematic reviewers need to use the Freedom of Information Act to gain access to FDA information; this is open to non-US residents although at some expense.



**Study reference:**

Benzies K M, Premji S, Hayden K A, Serrett K. State-of-the-evidence reviews: advantages and challenges of including grey literature. *Worldviews on Evidence-Based Nursing*, 2006;3(2):55-61.

**Study objectives:**

To describe what constitutes grey literature, and the methods used to identify it and assess its quality, using a recent review of foetal alcohol spectrum disorder (FASD) as a model.

**Study methods:**

Various methods were used to identify grey literature: 23 grey literature databases were searched; notices and flyers requesting information on experts, websites, ongoing research and conferences were distributed at FASD meetings; letters asking for information on current and emerging projects were e-mailed to well-known national and international experts; Internet searches were focused on key authoritative websites and embedded links; and reference lists from all documents eligible for the review were checked. In addition, networks of local expert advisors, including clinicians and policy decision-makers from government and non-government agencies, were set-up and invited to workshops with the purpose of gaining useful leads, which were subsequently followed up.

**Study results:**

A significant amount of grey literature, including conference proceedings and practice guidelines, was obtained by hand-searching the personal libraries of two expert advisors. The yield of grey literature resulting from the distribution of notices and flyers was poor. The response from well-known experts was good but offered little new information. Systematically reviewing the references of all eligible documents was time-consuming and resource-intensive, but was considered essential for a comprehensive search. The various types of grey literature provided different or overlapping information. The authors commented that grey literature documents are often heterogeneous and can be very large as they are not bound by the size or presentation formats dictated by academic journals. The relevance of individual documents retrieved by the different approaches was often unclear until after the entire document had been reviewed, and incomplete or inaccurate information presented its own obstacles.

The Internet is one of the main approaches to identifying grey literature but such searches are difficult to design and time-consuming to execute given the diversity they must encompass. The credibility and quality of website information is questionable giving the potential for incomplete and inaccurate information.

**Study limitations as noted by study authors:**

The authors did not note any study limitations.

**Study limitations noted by abstractor:**

Quantitative results of the different approaches were not provided.

**Key messages:**

Identify and retrieving grey literature is challenging. The personal libraries of local expert advisors appear the most useful source of grey literature. The results of Internet-based searches should be used with caution.

**Study reference:**

Berry E, Kelly S, Hutton J, Harris K M, Smith M A. Identifying studies for systematic reviews. An example from medical imaging. *International Journal of Technology Assessment in Health Care*, 2000;16(2):668-672.

**Study objectives:**

To determine if published figures on the proportion of articles included in systematic reviews and identified in electronic databases are applicable to an example from medical imaging.

**Study methods:**

MEDLINE, ISI, the Cochrane Library, EMBASE, Inside Information Plus, FirstSearch, and SIGLE were searched from 1981 to 1996 for studies on the use of endoscopic ultrasound in gastroesophageal cancer. The authors also hand-searched citation lists of retrieved papers, and contacted equipment manufacturers, authors, and an electronic mail discussion list for references and unpublished data.

**Study results:**

Of the 47 studies included in the main review, 44 (94%) were found in MEDLINE. Two of the outstanding three studies were retrieved from the other databases and the third study was identified through hand-searches of citation lists. This third study was not indexed in any of the electronic databases.

The authors commented that widespread canvassing of expert opinion was avoided at the search stage, but they considered expert input to be useful in helping identify work in progress and essential for the critical appraisal of retrieved studies.

**Study limitations as noted by study authors:**

The authors did not note any limitations of their study.

**Study limitations noted by abstractor:**

Unpublished research does not appear to have been eligible for the systematic review. Although the search strategy involved personal communication, there were no specific details of the response obtained or yield of relevant references and unpublished material.

**Key messages:**

The results of medical imaging studies are published primarily in journals. Contact with experts may be a useful approach for identifying ongoing research.

**Study reference:**

Bohlius, J., Weingart, O., Trelle, S., & Engert, A. Disentangling the data: variations in data submissions from different players and their potential impact on a systematic review [abstract]. XIII Cochrane Colloquium; 2005 Oct 22-26; Melbourne, Australia.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To compare the results obtained from US Food and Drug Administration (FDA) reports and journal publications with data submitted by the pharmaceutical industry in a meta-analysis assessing the relative risks of thromboembolic events from erythropoietin/darbepoetin (EPO/Darb) in cancer patients.

**Study methods:**

Clinical trials data were presented by FDA reviewers and pharmaceutical companies at the Oncologic Drugs Advisory Committee of the Food and Drug Administration (FDA/ODAC) hearing on the safety of EPO/Darb in May 2004.

MEDLINE, EMBASE and the Cochrane Library were searched from 1985 to 2005 for randomized controlled trials of EPO/Darb, and all reports and presentations submitted to the FDA/ODAC were reviewed. Data from different sources were compared, with discrepant data categorized into subsets according to whether they came from abstracts, full texts and FDA reviewer reports, or pharmaceutical companies.

**Study results:**

Thirty-three trials reporting thromboembolic events from EPO/Darb were identified, of which twelve were described in more than one source. Data coming from different sources were identical for two of these studies, but were discrepant in the remaining ten studies.

There were discrepancies between company data and published/FDA data for identical trials, which gave rise to differences in the overall risk estimates calculated.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

This study assessed the impact of using discrepant data from published and unpublished reports, and not the method of identifying them. The number of unpublished studies identified was not reported.

**Key messages:**

Trial data obtained from pharmaceutical companies may differ from that reported in the published trial or FDA report. Such discrepancies may impact on overall effect estimates.

**Study reference:**

Bohlius J, Wilson J, Bayliss S, Brunskill S, Weingart O, Langensiepen S, et al. Where do completed trials come from? [abstract]. XIV Cochrane Colloquium; 2006 October 23-26; Dublin, Ireland.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To report the practicalities of identifying studies for inclusion in a Cochrane review on the use of erythropoietin in cancer patients and its update four years later.

**Study methods:**

Several methods were used to identify relevant trials. MEDLINE, EMBASE and Cochrane CENTRAL were searched for published trials, relevant conference proceedings were searched for abstracts, and Internet databases were searched for ongoing trials. The original review was completed in 2001 and the searches were repeated in 2005 for the subsequent update.

**Study results:**

Searches for the 2001 review yielded 57 randomized controlled trials from 1592 references. Of the 24 trials identified as ongoing, three were subsequently completed, published and included in the updated review, and five that had been published (as abstracts or full-text articles) did not meet the inclusion criteria. Thus, 16 of the original 24 studies remained ongoing. Thirty completed trials (1859 references) were obtained for the 2005 update. Of these, three had been identified as an ongoing trial in the original 2001 review whilst the remaining twenty-seven had not been registered in the ongoing trials databases at that time.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

The abstract does not provide details of the Internet databases searched. It is unclear whether any interim data for trials that remained ongoing had been published as conference abstracts since 2001.

**Key messages:**

A substantial amount of research in progress is not recorded in ongoing trials databases. Central registration of all ongoing studies is essential.

**Study reference:**

Bonfill, X., Marti, J., & Garcia, F. Identification of clinical trials (CTs) conducted in Spain (1971-1995) [abstract]. Second International Conference Scientific Basis of Health Services & Fifth Annual Cochrane Colloquium; 1997 Oct 8-12; Amsterdam, The Netherlands.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To find and describe all published and unpublished clinical trials conducted in Spain from 1971 to 1995.

**Study methods:**

Several methods were used to identify clinical trials conducted in Spain from 1971 to 1995. Electronic searches of MEDLINE, EMBASE, IME (Spanish Index Medicus) and TESEO (doctoral theses from Spanish universities) were conducted. Spanish journals were searched by hand. The Spanish Clinical Trials Database (Ministry of Health Pharmacy Department) was searched from 1983 to 1995 for clinical trials submitted for administrative approval. The authors contacted the following: clinical research ethics committees; research committees, units and financing agencies; pharmacy and clinical pharmacology departments; and pharmaceutical companies and similar industries in Spain.

**Study results:**

Only the results of the hand-searches were available (April 1997). The hand-searches yielded 1402 possible clinical trials. Of the 890 records reviewed, 387 (43.5%) were identified as clinical trials. The majority (336 trials; 87%) were published in journals indexed by the IME.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

The results of efforts to identify unpublished trials were not available.

**Key messages:**

Manual journal searches are essential for the retrieval of clinical trials. Linking of information sources should ensure comprehensive identification of most clinical trials developed in Spain and enable the analysis of publication bias.

**Study reference:**

Brown, T., & Hooper, L. Effectiveness of brief contact with authors [abstract]. *XI Cochrane Colloquium: Evidence, Health Care and Culture*; 2003 Oct 26-31; Barcelona, Spain.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To assess the effectiveness of contacting trial authors, as identified in four systematic reviews on NSAID-induced gastro-intestinal toxicity, for additional information.

**Study methods:**

Trial authors were contacted by e-mail (preferentially) or letter for additional data, which they recorded on a semi-personalised information retrieval sheet. The time and costs incurred were also recorded.

**Study results:**

E-mails (39) and letters (77) were sent to 112 authors of 139 studies. Twenty-one authors (19%) replied. Nine responses provided relevant outcome and quality data, one provided data on study quality alone, and one provided information on duplicate publications. Eleven responses did not provide any useful data, of which five suggested contacting the sponsoring pharmaceutical company. The number of responses was broken down according to publication year: 1980-84 (1 study, no response), 1985-89 (9 studies; 2 responses), 1990-94 (41 studies; 6 responses), 1995-99 (38 studies; 8 responses) and 2000-02 (21 studies; 4 responses). The additional data resulted in changes to 11 of the 44 outcomes in the four systematic reviews.

The process resulted in 43 hours of time spent plus printing and postage costs.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

The nature of the information requests was not described in any detail. There appears to be a discrepancy in the numbers of responses reported throughout this abstract.

**Key messages:**

Trying to obtain unpublished data directly from trial authors can be time consuming (and costly) with little result.



**Study reference:**

Brunton G, McNair S, Goldblatt E, O'Brien MA, & Thomas H. (1999). Searching for evidence in public health research: which source is most effective! [abstract]. 7th Annual Cochrane Colloquium; 1999 Oct 5-9; Rome, Italy.

Retrieved from <http://www.mrw.interscience.wiley.com/cochrane/clcmr/articles/CMR-3037/frame.html>

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To determine the precision and sensitivity of searching various sources in order to identify research studies for three specific systematic reviews of intervention effectiveness in public health: parenting groups led by professionals; the use of coalitions in public health; and adolescent sexually transmitted disease (STD) prevention.

**Study methods:**

Electronic searches (typically from origin to 1998) were conducted in ten core databases and an unspecified number of topic-specific databases. Six key public health journals were hand-searched and the bibliographies of all relevant articles were checked. The authors also contacted key informants.

**Study results:**

The sources that offered the highest precision and sensitivity were PsycINFO for the parenting review, bibliographies for the coalitions review and CINAHL for the adolescent STD prevention review. MEDLINE provided a consistently high retrieval rate. Topic-specific databases such as AIDSLINE did not yield high numbers of unique studies.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

It was unclear whether both published and unpublished studies were sought. The success of contacting key informants was not reported.

**Key messages:**

No single source provided optimal precision or sensitivity across the public health topics of interest.

**Study reference:**

Campbell, O. J., Daly, C., Cody, J., Khan, I. H., Campbell, M. K., Wallace, S. A., & MacLeod, A. M. Surfing systematically - experience of searching the internet. First Symposium on Systematic Reviews: beyond the basics; 1998 Jan 8-9; Oxford, UK.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To assess the Internet as an additional source to five conventional electronic databases for the identification of randomized controlled trials (RCTs) for systematic literature reviews on the use of recombinant human erythropoietin in end-stage renal disease.

**Study methods:**

Electronic searches of MEDLINE, EMBASE, CINAHL, BIOSIS and the Cochrane Library were conducted using a modified version of the Cochrane Collaboration strategy for RCTs. A simplified version of this strategy was used to search the World Wide Web using the Hotbot Internet search engine. The results were assessed for relevance to the topics of interest.

**Study results:**

The simplified Internet search strategy produced 142 hits, of which 19 were duplicates, 15 were deemed unavailable or out-of-date, and 108 were assessed. A total of 39 trials were identified from the 27 hits that contained relevant information. Nine trials were considered possible (quasi) RCTs or meta-analyses and, of these, four were of relevance to the reviews. Of these four trials, three had been identified by the electronic database searches; the fourth trial had been terminated early and had not been published conventionally.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

There are insufficient details to assess whether differences between the strategies used for the conventional database and Internet searches would have impacted on the search yield. The abstract does not report how many unpublished trials, if any, were retrieved.

**Key messages:**

Published trials are best identified from searches of established electronic databases. The Internet may be a useful source of unpublished trials.

**Study reference:**

Carson, S., Cohen, A., Hersh, W., Brown, N., & Helfand, M. Systematic evaluation of web-based, publicly accessible clinical trials results databases [abstract]. XIV Cochrane Colloquium; 2006 October 23-26; Dublin, Ireland.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To identify and evaluate the usefulness of existing web-based, publicly accessible clinical trial results databases as a resource for conducting systematic reviews.

**Study methods:**

Clinical trial databases were identified through Internet searches, the International Federation of Pharmaceutical Manufacturers and Associations Clinical Trials Portal, and expert referrals. The databases were evaluated in terms of the sponsor's inclusion policies, methods of determining completeness, types of studies and products currently included, and whether trial summaries followed the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for the Structure and Content of Clinical Study Reports (ICH E3) and identified which elements were searchable.

**Study results:**

Thirteen web-based clinical trials results databases were identified, of which eight were sponsored by the pharmaceutical industry (one contained records from several different companies: ClinicalStudyResults.org). All databases provided information on their policies for including trials, whereas policies for ensuring completeness lacked transparency. None of the databases had registered all eligible or required studies, and none provided a target date for study completion. Industry-sponsored databases were limited in their search capabilities and the range of marketed drugs they covered, but their trial summaries did follow ICH E3 guidelines, unlike most other databases. Government-sponsored databases used user-friendly search engines and provided study design details of interest to systematic reviewers.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

The approaches used to identify the databases lacked detail, e.g. any restrictions on country or language of the database. The abstract does not report extracting data on whether the databases provided information on the publication of included clinical trials, or whether there were any policies for maintaining currency of the records.

**Key messages:**

Existing clinical trials databases need to provide further information and improve their access if they are to be a useful resource for systematic reviewers.

**Study reference:**

Chalmers T C, Levin H, Sacks H S, Reitman D, Berrier J, Nagalingam R. Meta-analysis of clinical trials as a scientific discipline. I: control of bias and comparison with large cooperative trials. *Statistics in Medicine*, 1987; 6:315-325.

**Study objectives:**

To analyse efforts made to control biases in meta-analyses of clinical trials, for example the inclusion of unpublished data.

**Study methods:**

This was a discussion of meta-analyses of clinical trials. Particular attention was paid to the quality of published meta-analyses and the trials they include, the pros and cons of using unpublished data, and publication and selection bias. Examples were provided to illustrate certain points.

**Study results:**

In groups that stressed the importance of using all 'relevant' published and unpublished data in their analysis, the preferred method of obtaining additional data for unpublished studies and those published only as abstracts or letters was informal communication (i.e. contact with investigators). This approach was also favoured for acquiring individual patient data. However, the accuracy of this data cannot be assured. Unlike a formal publication process, it is not possible to control for bias in obtaining the data. In a particular example of two conflicting meta-analyses, informal communication with the trial investigator led to opposite answers to a crucial question of whether their study was double-blind. This led to the exclusion of this positive study from one of the meta-analyses, despite the presence of other studies with similar inadequacies in the randomization process.

The authors believe that the concern that publication bias threatens the validity of meta-analysis as a scientific discipline is poorly handled by the process of informal communication.

**Study limitations as noted by study authors:**

The authors did not note any limitations.

**Study limitations noted by abstractor:**

This was a discussion paper presenting selected examples to illustrate factors affecting bias in meta-analyses. The small section on the inclusion of unpublished data focused on informal communication and did not consider other sources of unpublished trials and grey literature.

**Key messages:**

Personal communication with trial investigators is the preferred method of obtaining unpublished data. Since the accuracy of such data may impact on publication bias in meta-analysis, investigators and editors should be encouraged to publish all completed trials. Registers of planned and in-process trials, in addition to published ones, are needed.

**Study reference:**

Chan A-W. Out of sight but not out of mind: how to search for unpublished clinical trial evidence. *BMJ*, 2012;344:d8013. doi:<http://dx.doi.org/10.1136/bmj.d8013>

**Study objectives:**

This abstract is based on an overview of useful approaches to search for additional information on unpublished trials, and to a lesser extent published trials.

**Study methods:**

Approaches used to identify unpublished information on ongoing and completed trials were categorized as trial registries and results databases, regulatory agencies, contact with trialists and sponsors, and other sources of information.

**Study results:**

Basic trial protocol information can be identified using the World Health Organization's International Clinical Trials Registry Platform Search Portal, which searches records from national and international trial registries that meet certain standards. Some government, pharmaceutical company and industry registries may also house study results. Trial data from regulatory agencies is best obtained from scientific reviews posted in online databases (such as those provided by the US Food and Drug Administration and the European Medicines Agency), or by written request for access to trial protocols and detailed clinical study reports. Contacting trialists, clinicians and sponsors for information about unpublished trials has been of limited success; higher response rates have been achieved with surveys soliciting further details of unreported trial outcomes for published trials. Other potential sources of information include litigation documents, conference abstracts and internet keyword searches. Limitations associated with each of the approaches were discussed. Key issues were no universal requirement for trial registration, selective data suppression, biased study design or conduct, quality of the information, confidentiality, a lack of information on non-regulated or unapproved interventions, and currency of the data.

**Study limitations as noted by study authors:**

The authors did not note any limitations of their review-type article.

**Study limitations noted by abstractor:**

This was an overview of potential sources of unpublished information. It was not a formal evaluation designed to assess alternative methods.

**Key messages:**

Trials registers and regulatory agencies are important sources of additional unpublished trial information. Personal contact with trialists, clinicians and sponsors has met with varying success, and surveys may be more fruitful. The strengths and limitations of each potential source need evaluation.



**Study reference:**

Clarke M, Greaves L. Identifying relevant studies for systematic reviews. *BMJ*, 1995;310:741.2.

**Study objectives:**

This abstract is based on a letter providing brief details of the methods used to identify randomized controlled trials for a systematic review of treatments for multiple myeloma.

**Study methods:**

Relevant trials were sought using electronic searches, hand-searches, searches of trials registers, personal contact, and a review of reference lists in relevant studies.

**Study results:**

The initial list of studies comprised 123 trials. Trials registers yielded the most studies (29), followed by personal contacts (28), published abstracts (20), published papers (18), computer-assisted literature searching (15), and leads or hints in a publication (13). One of the trials identified through personal contact with trialists had not been previously identified, despite its relevance to two prior reviews, as it had neither been published nor included in a widely available trials register.

**Study limitations as noted by study authors:**

The authors did not note any limitations.

**Study limitations noted by abstractor:**

The results suggest that each trial was identified through only one approach, which is surprising. The number of unpublished studies uncovered was not reported. This research would benefit from being published in greater detail.

**Key messages:**

Trials registers and personal contact are amongst the most useful approaches of the many strategies needed to maximize retrieval of all relevant published and unpublished trials.

**Study reference:**

Coad J, Hardicre J, Devitt P. How to search for and use “grey literature” in research. *Nursing Times*, 2006;102(50):35-36.

**Study objectives:**

To provide nurses with a practical guide to searching for grey literature and incorporating it in their research and reports. The authors have drawn on their own experiences to produce this guidance.

**Study methods:**

The article outlined several ways to search for grey literature from a variety of sources. The most basic involved identifying what information was readily available in libraries, institutions, trusts, industries, health centres, etc. Internet-based searches were conducted using many search engines and online databases, some specific to grey literature; general searches were used for image-related information. Written information (internal reports, unpublished theses, minutes of meetings, research in progress, newspapers, magazines, letters) was sought through organizations, higher educational institutions, voluntary or pressure groups, and the British Library. Oral information was obtained from sources including conference proceedings, symposia, seminars, personal contact and ad hoc meetings.

**Study results:**

The Internet is a useful resource for identifying grey literature, but users should be aware that websites and links can change rapidly. Substantial amounts of information can be retrieved from dedicated grey literature databases and websites. Written grey literature represents the most valuable source of current and original information. However, obtaining full-text copies of research reported in abstracts or short articles is problematic. Conference presentations and/or supportive literature may be accessible through the Internet. The quality and value of information obtained from grey literature, and the lack of peer-review, needs consideration.

**Study limitations as noted by study authors:**

The authors highlighted common pitfalls they had experienced when searching for and using grey literature.

**Study limitations noted by abstractor:**

The article focused more on Internet-based searches than other approaches. Guidance on obtaining written grey literature was too general given the recognised value of it.

**Key messages:**

Grey literature is an invaluable resource and can be identified through many different approaches, in particular the Internet.

**Study reference:**

Conn V S, Isaramalai S A, Rath S, Jantarakupt P, Wadhawan R, Dash Y. Beyond MEDLINE for literature searches. *Journal of Nursing Scholarship*, 2003;35(2):177-182.

**Study objectives:**

To describe strategies for a comprehensive literature search.

**Study methods:**

Strategies to identify published and unpublished research included: electronic searches (e.g. MEDLINE); ancestry searches (review of citations from relevant studies and reviews); citation index searches; searches of research registries; hand-searching journals; contact with experts in the field; searching conference proceedings; Internet searches; searching for international literature; finding fugitive literature (i.e. clues to other potentially useful studies) from search results, author searches, company reports, press releases, government material and policy documents, for example. Some strategies require follow-up by personal contact to elicit further information. The recall (sensitivity) and precision / specificity of each search strategy was considered.

**Study results:**

The strategies vary in their recall and precision. Electronic databases, journal hand-searches, research registries and conference proceedings have both high recall and precision. Journal hand-searching is labour intensive but can yield publications not yet indexed in electronic databases. Research registries are a valuable source of information about studies that avoids publication bias. Citation index searches and conference proceedings may provide high recall and precision when used to identify studies in more specialized areas. Expert contact is useful to locate unpublished or non-indexed research, but recall is dependent on the response rate. Ancestry searches increase the number of retrieved studies, but not always the diversity, and publication bias remains an issue. Internet searches are generally low in precision and recall but may locate grey literature and ongoing research.

**Study limitations as noted by study authors:**

The authors did not note any limitations of their review-type article.

**Study limitations noted by abstractor:**

This was an overview of search strategies and not a formal evaluation designed to assess alternative methods.

**Key messages:**

Research registries, expert contact and the Internet are valuable sources of ongoing research, unpublished information and grey literature. A diverse range of search strategies beyond MEDLINE is needed for a comprehensive search of the literature.

**Study reference:**

Cook A M, Finlay I G, Edwards A G, Hood K, Higginson I J, Goodwin D M, et al. Efficiency of searching the grey literature in palliative care. *Journal of Pain & Symptom Management*, 2001;22(3):797–801.

**Study objectives:**

To report on the methodology and success of searching the grey literature in a review of palliative care.

**Study methods:**

Journal hand-searches and conventional electronic database searches (MEDLINE, CINAHL, Cancerlit, PsycINFO, EMBASE, PallCare Index, EPOC register, ASSIA, SSCI and SCI) were conducted. Grey literature was sought through information requests, personal contacts and the SIGLE database. Requests for information, in particular unpublished data, were made in the newsletters of six key UK national cancer/palliative care organizations. Over 100 letters were sent to a systematically chosen range of service providers, commissioners and experts; 25 faxes were sent to experts in 12 European countries and Australia. The process was inclusive, for example, all health authorities, not just one, would be approached. Letters were followed up by telephone. Individuals who contacted the review team to query the relevance of a piece of work were encouraged to send it in. SIGLE was searched using a simplified version of the strategy used for the conventional databases.

**Study results:**

Sixty-nine relevant publications relating to 44 unique studies were identified from the conventional searches; these formed the main body of the review.

The grey literature search was conducted over 10 months. A total of 300 hours was spent contacting experts, with 75% of cases followed-up by telephone, and 2 to 3 hours were spent searching SIGLE. Only one of the 25 document hard copies received was eligible for the review. This was identified through both SIGLE and a personal contact, and has since been published. The other documents were annual reports, needs assessments and service descriptions. No appropriate theses or conference abstracts were identified. Overall, the search was considered unsuccessful in obtaining unpublished studies of potential relevance.

**Study limitations as noted by study authors:**

The authors did not note any limitations of their study, but did highlight factors which could have influenced study retrieval.

**Study limitations noted by abstractor:**

The article did not report the success rate of each individual approach.

**Key messages:**

Comprehensive searches of the grey literature are not efficient and add little, if anything, to the overall search strategy in palliative care systematic reviews.

**Study reference:**

Cooper H M. Literature-searching strategies of integrative research reviewers: a first survey. *Science Communication*, 1986;8:372-383

**Study objectives:**

To describe how authors locate material for reviews or discover correlates of searching strategies.

**Study methods:**

The author surveyed reviewers of integrative research reviews on psychology and education that had been published in journal articles, edited books and Information Analysis Products sponsored by ERIC Clearinghouses. Reviewers responding to the initial request for participation were sent a questionnaire, to elicit information on their background, literature coverage goals, literature searching strategies and citation practices. In particular, reviewers were asked questions about the sources they accessed and how useful they were (utility), and the value of the source in retrieving key information (centrality).

**Study results:**

Of the 112 initial requests, 77 reviewers agreed to participate but only 68 returned the questionnaire. Survey results were reported for the 57 authors who responded that the first or second goal of their paper was 'to integrate empirical research in the topic area'.

The 57 reviewers used 15 different ways to locate research, with each reviewer using on average 6.7 different strategies.

The most common strategies involved reference list checking in review papers (n=53), books (n=47) and non-review papers subscribed to (n=40). Approaches revolving around communication were widely used, be it communication with people who typically shared information with them (n=44), informal conversations at conferences or with students (n=22), formal requests to scholars active in the field (n=20), comments from readers/reviewers of past work (n=9) or general requests to government agencies (n=5). However, these did not rank high on utility or centrality by reviewers who used them. Nearly a quarter of reviewers browsed library shelves. Citation searching was not commonly used.

**Study limitations as noted by study authors:**

The authors did not note any limitations of the study.

**Study limitations noted by abstractor:**

This was a questionnaire survey that elicited responses on literature searching from a select sample of reviewers. It did not specifically focus on methods of locating unpublished research, nor did it report the amount of unpublished material retrieved.



**Key messages:**

Reference list checking and personal communication are widely used in strategies to locate published and unpublished material for reviews.

**Study reference:**

Crumley E T, Wiebe N, Cramer K, Klassen T P, Hartling L. Which resources should be used to identify RCT/CCTs for systematic reviews: a systematic review. *BMC Medical Research Methodology*, 2005;5:24. <http://www.biomedcentral.com/1471-2288/5/24>

**Study objectives:**

To review and assess the value of different resources used to identify randomized controlled trials and controlled trials for inclusion in systematic reviews.

**Study methods:**

Eligible studies were those that compared at least two different resources. Electronic searches were conducted in MEDLINE, EMBASE, CINAHL, ERIC, PsycINFO, Web of Science and the Cochrane Library from inception to April 2004. Four journals were hand-searched from 1990 to 2004: *Health Information & Libraries Journal (Health Libraries Review)*, *Hypothesis*, *Journal of the Medical Library Association (Bulletin of the Medical Library Association)*, and *Medical Reference Services Quarterly*. In addition, all abstracts presented at Cochrane Colloquia from 1993 to 2003 were hand-searched, key authors were contacted via e-mail, and the references of relevant articles were screened. No date or language restrictions were applied.

**Study results:**

Sixty-four studies met the inclusion criteria. MEDLINE versus hand-searching (n=22) and MEDLINE versus MEDLINE plus hand-searching (n=12) were amongst the most common comparisons. Other comparisons were evaluated in only one or two studies.

Trial registries achieved the best recall and precision (median 89% and 96.5%, respectively, versus reference standard), but were only evaluated in two studies. One study that compared the Internet with a reference standard had both low recall and precision (median 24% and 17%, respectively). The only study that explored searching Cochrane CENTRAL had a median recall of 78% versus reference standard; precision was not reported.

Forty-two studies reported reasons why trials were missed. For hand-searches, where reported, the reasons included inexperienced hand-searchers (2 studies), fatigue/boredom (1 study), and the journal issue not being hand-searched (2 studies).

**Study limitations as noted by study authors:**

There is no validated quality score for comparative studies. It is difficult to compare reference standards as they generally differ or are reported in insufficient detail to be reproducible. The topic chosen to search can determine the success of the strategy, and there are limitations to using precision and recall for assessment purposes.

**Study limitations noted by abstractor:**

The article focused on comparisons involving electronic or manual searches, and there were few comparisons of approaches used specifically to identify unpublished studies. The reference standard was not described in many instances, which hampers interpretation of the results.

**Key messages:**

Hand-searching combined with searches across multiple bibliographic databases remains the gold standard for researchers conducting systematic reviews. Other resources, such as trials registries and the Internet, need further evaluation. The Cochrane Controlled Trials Register (CENTRAL) contains a significant amount of unique information which is not found in other sources.

**Study reference:**

De Luca J B, Mullins M M, Lyles C M, Crepaz N, Kay L, Thadiparthi S. Developing a comprehensive search strategy for evidence based systematic reviews. Evidence Based Library and Information Practice 2008;3:1.

**Study objectives:**

To develop and test a comprehensive search strategy, looking beyond randomized controlled trials, for literature on the prevention of HIV/AIDS and sexually transmitted diseases in order to create a database of relevant research for the CDC's HIV/AIDS Prevention Research Synthesis (PRS) project.

**Study methods:**

Various methods were used to identify published and unpublished citations between 1988 and 2006. The search results of four electronic databases (MEDLINE, EMBASE, PsycINFO and Sociological Abstracts) were used in the analysis. In addition, 35 journals were hand-searched biannually; for updates, the choice of journals was re-evaluated annually. Relevant published and unpublished reports were identified by networking with researchers. Other sources checked for additional citations were relevant electronic mail lists, clinical trial databases (e.g., The Cochrane Library, CRISP), conference proceedings, and the reference lists of relevant HIV behavioural prevention research literature.

**Study results:**

A combined total of 18,108 relevant citations from 1988-2005 were retrieved through electronic (n=17,493) and manual (n=1,232) searches, of which 617 (3%) were identified by both approaches. Across all citations, 615 (3%) were unique to manual methods and 12,965 (74%) were identified by only one electronic database. Overlap between manual and automated methods was 16% for articles reporting behavioural or biologic outcomes, which was the primary focus of the PRS, and 6% for in-scope citations. Manual approaches alone accounted for 9% (n=109) of behavioural or biologic citations and 6% (n=570) of in-scope citations.

**Study limitations as noted by study authors:**

The authors highlighted that the results of the analysis should be interpreted with caution and may not be generalizable to other research fields.

**Study limitations noted by abstractor:**

The results were broken down according to each electronic database, but reported overall for the manual approach and other sources, and not for each individual search element. There was no indication of how many of the citations represented unpublished research.

**Key messages:**

A combination of automated and manual approaches is essential to increase the likelihood of retrieving all relevant published and unpublished research.

**Study reference:**

De Pablo Lopez de Abechuco I, Aguilar-Jimenez M, Galvez-Mugica M A, Serrano Olmeda M, Revilla-Monaj A, Sanchez-Rodriguez M. Early interruption in clinical trials: Are these results published? *Basic and Clinical Pharmacology and Toxicology*, 2011;109:34. <http://dx.doi.org/10.1111/j.1742-7843.2011.00777.x>

**Study objectives:**

This abstract is based on an abstract of a conference presentation.  
To assess the publication rates of clinical trials that are suspended or terminated early.

**Study methods:**

The authors reviewed the files of all clinical trials evaluated by their hospital ethics committee from January 1999 to January 2009 for those that had been suspended or terminated early. The reason for suspension or early termination of each clinical trial was noted. Google, PubMed and ClinicalTrials.gov were searched for these trials using the drug's name, pathology and clinical trial as keywords.

**Study results:**

Two hundred and seventy (25%) of the 1088 clinical trials analysed were identified as suspended, of which 227 (84%) were never started. Sixteen of the 43 remaining clinical trials were interrupted due to 'lack of efficacy' (n=6) or 'safety reasons' (n=10) and were included in the analysis. Twelve (75%) of these 16 trials had published results: three (50%) of those which were interrupted due to efficacy and nine (90%) of those which were interrupted with safety concerns. The analyses of the scientific literature alone identified nine (56%) of these interrupted trials: three related to efficacy and six related to safety. In ClinicalTrials.gov, eight (50%) of these trials were assigned a status of 'completed' rather than 'terminated'. Publication is less common when the outcome is a lack of efficacy versus safety (50% versus 90%), and the publication rate in scientific literature decreases.

**Study limitations as noted by study authors:**

The abstract does not note limitations.

**Study limitations noted by abstractor:**

Only trials interrupted for lack of efficacy or safety reasons were selected for analysis; it is unclear why trials with other reasons for interruption were not included. The yield of each resource searched was not reported.

**Key messages:**

Searching the scientific literature alone is insufficient to obtain the results of suspended clinical trials, which are generally published but in different media. Publication of trials interrupted because of a lack of efficacy is less frequent than those interrupted because of safety concerns. The status 'completed' versus 'terminated' in ClinicalTrials.gov did not always match the status recorded in the hospital's own files.

**Study reference:**

De Smidt G, Gorey K M. Research note. Unpublished social work research: systematic replication of a recent meta-analysis of published intervention effectiveness research. *Social Work Research*, 1997;21(1):58-62.

**Study objectives:**

To address the impact of publication bias in reviews of the effectiveness of social work by systematically replicating a recent meta-analysis of published research (Gorey KM. *Social Work Research* 1996;20:119–28) with conceptually similar, although unpublished, studies.

**Study methods:**

Dissertation Abstracts Ondisc (which includes Dissertation Abstracts International, Masters Abstracts International, Comprehensive Dissertation Index, and American Doctoral Dissertations) was searched from 1990 to 1994 for doctoral dissertations and master's theses affiliated with schools of social work that reported empirical findings of research on social work effectiveness. The meta-analysis examined the same subject keyword search scheme as in the original analysis of published research and conducted similar analysis. For convenience and efficiency, only the extended abstracts of the retrieved studies were used for the meta-analysis.

**Study results:**

Twenty-four unpublished social work dissertations and theses were identified. The unpublished studies were generally similar to their published counterparts except in terms of the level of intervention evaluated, the type of comparison group, and their use of follow-up assessment procedures. No variables were found to be associated with intervention effect size among either the unpublished studies or the previously reviewed published studies. Similarly, when combining the results of the 24 unpublished studies, the overall effect size did not differ significantly from that estimated using published research. Publication bias does not seem to confound recent inferences about effectiveness that were based on published social work research.

**Study limitations as noted by study authors:**

There is a potential for misclassification bias due to subsequent publication of unpublished works in the professional literature (the authors found this not to adversely impact upon their main findings). The unpublished research was retrieved from what the authors refer to as a "a conveniently sampled accessible population" of dissertations and theses.

**Study limitations noted by abstractor:**

The impact of including unpublished studies along with published studies in the original meta-analysis does not appear to have been examined. The overall quality of the unpublished studies was not commented upon.

**Key messages:**

Unpublished social work studies identified through dissertations and theses are similar to their published counterparts and are unlikely to confound the generally positive inferences about the effectiveness of social work. The findings of social workers' day-to-day practice experiences are a valuable source of unpublished research that should be accessed.



**Study reference:**

Dickersin K, Chan S, Chalmers T C, Sacks H S, Smith H. Publication bias and clinical trials. *Controlled Clinical Trials*, 1987;8(4):343-353.

**Study objectives:**

To evaluate the extent to which the medical literature may be misleading on account of preferentially publishing randomized clinical trials (RCTs) that show a statistically significant treatment effect.

**Study methods:**

A sample of over 2400 reports of published RCTs from 1963 to 1981 provided the index papers for this study. In the first stage, 146 authors of published RCTs were mailed a postcard survey about their participation in any unpublished RCTs.

In the second stage, two questionnaires were mailed to 56 postcard respondents (primarily those who had unpublished studies) and a new sample of 262 publishing authors requesting specific and detailed information about the RCTs they had participated in. Non-respondents to the first questionnaire were sent it a second time.

**Study results:**

In the first stage, 53 of the 146 responses to the postcard survey reported at least one unpublished RCT (average 1.1). In the second stage, 212 responses were obtained overall (67%). Fifty-six responses were not included in the analysis as the authors refused to participate, claimed they had never been the primary author of a published RCT, provided insufficient or contradictory details, or were associated with a large cooperative group which might have specific publishing practices.

The 156 responses reported 271 unpublished and 1041 published trials. The majority of unpublished trials had been completed (n=238). The number of completed unpublished RCTs ranged from 1 (40 authors) to 6 to 10 (7 authors); one author claimed 34 completed unpublished RCTs but was excluded from the analysis.

The authors noted that postcards generated slightly more conservative responses, and slightly more unpublished trials were reported in the postcard plus questionnaire group. The main reasons for not submitting research for publication were 'negative' results and lack of interest.

**Study limitations as noted by study authors:**

The sample was drawn from an individual's personal collection of RCTs and may not reflect the overall population of RCTs or other areas of medical research. The sample of unpublished work was unlikely to be random, and the methods (survey) used to select it could introduce bias into the results. The questionnaire response rate was not high, and there was the potential for selective reporting from individuals with an opinion relating to the

study hypothesis. Questionnaire responses were open to problems concerning subjectivity and accuracy.

**Study limitations noted by abstractor:**

No other limitations were noted.

**Key messages:**

Surveying authors of published RCTs for unpublished research is a fruitful exercise but yields mixed response. Authors may not be willing to share unpublished information and the accuracy and subjectivity of any such data needs evaluation. There is a degree of apathy in terms of publishing research, especially that showing negative trends.

**Study reference:**

Dundar Y, Dodd S, Williamson P, Walley T, Dickson R. Searching for and use of conference abstracts in health technology assessments: policy and practice. *International Journal Of Technology Assessment In Health Care*. 2006;22-3:283-287.

**Study objectives:**

To examine current policy and practice relating to the identification and extent of use of data from conference abstracts in health technology assessment reviews (TARs).

The research described in this paper has been published as part of a wider health technology assessment (HTA) [Dundar et al., *Health Technology Assessment* 2006;10(5)], for which a structured abstract is also available.

**Study methods:**

The authors surveyed all seven TAR groups in the UK in August 2004 regarding their practices of identification, inclusion and assessment of data from conference abstracts in TARs. They also conducted an audit of all TARs commissioned by the HTA programme and published between January 2000 and October 2004.

The term 'abstract' referred to conference abstracts and presentations (oral or poster) given at conferences, meeting, symposiums and workshops.

**Study results:**

All seven TAR groups completed and returned the survey.

Five TAR groups reported a general policy of searching for abstracts: four used both general and explicit searches, and the fifth only general searches. Three groups raised concerns related to inadequate indexing, difficulties in locating abstracts, and the costs of retrieving such studies.

The audit included 63 TARs, of which 47 (75%) searched for abstracts. Seventeen TARs explicitly sought abstracts of trials by searching the websites of conference or professional societies, or hand-searching online or print copies of journals or supplements. Electronic databases were searched as part of either a general strategy in 38 TARs (60%) or in both general and explicit searches in 8 TARs (13%). Thirty-eight TARs identified at least one trial reported as an abstract/presentation, of which 26 (68%) included such studies. Twenty-two TARs were unpublished.

In addition to issues raised by the TAR groups, the authors noted that search strategies are difficult to design, the process is time-consuming, and the results may not be representative. They also raised concerns about insufficient and inaccurate reporting of studies, the methodological quality of the studies described, and the potential for publication bias.

**Study limitations as noted by study authors:**

The study may not be generalizable to TARs that include data from abstracts of studies other than randomized controlled trials.

**Study limitations noted by abstractor:**

This paper collates experiences on the retrieval and use of conference abstracts during the conduct of TAR reviews. It was not a formal evaluation of search strategies.

**Key messages:**

Conference abstracts are important sources of information on unpublished studies, especially planned or ongoing trials. However, the identification and use of them is time-consuming, costly and challenging.

**Study reference:**

Dundar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson P R. Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies. *Health Technology Assessment*, 2006; 10(5).

**Study objectives:**

To assess the extent of use of data from conference abstracts and presentations in health technology assessments (HTAs).

Other objectives were to assess the methodological quality of trials included in HTAs, the consistency of outcome data between abstracts and full-text publications, the impact of including such data on pooled effect estimates, and the availability of data from these sources when developing technology assessment reviews (TARs).

Some of the research described in this paper has been published elsewhere [Dundar et al., *International Journal of Health Technology Assessment in Health Care* 2006;22-3:283-287]; a structured abstract for this reference is also available.

**Study methods:**

The authors surveyed all seven TAR groups in the UK in August 2004 to obtain information on the identification and use of conference abstracts and presentations for TAR reports. In October 2004, non-respondents were reminded by e-mail with a further questionnaire attached. This process was repeated until all completed questionnaires were obtained.

In addition, an audit was conducted of all TARs commissioned by the HTA programme and published between January 2000 and October 2004, to identify reviews of rapidly evolving technologies and to determine the extent that conference material was used in TARs. TARs were obtained from the National Coordinating Centre for Health Technology Assessment (NCCHTA) website.

The authors also identified and retrieved RCTs published as abstracts from three case studies, then sought full publications through electronic searches (MEDLINE, EMBASE, the Cochrane CENTRAL Register, ISI Web of Knowledge: SCI Expanded). Principal investigators were contacted, where necessary, to confirm publication.

The term 'abstract' was defined as conference abstracts and presentations (oral or poster) given at conferences, meeting, symposiums and workshops.

**Study results:**

Five of the seven TAR groups reported a general policy of searching for abstracts using either general searches (1 group) or a combination of general and explicit searches (4 groups). All four groups searched ISI Proceedings amongst their databases. Other sources

were the Internet (3 groups), and hand-searches and professional societies (2 groups). Three groups raised concerns related to inadequate indexing, difficulties in locating abstracts, and the costs of retrieval.

The audit identified 63 TARs, of which 47 (75%) searched for abstracts. Seventeen TARs explicitly sought abstracts by searching the websites of conference or professional societies, or hand-searching journals or supplements. Electronic searches were conducted as part of a general strategy in 38 TARs (60%). Of those that included an explicit search, seven (41%) conducted electronic searches as part of the general strategy. The most commonly searched databases for conference abstracts were ISTP (Web of Science), CPI, BIOSIS, Inside Conferences (DIALOG) and Internet Database of Evidence-based Abstracts. Thirty-eight TARs identified at least one trial that was reported as an abstract/presentation, of which 26 (68%) included such studies.

The case studies used a combination of the following: electronic databases, Internet searches, electronic and manual searches of conference proceedings, and hand-searches of FDA submissions, European Medicines Agency (EMA) reports and company submissions to the National Institute for Health and Clinical Excellence (NICE).

Two case studies reported explicit searches to identify relevant studies available as conference abstracts/presentations. The first identified nine relevant conference abstracts (4 trials) and one clinical trial report, which remained unpublished. Clinical trial reports for a further three trials were provided by the manufacturers. The second study identified a number of abstracts and presentations reporting trials, none of which remained unpublished. The third case study identified four relevant conference abstracts (2 studies) and one unpublished trial, and obtained clinical trial reports with additional information for another four included trials. The review authors highlighted the poor reporting and uncertain quality of trials in conference abstracts.

#### **Study limitations as noted by study authors:**

Only abstracts of RCTs were sought and not other study designs included in TARs. The study may not be generalizable to other clinical areas or TARs that include data from abstracts of studies other than randomized controlled trials. Limitations of data in two case studies meant quantitative analysis was not possible. The authors stated that analyses should be repeated as more TARs accrue, or should include the work of other international HTA groups.

#### **Study limitations noted by abstractor:**

No other limitations noted. This was not a formal evaluation of approaches to identify unpublished material.

**Key messages:**

TAR groups vary in their policy and practice of searching for and including conference material. Comprehensive searching for trials available as conference abstracts and presentations is time-consuming and costly, and may be of questionable value. Contact with manufacturers is an important source of unpublished information.

**Study reference:**

Dwan K, Altman D G, Arnaiz J A, Bloom J, Chan A W, Cronin E, et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. PLoS ONE, 2008;3(8):e3081.

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0003081>

**Study objectives:**

To review and summarise the evidence from empirical cohort studies that have assessed study publication bias and/or outcome reporting bias in randomized controlled trials (RCTs) approved by a specific ethics committee or other inception cohorts of RCTs.

**Study methods:**

Electronic searches were conducted in MEDLINE (1950 to 2007), SCOPUS (1960 to 2007) and the Cochrane Methodology Register (1898 to 2007). The authors also checked the reference list in the relevant section of a health technology assessment, and contacted the lead/contact authors of a relevant Cochrane protocol and all identified studies for further studies.

**Study results:**

The searches retrieved 3247 potentially eligible references. Only one study was identified through the references of included studies and two studies from contact with authors. Fifteen of the 16 studies eligible for the review were identified by the Cochrane Methodology Register, of which six were found through this source alone. Three of these unique studies were only available as abstracts presented at the Cochrane Colloquium. One eligible reference was located through contact with the author, whilst another author provided information on one of the eligible studies. Personal communication also provided details of three ongoing studies.

**Study limitations as noted by study authors:**

The main limitation was that information on RCTs could not be separated from information on other study designs for half of the included cohorts.

**Study limitations noted by abstractor:**

This was not a review of the approaches used to identify unpublished research that could impact on biases arising from nonpublication and selective outcome reporting.

**Key messages:**

The Cochrane Methodology Register and contact with authors are useful ways of identifying published and unpublished studies reporting empirical evidence of biases that can arise during the completion of an RCT.



**Study reference:**

Dwan, K., Altman, D. G., Cresswell, L., Blundell, M., Gamble, C. L., & Williamson, P. R. (2011). Comparison of protocols and registry entries to published reports for randomised controlled trials. *Cochrane Database of Systematic Reviews*, (1), MR000031.

**Study objectives:**

To systematically review studies of cohorts of randomized controlled trials (RCTs) to compare the content of trial reports with the information contained in their protocols, or entries in a trial registry, and to assess whether these differences are related to trial characteristics.

**Study methods:**

Electronic searches were conducted in MEDLINE (1950 to August 2010), EMBASE (1980 to August 2010), ISI Web of Science (1900 to August 2010) and the Cochrane Methodology Register (Issue 3, 2010) to identify published and unpublished RCTs. In addition, reference lists were checked and authors of eligible studies were contacted for details of additional relevant studies. Articles citing references to items known to be pertinent ('known item searching') were also screened.

Published reports included any report published in a peer-reviewed journal resulting from the RCT.

**Study results:**

Overall, 4487 records were identified, of which only seven were obtained through sources other than database searching. These seven records related to one known study not picked up by the electronic searches, one study detected through searching conference proceedings, one study located through contact with authors, and four ongoing studies. No studies were identified from reference list checking. None of the 16 included studies were unpublished.

**Study limitations as noted by study authors:**

Eight studies were awaiting assessment and could potentially contribute data to an update of the review. The results of the studies had to be discussed narratively because of difficulties in pooling the studies.

Study limitations noted by abstractor:

No other limitations noted.

**Key messages:**

Personal communication with authors may yield details of ongoing studies, but little else.

**Study reference:**

Egger M, Juni P, Bartlett C, Holenstein F, Sterne J. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. *Health Technology Assessment*, 2003;7(1).

**Study objectives:**

This abstract is based on the Executive Summary of the full assessment.

To examine the characteristics of clinical trials that are difficult to locate (unpublished trials, trials published in non-English languages and trials published in journals not indexed in MEDLINE); to compare within meta-analyses the treatment effects reported in such trials; and to assess the impact of excluding such trials on the pooled effect estimates.

To evaluate trials of lower quality in the same manner as that described for trials that are difficult to locate.

**Study methods:**

Electronic searches and hand-searches were used to identify systematic reviews and reports of meta-analyses which combined the outcomes of at least five controlled clinical trials. Electronic searches were conducted in the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effectiveness (DARE). Eight medical journals that regularly publish systematic reviews and Health Technology Assessments were searched by hand. Analyses of trial quality were based on allocation concealment and blinding.

**Study results:**

The searches yielded 159 systematic reviews, not all of which were considered to be reviews of studies difficult to locate. Comparisons of treatment effects were based on 50 to 66 meta-analyses for studies difficult to locate, and 39 to 45 meta-analyses for trials of lower quality. Trials that are difficult to locate varied across medical speciality; unpublished trials were particularly prevalent in oncology. Unpublished trials showed less beneficial treatment effects than published trials and had the effect of reducing funnel plot asymmetry; non-English language trials and non-indexed trials tended to have the opposite effect. Trials that are difficult to locate tended to be smaller and of lower methodological quality than those that were easily accessible and published in English. Beneficial effects were observed more often in open trials and in trials with inadequate or unclear concealment of allocation. The exclusion of these trials generally led to an often substantial less beneficial treatment effect. The authors commented that the finding that trials which are difficult to locate are often of lower quality raises the possibility of introducing bias. This is contrary to the premise that the use of extensive literature reviews should prevent bias.

**Study limitations as noted by study authors:**

The authors did not report any limitations in this Executive Summary [abstractor's comment: this does not mean the study was without limitations, merely the authors did not consider them of sufficient importance to justify mention in the Executive Summary].

**Study limitations noted by abstractor:**

This was an Executive Summary of a Health Technology Assessment and thus provided limited information. The full text article may provide further details of the sources and strategies used to find trials that are difficult to locate in the individual meta-analyses, the trials themselves (e.g. quality), and the relative proportions of meta-analyses and trials that were unpublished, not indexed in MEDLINE, or published in a foreign language.

**Key messages:**

Trials that are difficult to locate are often smaller and of lower quality than those that are easily accessible and published in English. The inclusion or exclusion of trials of low methodological quality can have a substantial impact on the results and conclusions of systematic reviews and meta-analyses. Unpublished trials in particular often show less beneficial effects.

**Study reference:**

Eliasson, M., & Bergqvist, D. [Research results should be freely accessible!-- Case reports demonstrate obstacles to contact with drug industry]. *Lakartidningen*. 2001;98(37):3913-3916.

**Study objectives:**

The paper is not in English and this abstract is based on the paper's abstract and the tables within the paper.

To obtain unpublished data on clinical trials of antithrombotic drugs registered in Sweden.

**Study methods:**

The authors contacted six companies with antithrombotic drugs registered in Sweden for details of unpublished trials. Reminders were sent by telephone, fax and email.

**Study results:**

Answers were received over a time period ranging from 4 to 60 weeks. All but one company had to be reminded more than once.

No relevant unpublished studies were received, despite the authors knowing that there was at least one known large negative unpublished trial. Two publications unknown to the team were identified. The process was time consuming with little result.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

There are insufficient details in the abstract to comment on any likely limitations of the study.

**Key messages:**

Trying to obtain unpublished data directly from pharmaceutical companies can be time consuming with little result.

**Study reference:**

Enkin M, Hetherington J. Collecting the evidence systematically. Ensuring that it is complete and up-to-date. *International Journal of Technology Assessment in Health Care*, 1996;12(2):276–279.

**Study objectives:**

Some of the research described in this paper has been published elsewhere [Hetherington J, Dickersin K, Chalmers I, Meinert C L. Retrospective and prospective identification of unpublished controlled trials: lessons from a survey of obstetricians and pediatricians. *Pediatrics*, 1989;84(2):374–380.]; a structured abstract for this reference is also available.

To identify published and unpublished randomised or quasi-randomized controlled trials (RCTs) of care in pregnancy and childbirth using a variety of methods. This seems to be a report of experience rather than a formally designed study.

**Study methods:**

Several methods were used to identify reports of RCTs. Electronic searches of MEDLINE (1966 onwards) were conducted. A systematic hand-search of 60 selected core journals (1950 onwards) was carried out. The reference lists in trials and reviews were assessed to identify additional reports of trials. Studies were also identified through ad hoc reading and discussion and correspondence with colleagues, and reading conference abstracts and proceedings. During the second half of 1986 and early 1987 the authors surveyed approximately 42,000 obstetricians and paediatricians internationally to identify unpublished trials.

**Study results:**

The various search approaches identified almost 6000 RCTs and quasi-randomized trials. The survey of obstetricians and paediatricians identified only a few unpublished trials.

**Study limitations as noted by study authors:**

The authors do not report limitations, probably because this was not a formal evaluation.

**Study limitations noted by abstractor:**

Some of the search approaches evolved over time and detailed descriptions of the methods (particularly of the methods of conducting the survey) and comparative results of the different approaches are not provided. However, this was not a formal evaluation designed to evaluate alternative methods.

**Key messages:**

Surveying clinicians yields little information in terms of additional unpublished studies. Prospective trial registration is required.

**Study reference:**

Eysenbach, G. Use of the world-wide-web to identify unpublished evidence for systematic reviews - the future role of the internet to improve information identification [abstract]. 7th Annual Cochrane Colloquium; 1999 Oct 5-9; Rome, Italy.

**Study objectives:**

This abstract is based on an abstract of a conference presentation. The research it describes has subsequently been published in the journal *Medical Informatics & the Internet in Medicine* [Eysenbach et al. *Med Inform* 2001;26(3);203–18], for which a structured abstract is available.

To determine whether, and to what extent, randomized controlled trials (RCTs) and other unpublished evidence can be found by searching the World Wide Web, to identify those websites that potentially offer leads to unpublished RCTs, to develop possible search strategies and tools for the Internet, and to direct future research in this area.

**Study methods:**

Various approaches were used to search the Internet for leads to potentially relevant unpublished or ongoing trials. The search strategies of eight randomly selected, completed and recently updated Cochrane Systematic Reviews (CSR) were retrospectively adapted for the Worldwide Web. Different Internet search engines were evaluated for their suitability to handle complex queries.

**Study results:**

Optimal retrieval was obtained using an advanced AltaVista search with the Boolean expression "(intervention OR intervention-synonym) NEAR (condition OR condition-synonym)". No additional relevant unpublished trials were identified via the Internet, although for half of the CSRs the Internet search found leads to several ongoing and recently published trials that the CSR authors were not fully aware of.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

The abstract lacked details of methodology and results (a more comprehensive report of this research has subsequently been published – see reference above).



**Key messages:**

Internet searches may provide useful leads to ongoing and recently published trials and should be routinely included in the search strategies for Cochrane Systematic Reviews. A specialised Cochrane search engine should be developed to facilitate such searches.

**Study reference:**

Eysenbach G, Tuische J, Diepgen T L. Evaluation of the usefulness of Internet searches to identify unpublished clinical trials for systematic reviews. *Medical Informatics & the Internet in Medicine*, 2001;26(3):203–218.

**Study objectives:**

To develop a search strategy for finding trials on the Internet.

To evaluate the usefulness of Internet searches in the identification of additional unpublished and ongoing clinical trials.

**Study methods:**

A pilot study evaluated the ability of nine major generic and two medical Internet search engines to handle complex queries. Following this, the search strategies of seven updated Cochrane Systematic Reviews (CSRs) were retrospectively adapted to find additional randomized controlled trials using the AltaVista Internet search engine. Internet searches were conducted in December 1998 using the general expression 'study methodology NEAR intervention NEAR condition'. Web pages were screened and links followed where appropriate. The search strategy was evaluated in terms of recall and precision. Critical appraisal involved MEDLINE searches, gathering further information on the identified studies, and contacting CSR authors. In March 2000, MEDLINE and the latest version of the CSRs were checked to see whether any of the unpublished research had since been published.

**Study results:**

A review of 429 web pages in 21 hours resulted in 59 leads to published studies and 14 leads to unpublished studies. The latter came from departmental/institution homepages (5), personal homepages of researchers (2), published conference proceedings or meeting abstracts (2), announcements of grants or funding (2), press releases (1), online unrefereed publications (1), and websites recruiting study participants (1). There was no web-based information from institutional review boards or ethics committees detailing protocols or approved research project listings.

At least nine of the 14 leads to unpublished research were considered relevant to four CSRs; of the remaining five, two studies were considered probably not relevant and the relevance of three trials was unclear. The search strategy had a recall of 0 to 43.6% in finding references to published studies. Its precision in identifying leads to published, ongoing and unpublished studies ranged from 0 to 20.2%. The quality of information retrieved was of concern since web pages may be out-of-date and not reflect the true status of trials. There is also the potential for discrepancies between material published both online (i.e. non peer-reviewed) and in peer-reviewed journals.

**Study limitations as noted by study authors:**

The Internet searchers were not experts in the area of interest and may have missed evidence or misjudged the relevance of some identified studies. Systematic reviewers were enlisted for appraisal of the identified studies, in an attempt to minimize these limitations.

The search was restricted to English and German sites and the search was optimized to find English documents.

**Study limitations noted by abstractor:**

The authors defined 'unpublished' studies as those that were not published in peer-reviewed journals as full papers. There was no differentiation between grey literature and studies that had not been published in any format. There were no details of the accessibility of the evaluated search engines.

**Key messages:**

The Internet is a useful, additional source of information on unpublished and ongoing trials, but there may be discrepancies between material published online and in peer-reviewed journals. The appraisal of non peer-reviewed electronic publications of uncertain quality is a potential problem. A defined syntax for publishing trials on the web is needed to ensure interoperability across trial registers and to increase the recall and precision of specialist search engines.

**Study reference:**

Eysenbach G, Tuische J, Diepgen T L. Evaluation of the usefulness of internet searches to identify unpublished clinical trials for systematic reviews. *Chinese Journal of Evidence-Based Medicine*, 2002;2(3):196-200.

**Study objectives:**

The paper is not in English and this abstract is based on the paper's abstract. The research it describes has also been published in the English-language journal *Medical Informatics & the Internet in Medicine* [Eysenbach et al. *Med Inform* 2001;26(3);203–18], for which a structured abstract is available.

To determine the usefulness of World Wide Web searches in the identification of additional unpublished and ongoing clinical trials.

**Study methods:**

The search strategies of seven Cochrane Systematic Reviews were retrospectively adapted in an attempt to find additional randomized controlled trials via the World Wide Web. A search strategy for the AltaVista Internet search engine, using the general expression 'study methodology NEAR intervention NEAR condition', was evaluated in terms of its recall in finding references to published studies and its precision in identifying leads to published or unpublished studies.

**Study results:**

A review of 429 web pages in 21 hours resulted in viable leads to 14 unpublished, ongoing or recently finished trials. At least nine of the 14 leads were considered relevant to four systematic reviews. The search strategy had a recall of 0 to 43.6% and its precision ranged from 0 to 20.2%.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

This paper is published in Chinese. Comments on the study have been included in the Structured Abstract of the English-language report (see reference above).

**Key messages:**

Information on unpublished and ongoing trials can be found on the Internet, but more powerful search tools are needed. A defined syntax for publishing trials on the web is

needed to ensure interoperability across trial registers and to assist specialist search engines in their goal. The appraisal of non peer-reviewed electronic publications of uncertain quality is a potential problem.

**Study reference:**

Fayers P, Gibson D, Mossman J. UKCCCR Register of U.K. Cancer Trials. *Controlled Clinical Trials*, 1995;16(3):172–181.

**Study objectives:**

This report discusses the development and use of an online database of all Phase II/III randomized trials of cancer therapy in the UK, whether ongoing or completed. One of the register's aims is to facilitate overviews and meta-analyses.

**Study methods:**

Compilation of the new United Kingdom Coordinating Committee on Cancer Research (UKCCCR) database, which is largely based on the 1986 updated and expanded version of the original register, was described. Bibliographic database searches, hand-searching of journals, pharmaceutical companies and expert contact were used to identify trials. Information was obtained from major trials offices, research funding agencies, special interest groups, cancer registries, local ethical review boards, and the NHS Research and Development Register. In addition, circulars were sent to all members of relevant professional bodies, and announcements and advertisements were made in medical journals and at conferences. To ensure the completeness of the register, questionnaire surveys were sent out to UK oncologists and clinicians in related disciplines, and are regularly sent (every 6 months) to investigators who have contributed studies. At the end of the article, the authors requested readers contact them with details of any further UK randomized cancer trials that are believed not to be registered.

**Study results:**

The UKCCCR register is intended to be a comprehensive database of all randomized trials of cancer therapy conducted in the UK, as well as international collaborative trials involving UK trials offices. It stores brief summaries and abstracts of trials, along with summary analyses and abstracts of associated publications where available. The initial pass at data collection was completed in 1994. The UKCCCR register is to be incorporated in the European Cancer Clinical Trials Register.

**Study limitations as noted by study authors:**

The authors did not note any limitations since their report was one describing the development of the UKCCCR register.

**Study limitations noted by abstractor:**

Although the article described many approaches to identify ongoing and completed trials, this was not a study evaluating search strategies and the yields of different resources in identifying trials for inclusion in the register was not reported.

**Key messages:**

Numerous varied approaches are essential to identify published and unpublished trials for a register of all randomized trials of cancer therapy conducted in or involving trial centres in the UK, few of which have protocols available on the US National Cancer Institute's PDQ database.

**Study reference:**

Furukawa T A, Inada T, Adams C E, McGuire H, Inagaki A, Nozaki S. Are the Cochrane group registers comprehensive? A case study of Japanese psychiatry trials. *BMC Medical Research Methodology*, 2002;2:6.

**Study objectives:**

To investigate whether the Cochrane Controlled Trials Register provides comprehensive coverage of non-English trials, in particular Japanese trials of psychiatry.

**Study methods:**

The Japanese register of randomized controlled trials (RCTs) of psychotropic drugs was established through contact with pharmaceutical companies, electronic searches of MEDLINE, and hand-searches of psychiatric and medical journals. It did not contain abstracts from academic meetings or RCTs undertaken in Japan that had been published in English-language journals.

The Cochrane Schizophrenia Group (CSG) and the Depression, Anxiety and Neurosis Group (CCDAN) searched their specialized registers for reports of trials possibly conducted in Japan.

**Study results:**

There were 56 reports of RCTs of antidepressants for depression in the Japanese register. The CCDAN register identified 18 reports, of which nine were in both registers, six were English-language duplicate publications (of 5 Japanese RCTs), and three were English-language reports of RCTs conducted in Japan. Thus, only 14 (25%) of all relevant RCTs reported in Japanese were retrieved.

There were 61 reports of RCTs of neuroleptics for schizophrenia in the Japanese register. The CSG register identified 36 reports, of which six were in both registers, 18 were English-language duplicate publications (of 13 Japanese RCTs), and 12 were English-language reports of RCTs conducted in Japan. Thus, only 19 (31%) of all relevant RCTs reported in Japanese were retrieved.

The authors commented that their results clearly demonstrated the limitations of the current Cochrane registers, despite extensive searching, and similar or worse yields could be expected for RCTs conducted in other East Asian countries.

**Study limitations as noted by study authors:**

The authors did not note any limitations of their study.



**Study limitations noted by abstractor:**

The authors did not comment on the feasibility of searching for Japanese reports that contain insufficient detail in English to facilitate identification.

**Key messages:**

Cochrane specialized registers may be incomplete in terms of RCTs undertaken in non-Anglophone foreign countries and not reported in English. Such countries should consider establishing their own registers of RCTs. The Japanese database of psychiatry trials has now been merged with the Cochrane groups' registers.

**Study reference:**

Gherzi, D., Clarke, M. J., & Reveiz, L. Do Cochrane reviews search databases of ongoing trials, and how well do they report these searches? Oral presentation at the Joint Cochrane and Campbell Colloquium; 2010 Oct 18-22; Keystone, Colorado, USA [abstract].

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To assess if, and how, Cochrane reviewers are searching databases of ongoing studies.

**Study methods**

The search strategies of all new protocols and reviews published in Issue 2, 2010 of The Cochrane Database of Systematic Reviews were evaluated by two independent reviewers. Data relevant to searches of databases of ongoing studies were extracted.

**Study results:**

Of the 41 protocols and 26 reviews identified, 25 (61%) protocols and 10 (38%) reviews mentioned a search of a database of ongoing studies. Only one protocol and one review specified the search terms for this search. There is a lack of understanding of the various databases and registers that exist and the overlap between them. The WHO International Clinical Trials Registry Platform (ICTRP) database contained records from the majority of databases mentioned by review authors but is underused. Key issues associated with the identification of ongoing studies in general were the use of only one database, searching the same data through different websites, not searching structured databases of trials, imprecise information, and poor reporting of the methods used.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

There are insufficient details in the abstract to comment on any likely limitations of the study.

**Key messages:**

Search strategies for ongoing or prospectively registered trials in Cochrane protocols and reviews are poorly documented.

**Study reference:**

Gilbody S M, Song F. Publication bias and the integrity of psychiatry research. *Psychological Medicine*, 2000;30(2):253–258.

**Study objectives:**

This abstract is based on an editorial which discusses methods to detect and reduce publication bias, for example by searching for unpublished studies, in the field of psychiatry.

**Study methods:**

Methods to search for unpublished studies of drug trials have included contacting key experts in the field and pharmaceutical companies. A ‘trials amnesty’, which encouraged researchers to register unpublished results in the public domain, was also reported. The amnesty was widely publicized through editorials in major biomedical journals, but not psychiatric journals, in 1997.

**Study results:**

Personal communication with experts in the field and pharmaceutical companies may yield unpublished material, but it is difficult to know whether this represents all relevant unpublished research given the issues of commercial sensitivity and difficulty in identifying the original authors. At the time of the editorial, 150 studies had been identified through the trials amnesty and their details included in the Cochrane Library. However, no unpublished psychiatric research had surfaced. The existence of unpublished research is often evident in promotional material where pharmaceutical companies frequently cite ‘data on file’.

**Study limitations as noted by study authors:**

The author did not note any limitations of their editorial.

**Study limitations noted by abstractor:**

This was an editorial and not a formal study or evaluation.

**Key messages:**

Use of a ‘trials amnesty’ did not uncover any unpublished psychiatric research. Contact with experts in the field and pharmaceutical companies offers limited success. A mandatory prospective register of clinical trials in psychiatry could offer the solution.

**Study reference:**

Gilbody S M, Song F, Eastwood A J, Sutton A. The causes, consequences and detection of publication bias in psychiatry. *Acta Psychiatrica Scandinavica*, 2000;102:241-249.

**Study objectives:**

To present a systematic overview of publication bias, including a summary of the methods used in its detection and minimization as illustrated in a case example (Cochrane review).

**Study methods:**

The Cochrane review used various approaches to identify studies investigating the efficacy of risperidone for schizophrenia. Extensive literature searches were conducted in MEDLINE, EMBASE, PsycLIT, BIOSIS, Current Contents and other electronic databases. Study authors and the manufacturer of risperidone were contacted for unpublished studies and missing data. Rosenthal's file drawer method was used to estimate the 'fail-safe N', the number of unpublished studies with a zero treatment effect required to overturn a significant result in the meta-analysis.

**Study results**

In the case study, 14 individual studies (29 publications) were identified through electronic database searches (n=10), grey literature (n=3) and contact with the manufacturer (n=1). One of the 4 studies with unpublished data was an unpublished trial and the remaining three were reported in conference abstracts, although the original authors had been contacted for further details. At least 13 unpublished studies with a zero treatment effect would be required to alter the significance of the result.

**Study limitations as noted by study authors:**

The authors did not note any limitations of their study.

**Study limitations noted by abstractor:**

The case example used to illustrate the problems of publication bias was somewhat limited in its approach to identifying unpublished studies. Other reviews may have been more informative.

**Key messages:**

Attempts to locate unpublished information through conference abstracts and personal contact met with limited success. The extent of publication bias in psychiatric research is unknown and the only real solution is a mandatory prospective register of clinical trials.

**Study reference:**

Glanville J. Searching key trials registers – best strategies. Presentation during a panel session. HTAi conference, Bilbao, Spain, June 25-27, 2012.

**Study objectives:**

This abstract is based on slides of a conference presentation.

To assess the evidence for which trials registers should be searched; what the strengths and weaknesses are of the main registers from a search perspective; what the key considerations are when searching registers in order not to miss studies.

To explore two aspects of retrieval from the International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov: does varying the sensitivity of the strategy assist with identifying relevant studies; does using the basic or advanced search options assist with improving sensitivity or precision?

**Study methods:**

Included studies in eight recently updated Cochrane Reviews were matched to trial records in ICTRP and/or ClinicalTrials.gov. The systematic review search strategies were re-run or adapted to find the identified studies in each register. The yield of the individual search strategies in ICTRP and/or ClinicalTrials.gov was assessed and the value of using the basic and advanced search options in those registers was explored.

**Study results:**

Two of the eight reviews had no matching trial records in either ClinicalTrials.gov or ICTRP. Between 0% and 54.5% of included studies had matching trial records. Of 6 reviews with trial records, more unique trials were identified in ICTRP than ClinicalTrials.gov in 3/6 reviews. The author noted that the presence of records within databases did not mean that search strategies could retrieve those records.

With respect to use of the basic versus the advanced interface for ICTRP and ClinicalTrials.gov respectively the test strategies seemed to indicate that the advanced search in ClinicalTrials.gov offered improved precision without loss of sensitivity. However, the advanced search in ICTRP did not offer improvements in precision and also does not offer the download option.

**Study limitations as noted by study authors:**

Low percentages of included studies could be identified (using 'known item searching') in either register.

**Study limitations noted by abstractor:**

This is a relatively small study focussing on the included trials from eight recently updated Cochrane Reviews and may not be generalizable to other health care topics, other Cochrane or non-Cochrane reviews or searches conducted in ClinicalTrials.gov or the ICTRP for other purposes.

**Key messages:**

Searching for intervention AND condition seemed the most reliable approach for achieving 100% sensitivity. A highly sensitive approach did not seem generally to be required. Using the advanced interface in ClinicalTrials.gov improved precision but appeared to offer no advantage in ICTRP and search results could not be downloaded from ICTRP using the advanced interface. Due to differences in retrievability and functionality, both resources should be searched.

**Study reference:**

Golder S, Loke Y, McIntosh H M. Poor reporting and inadequate searches were apparent in systematic reviews of adverse effects. *Journal of Clinical Epidemiology*, 2008;61:440-448.

**Study objectives:**

To survey the methods used to identify relevant studies in existing systematic reviews of adverse effects. The analysis presented was conducted as part of a larger survey (Golder S, Loke Y, McIntosh H. *BMC Med Res Methodol* 2006;6:3).

**Study methods:**

The Cochrane Database of Systematic Reviews (CDSR; The Cochrane Library, Issue 2: 2005) and the Database of Abstracts of Reviews of Effects (DARE; CRD Website, April 2005) were searched for relevant systematic reviews published since 1994. Data on how the review authors identified information on adverse effects was extracted, in particular the databases searched, the interfaces, and other sources or approaches used.

**Study results:**

Of the 277 reviews that met the inclusion criteria, 269 (97%) reported the methods used to identify relevant studies, five did not, and three provided limited details. All but three reviews searched bibliographic databases, with MEDLINE being the most frequently reported (93.9%). At least one additional method of identifying information was reported in 240 reviews (88%), of which reference list checking was the most frequent (76.2%). Other sources or approaches used to find grey literature and unpublished data were expert contact (22.4%), industry data (13.7%), hand-searching (11.6%), textbooks/bulletins (7.6%), personal files (6.9%), conference reports (6.9%), surveillance data (5.1%), the Internet (2.5%), Dissertation Abstracts (2.5%) and SIGLE (<1%).

Relatively few reviews (14%) attempted to solicit information from pharmaceutical companies. Five reviews searched for ongoing studies in the National Research Register (4 reviews), ClinicalTrials.gov (2 reviews) and / or the National Institutes of Health Website (1 review). The authors stated that most Cochrane Reviews use specialist registers that typically include extensive database searches and hand-searches of journals, thus the reported number of sources searched was likely underestimated. Where possible, the study results were compared with those of other researchers.

**Study limitations as noted by study authors:**

The sample of reviews included in this study is likely to be of a higher quality than a sample obtained from general bibliographic databases. It is difficult to compare the results with those of other studies as a comparative study on all types of systematic reviews of clinical effectiveness from CDSR and DARE has yet to be conducted.

**Study limitations noted by abstractor:**

The authors have already highlighted the main limitations of their study. Some of the results appear to have been discussed under several headings; this makes it difficult to assess the various sources of unpublished and grey literature.

**Key messages:**

There is a wide range of approaches to identifying unpublished information and grey literature, ranging from personal communication to specialist databases. A formal evaluation of these resources is needed.:



**Study reference:**

Golder S, Loke Y. Search strategies to identify information on adverse effects: a systematic review. *Journal of the Medical Library Association*, 2009;97(2):84-92.

**Study objectives:**

To evaluate studies of electronic database search strategies designed to retrieve adverse effects data for systematic reviews.

**Study methods:**

Searches were conducted in 10 electronic databases in 2007, with updates conducted in 2008: MEDLINE, MEDLINE In Process, EMBASE, CDSR, CMR, DARE, HTA, HMIC, Index to Theses and LISTA. Eight key journals in librarianship, drug safety and research methodology were hand-searched for articles not indexed or easily identifiable in electronic databases. Sources of unpublished material included five conference proceedings, two evidence-based web sources (the Agency for Healthcare Research and Quality (AHRQ) and the Health Technology Assessment database (via the Centre for Reviews and Dissemination)), and contact with experts (Cochrane Adverse Effects Methods Group). The bibliographies of all eligible articles were checked and citation searches were conducted using ISI Web of Knowledge. No date or language restrictions were applied. Eligible studies had to include a comparative evaluation of the different search strategies used to identify relevant studies. The methodological quality of the included studies was assessed.

**Study results:**

Twenty studies of potential relevance were identified, of which three were included in this review. Two were published as full-text papers and one was a conference abstract in limited detail. The source of the reference sample of records was electronic database searches in one study and systematic reviews (various combinations of electronic databases, reference checks, expert contact and industry submissions) in the other two studies. All three studies reported high sensitivity ( $\geq 95\%$ ) but precision was poor in the two studies that reported it ( $< 3\%$ ).

**Study limitations as noted by study authors:**

Relevant studies might have been missed given the difficulty in searching electronic databases for methodology papers. There was a potential for bias since one of the authors of this review had authored one of the included studies.

**Study limitations noted by abstractor:**

This abstract focused on the evaluation of strategies for electronic database searches. The amount of unpublished material retrieved was not reported, and studies missed by the

search strategies were not elaborated on. The appropriateness of the reference set of records deserves discussion.

**Key messages:**

Electronic searching should be supplemented with approaches such as reference checking, citation searching, expert contact and industry submissions. These approaches are invaluable when compiling reference set of records for evaluations of search strategies.

**Study reference:**

Golder S, Loke Y K. Sources of information on adverse effects: a systematic review. *Health Information and Libraries Journal*, 2010;27:176-190.

**Study objectives:**

To identify and summarise studies that have evaluated different sources of information on the adverse effects of healthcare interventions.

**Study methods:**

Searches were conducted in 10 electronic databases in 2007 and updated in 2009: MEDLINE, MEDLINE In Process, EMBASE, CDSR, CMR, DARE, HTA, HMIC, Index to Theses and LISTA. In addition, selected key journals, conference proceedings and websites were hand-searched, references were checked, and citation searches were conducted using ISI Web of Knowledge. Key experts in the field of adverse events were contacted for further information. No date or language restrictions were applied. Eligible studies had to include a comparative evaluation of the different search strategies used to identify relevant studies. The methodological quality of the included studies was assessed.

**Study results:**

Nineteen of the 56 studies of potential relevance were included in this review. Twelve compared data sources by the number of relevant references identified. Bibliographic databases were the main information sources in the majority of these studies, with MEDLINE and EMBASE the most frequently reported. Non-database sources reviewed were hand-searching, reference checking, internet sites, personal communication, drug monographs, bulletins, industry submissions, the US Food and Drug Administration website, and an in-house company database. The majority retrieved relevant references but the rate of retrieval was often not recorded, in particular for drug monographs. Few of the non-database sources were involved in more than one methodological evaluation. Industry submissions and a company database were shown variously to provide unique references, more information on adverse effects, and identify fewer relevant records than only MEDLINE and EMBASE. The in-house database retrieved a high proportion of conference abstracts.

The authors noted that electronic and paper information sources are susceptible to content change, closure/out-of-print, or the emergence of new information sources. Thus, any studies assessing the importance of these sources are likely to become quickly out-dated. In addition, there are many other potential sources of data which were not fully explored: database gateways (e.g. TOXICOLOGY), sources of conference proceedings, sources of post-marketing surveillance data (e.g. Vigibase), industry clinical trial registries, specialist bulletins, textbooks and journals, discussion web sites, informal communication with authors and citation searching

**Study limitations as noted by study authors:**

There appeared to be a lack of recent research in this area. Direct comparisons of studies were difficult because of the inconsistency in outcome measures and the use of different information sources.

**Study limitations noted by abstractor:**

The review did not specifically report on the identification and retrieval rate of unpublished material. A summary table listing each source, the number of studies using it, and the number of retrieved relevant studies (published/unpublished) would have been helpful. There is a potential for bias since one of the authors of this review had authored one of the included studies.

**Key messages:**

Next to MEDLINE and EMBASE, Derwent Drug File, industry submissions and company databases are potentially the most valuable sources of published and unpublished studies of adverse effects. The current value of different information sources needs evaluation.

**Study reference:**

Golder S, Loke Y K, Bland, M. Unpublished data can be of value in systematic reviews of adverse effects: methodological overview. *Journal of Clinical Epidemiology*, 2010;63:1071-1081.

**Study objectives:**

To assess the impact of including unpublished data on adverse effects in systematic reviews.

**Study methods:**

Broad non-specific searches were conducted in 10 electronic databases in 2007 and updated in 2009: MEDLINE, MEDLINE In Process, EMBASE, CDSR, CMR, DARE, HTA, HMIC, Index to Theses and LISTA. The reference lists of eligible articles were checked and citation searches were conducted using ISI Web of Knowledge. In addition, selected key journals, conference proceedings and websites were hand-searched, and other researchers in the field were contacted. Eligible articles had to review cohorts of published and unpublished studies and compare the quantitative reporting of adverse effects. 'Published' articles were considered to be manuscripts found within peer-reviewed journals. The validity of the included evaluations was assessed.

**Study results:**

Ten methodological evaluations were included in this review, of which only two provided clear definitions of what defined 'unpublished' data. Published data were typically retrieved from electronic databases and reference checking, whilst unpublished data were mainly obtained from regulatory authorities. However, one study identified published trials through licensing applications, and two studies obtained unpublished data by either contacting the manufacturer or through health professionals, the public and medical records. One study found that adverse effects were reported more often in unpublished trials submitted to a regulatory authority. Two studies found a greater proportion of unpublished case reports, one study found a higher proportion of published cases, and a fourth study suggested that publication of case reports could be topic dependent.

Three studies looked for differences in quality between published and unpublished studies, one of which found the completeness of reporting of individual case reports varied according to the source of the data: published case reports and reports from clinical trials provided the most information, whilst MEDWATCH reports were the least complete. The authors noted that other studies have reported problems in using unpublished data from regulatory agencies. Five studies evaluated the impact of the addition of unpublished data and found no significant change in the relative risk estimates for adverse effects.

The authors commented that the sources used in each methodological evaluation to retrieve published and unpublished data may have influenced the results.

**Study limitations as noted by study authors:**

Review articles may have been missed where published and unpublished data were not the primary outcome. The meta-analysis should be interpreted with caution given the diverse range of data sources used. Conclusions on the impact of other categories of literature distinct from journal articles (e.g. conference proceedings, regulatory reports, websites) could not be drawn. There is the potential for reporting or publication bias if comparisons failed to find any significant differences between published and unpublished studies.

**Study limitations noted by abstractor:**

There is a potential for bias since one of the authors of this review had authored one of the included studies. A table summarising the numbers of published and unpublished reports of adverse effects, according to source, would have been helpful.

**Key messages:**

Unpublished studies may provide additional information on adverse effects, over and above that reported in published studies. Regulatory authorities are a major source of unpublished data. Unpublished case reports, which may provide a different outlook on the relative frequencies of specific adverse effects, are of particular importance.

**Study reference:**

Golder, S., & Loke, Y. The usefulness of different information sources for retrieving adverse effects data for a systematic review. Poster presentation at the 19th Cochrane Colloquium; 2011 Oct 19-22; Madrid, Spain [abstract].

**Study objectives:**

This abstract is based on the abstract of a conference presentation.

To determine the relative value and contribution of searching different sources to identify data on adverse effects during a systematic review of thiazolidinedione-related fractures in patients with type 2 diabetes mellitus.

**Study methods:**

Over 20 different information sources were searched. These included MEDLINE, EMBASE, Derwent Drug File, selected Internet sources and reference texts. For each relevant record, it was recorded how it was identified and whether it was indexed/available in MEDLINE at the time of searching. The sensitivity, precision and number needed to read of different search approaches and combinations of searches were assessed.

**Study results:**

The majority of the 58 references included in the review were retrieved using the Science Citation Index (35), followed by BIOSIS Previews (27) and EMBASE (23). The precision of the searches ranged from 0.88% (Scirus) to 41.67% (CENTRAL). At a minimum, all references could be retrieved by searching a combination of the GlaxoSmithKline (GSK) website, Science Citation Index, EMBASE, BIOSIS Previews, British Library Direct, Medscape DrugInfo, hand-searching and reference checking, American Hospital Formulary Service (AHFS) First, and Thomson Reuters Integrity or Conference Papers Index. The numbers needed to read were high with BIOSIS Previews and Medscape Drug Info, even when searched after other sources and with duplicates removed.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

Details of the type of studies sought and identified (e.g. published/unpublished) were not reported. It is unclear whether the degree of overlap between the different sources was evaluated.

**Key messages:**

Several different sources must to be searched to identify all relevant references for a review; MEDLINE is not an essential source.



**Study reference:**

Golder S, Mason A, Spilsbury K. Systematic searches for the effectiveness of respite care. *Journal of the Medical Library Association*, 2008;96(2):147-152.

**Study objectives:**

To examine which resources yielded references used in a recent systematic review of the effectiveness of respite care for carers of frail older people.

**Study methods:**

The original review searched a variety of databases with medical and/or social care content, in addition to databases of different types of studies (e.g. economic evaluations, systematic reviews), conference proceedings (Inside Conferences, ISI Proceedings), grey literature (Disseration Abstracts, Index to Theses, SIGLE) and ongoing and recently completed research (ClinicalTrials.gov, ESRC SocietyToday, MetaRegister of Controlled Trials, NRR, ReFER). References were checked, citations of key papers were searched, and authors and organizations were contacted.

**Study results:**

The initial searches retrieved 13,092 unique records of evidence, the majority from PsycInfo, MEDLINE and AgeLine. In addition, 3,768 records (before duplication) of ongoing studies were identified, of which the majority were retrieved from the NRR (2154) followed by ESRC SocietyToday (1,204), MetaRegister of Controlled Trials (254), ReFER (254) and ClinicalTrials.gov (20). Searches of conference proceedings databases identified around 50 to 150 potential records, whilst grey literature sources yielded 63 (SIGLE), 25 (Index to Thesis) and 20 (Dissertation Abstracts) records apiece.

The majority of the included references (37/44) were published as journal articles. Of the remaining references, three were books or book chapters, two were dissertations, one was a report and one was a conference abstract. Three of these included references (1 book chapter, 1 conference abstract, 1 dissertation) were identified only through reference checking or contact with authors.

**Study limitations as noted by study authors:**

The current study is limited to one systematic review, so the generalizability of the results has not been evaluated for other systematic reviews. The analysis did not consider the impact on the results of the systematic review if not all studies had been identified.

**Study limitations noted by abstractor:**

This was a retrospective analysis of the search methods used in a particular review. It sought to establish the most effective combination of sources to identify all relevant studies.

**Key messages:**

Databases of ongoing research, grey literature and conference proceedings are a good source of potentially relevant studies. However, reference checking and contact with authors may be more successful in identifying unique studies of relevance to a particular review topic. Search strategies should encompass a range of different sources.

**Study reference:**

Goss C, Roberts I, DiGiuseppi C. The utility for identification of best available evidence of a register of controlled studies that evaluate interventions to prevent alcohol-impaired driving. Poster presentation at the Joint Cochrane and Campbell Colloquium; 2010 Oct 18-22; Keystone, Col. *Injury Prevention*, 2010;16(Suppl 1):A162.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To evaluate whether a register of controlled studies can facilitate the conduct of systematic reviews.

**Study methods:**

The authors compiled a register of randomised, quasi-randomised, controlled before-after and interrupted time series studies of interventions to prevent alcohol-impaired driving. Studies were identified through searches of 11 bibliographic databases, hand-searches of conference proceedings, and contact with 97 government agencies. The utility of the register was tested against three published reviews. In addition, the full reports of unmatched register citations were examined against the reviews' inclusion criteria to detect studies not cited in the reviews. The comprehensiveness, added value and usefulness of the register for review updates were assessed.

**Study results:**

Compared with the reviews, the register included 16 (73%) of the 22 review citations that had eligible study designs, matching exact citations or related/follow-up studies. Agreement was 100% for designated-driver programs, 73% for school-based programs and 60% for mass media campaigns. The register contained 15 (83%) of the 18 journal articles, but only one (25%) of the 4 government/technical reports. Of the 764 unmatched register citations, three were found to be eligible studies of school-based programmes that had not been previously cited; this increased the total identified, relevant studies by 14%. Four studies completed since the reviews had been conducted were eligible for review updates. Quality assessments are ongoing.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

The government agencies contacted were not described, and the yields of different approaches to identify trials were not reported. The register included full-text reports but the overall proportion of unpublished studies was unclear.

**Key messages:**

Trials registers are important sources of evidence for systematic reviews but may not be the best source of government/technical reports and grey literature. The authors' register is regularly updated and accessible through the Cochrane Injury Group's specialised register.

**Study reference:**

Gotzsche P C, Jorgensen A W. Opening up data at the European Medicines Agency. *BMJ*, 2011;342:d2686. doi:<http://dx.doi.org/10.1136/bmj.d2686>

**Study objectives:**

This abstract is based on a report of efforts made to gain access to unpublished trial reports from the European Medicines Agency (EMA).

**Study methods:**

On 29 June 2007, the EMA was asked to provide access to the clinical study reports and corresponding protocols for 15 placebo-controlled trials of two anti-obesity drugs, rimonabant and orlistat, for which the manufacturers had applied for marketing approval in the European Union. Over the following 3 years, numerous requests for information were made to the EMA, with arguments supporting the case for disclosure. An appeal was also made to the EMA's Executive Director. In the absence of any documents being released, a complaint was lodged with the European Ombudsman and he took up the case. Following inspection of the requested documents and subsequent recommendations, the Ombudsman issued a press release (7 Jun 2010) accusing the EMA of maladministration.

**Study results:**

It took over 3 years and much correspondence to gain access to reports held by the EMA. During this time, the EMA largely ignored the authors' arguments for releasing the data or restated their arguments for avoiding document disclosure. Such arguments included protection of commercial interests, no over-riding public interest, the administrative burden involved, and the worthlessness of the data once the EMA had redacted them. The EMA also failed to respond to the Ombudsman's letter before the deadlines ran out, but eventually reversed its stance following a press release in which they were accused of maladministration. The authors commented that the EMA should be promoting access to full information that will aid rational decision making, instead of impeding it. On 30 November 2010 the EMA declared it would widen public access to documents, including trial reports and protocols. The data requested from the EMA was finally received on 1 February 2011.

**Study limitations as noted by study authors:**

The authors did not note any limitations as their report described their experiences of trying to obtain unpublished trial reports.

**Study limitations noted by abstractor:**

This was a report of experiences rather than a formally designed study.

**Key messages:**

The process of gaining access to unpublished trial reports held by drug regulatory agencies is lengthy, testing, and not guaranteed of success. The authors recommend that the FDA and other drug regulatory agencies should follow the example of the EMA declaration in November 2010. Agencies should make all documents publicly available, ensure prompt access, and introduce electronic submissions from drug companies to reduce the administrative paperwork.

**Study reference :**

Hannigan G G. Identifying controlled clinical trials for systematic reviews requires searching multiple resources - and, even then, comprehensiveness is questionable. Evidence-Based Library and Information Practice, 2006;1:4.

**Study objectives:**

This abstract is based on an evidence summary of a published study (Crumley ET, Wiebe N, Cramer K, Klassen TP, Hartling L. Which resources should be used to identify RCT/CCTs for systematic reviews: A systematic review. BMC Medical Research Methodology 2005;5.24), for which a structured abstract is available.

To determine the value of searching different databases to identify randomized controlled trials (RCTs) and clinical controlled trials (CCTs) for systematic reviews.

**Study methods:**

Eligible studies were those that compared at least two different resources. Electronic searches were conducted in MEDLINE, EMBASE, CINAHL, ERIC, PsycINFO, Web of Science and the Cochrane Library to April 2004. Four journals were hand-searched from 1990 to 2004: Health Information & Libraries Journal (Health Libraries Review), Hypothesis, Journal of the Medical Library Association (Bulletin of the Medical Library Association), and Medical Reference Services Quarterly. In addition, all abstracts presented at Cochrane Colloquia from 1993 to 2003 were hand-searched, key authors were contacted via e-mail, and reference lists were screened.

**Study results:**

Sixty-four studies met the inclusion criteria. MEDLINE versus hand-searching (n=22) and MEDLINE versus MEDLINE plus hand-searching (n=12) were amongst the most common comparisons. Recall and precision varied substantially across comparisons. Recall was higher for trial registries versus reference standard (89%; range 84-95%) but was only evaluated in two studies and four comparisons. Precision was similarly high (96-97%) but was based on only one study with two comparisons. Forty-two studies reported reasons why the searches missed relevant trials. The most common reason was inadequate or inappropriate indexing.

**Study limitations as noted by study authors:**

The reviewer commented that the authors' conclusions are limited by the variable quality of the included studies and the small number of truly comparable studies. There is a hint of bias in that the authors recommend consultation with a librarian, despite the lack of direct comparisons between librarian and non-librarian authored searches and the lack of supporting evidence from subgroup analyses.

**Study limitations noted by abstractor:**

Unpublished studies were not specifically sought. The amount of unpublished material uncovered was not reported. However, this article represented a summary of the evidence presented in the original study.

**Key messages:**

No single resource results in particularly high recall or precision when searching for randomized controlled trials and controlled clinical trials. Reviewers should use multiple resources when searching for clinical trials to ensure they identify those studies missed from database searches because of indexing issues.



**Study reference:**

Hart, B. L., Lundh, A., & Bero, L. A. Adding unpublished Food and Drug Administration (FDA) data changes the results of meta-analyses. Poster presentation at the 19th Cochrane Colloquium; 2011 Oct 19-22; Madrid, Spain [abstract].

And

Hart B, Duke D. Effect of reporting bias on meta-analyses of drug trials: reanalysis of meta-analyses. *BMJ*. 2011;343:d7202.

**Study objectives:**

This abstract is based on an abstract of a conference presentation and a report reanalysing meta-analyses of drug trials.

To examine the effect of including unpublished US Food and Drug Administration (FDA) trial data on the results of published meta-analyses across a variety of drug classes.

**Study methods:**

PubMed, EMBASE and the Cochrane Library were searched in November 2010 for relevant meta-analyses of any of 24 drugs approved by the FDA between 2001 and 2002 that had previously identified unpublished outcome data. The authors compared the FDA's medical and statistical reviews of the submitted data from drug trials with published trial reports to identify the unpublished outcomes for each drug. Relevant data were extracted from FDA reviews and retrieved meta-analyses from relevant systematic reviews. Only one systematic review for each drug was included.

**Study results:**

No eligible systematic reviews were identified for 15 of the 24 drugs of interest. The remaining 9 drugs each had 1 or more corresponding meta-analyses (42 meta-analyses [41 efficacy outcomes and 1 safety outcome] identified in total from 9 systematic reviews).

The addition of the unpublished trial outcome data caused 46% of the meta-analyses of each efficacy outcome to estimate decreased efficacy of the drug. 7% of the unpublished outcome data estimated the same drug efficacy and 46% estimated increased drug efficacy. One meta-analysis with a harm outcome estimated an increase in harm from the drug when unpublished data were added to the meta-analysis.

**Study limitations as noted by study authors:**

The authors reported three study limitations. The authors commented that they did not conduct a review of all the safety data that was submitted to the FDA to identify unpublished data on harms. The authors identified selectively reported outcomes from efficacy trials

submitted to the FDA. The authors noted that they couldn't determine the overall effect of unpublished data on the safety of drugs or on the risk-benefit ratio of each included drug.

**Study limitations noted by abstractor:**

Key studies may have been missed as the reviewers only included studies published in English.

**Key messages:**

The study results suggest that the inclusion of unpublished trial data can affect the results of meta-analyses.

**Study reference:**

Hartley J. On requesting conference papers electronically. *Journal of Information Science*, 2004;30(5):475-479.

**Study objectives:**

To determine the success of obtaining conference papers by e-mail, and to compare the results with those found previously for obtaining reprints of published papers.

**Study methods:**

One hundred first authors, based in the USA or Canada, were asked to provide a copy of a conference paper they had presented to the American Educational Research Conference (April 2004) approximately 2 weeks earlier. Papers delivered to discussion groups were not sought. The authors/presenters were selected from subject areas of interest within the Conference Programme: mainly, Evaluation, Internet and Education, Learning Processes, Studying, Textbooks, and Writing. Each author was sent a personally addressed e-mail requesting just one paper. Fifty authors were also sent a list of the researcher's most recent publications. Reminders were e-mailed to non-responders after 3 weeks.

**Study results:**

The overall failure rate in contacting authors was 17%. Nine e-mail addresses provided in the Conference Programme did not work. The success rate in obtaining papers was 54% after 6 weeks: 46 papers were received after the initial request and 8 following a reminder. All of the papers were sent electronically and the majority arrived within one day. There was no significant difference between return rates for requests made with and without an accompanying list of publications. The majority of the papers received were original or more detailed papers, often full-length draft journal submissions, upon which the conference paper was based. Five authors referred to further publications on their website, three sent additional relevant papers, and one offered a copy of their dissertation. Many papers lacked the necessary information for them to be adequately cited in other publications.

**Study limitations as noted by study authors:**

The low success rate may be partly attributed to the reliance on e-mail addresses for correspondence. It is possible that sending a publication list with the request may have dissuaded some respondents.

**Study limitations noted by abstractor:**

The proportions of published, draft and unpublished manuscripts received were not reported.

**Key messages:**

E-mailed requests are of limited benefit in retrieving conference papers. Designated websites for conference proceedings would improve access to presented research. Papers often lack sufficient details to enable their correct citation in other publications.

**Study reference:**

Hausner E, Kaiser T. [Searching clinical trials registries: procedure and documentation]. Zeitschrift für Evidenz Fortbildung und Qualität im Gesundheitswesen, 2010;104(4):292–297.

**Study objectives:**

The paper is not in English and this abstract is based on the paper's abstract and the tables within the paper.

This paper describes the approach taken by the German Institute for Quality and Efficiency in Health Care (IQWiG) when searching for unpublished data in clinical trials registries.

**Study methods:**

The various types of clinical trials registries were described. Guidance was given on the choice of trials registries to be searched given their varied functionality. Aspects of the search procedure, screening and selection of records, and documentation process were discussed, along with issues that need particular attention.

**Study results:**

The four types of trial registries identified were national registers, company registers, disease-specific clinical trials registers and metaregisters. Examples of each were given. Trials registers described in more detail included ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform Search Portal (ICTRP), clinical trials registries of individual pharmaceutical companies and ClinicalStudyResults.org.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

This paper describes the process of searching for unpublished trials in clinical trials registries. It was not a formal evaluation of different resources.

**Key messages:**

Trials registers are a valuable source of unpublished information for systematic reviews.

**Study reference:**

Hayward, S., Brunton, G., Thomas, K., & Ciliska, D. Searching for the evidence: source, time and yield [abstract]. Second International Conference Scientific Basis of Health Services & Fifth Annual Cochrane Colloquium; 1997 Oct 8-12; Amsterdam, The Netherlands.

**Study objectives:**

This abstract is based on the abstract of a conference presentation.

To determine the effectiveness of methods used to identify articles for a systematic overview based on the search yield by source and the time taken.

**Study methods:**

The approaches used to identifying relevant articles included searches of electronic databases (online, network and CD ROM databases) and hand-searches of key journals and books and bibliographic references, and contact with key informants. A defined search strategy was used. The time taken for searching, retrieval, copying, travel and recording time was noted. The quality of the retrieved articles was assessed.

**Study results:**

The electronic databases searches yielded a higher proportion of quality articles than other sources, with one article retrieved every 1.07 minutes of searching. Time was mainly spent on defining the research question and refining the search strategy. Hand-searching was the most time consuming approach, with one article retrieved every 27.73 minutes of searching. It also delivered the highest proportion of poor quality articles. However, it did identify some references not retrieved through the database searches. Articles requested from the library were delivered within 20 minutes, regardless of the source.

**Study limitations as noted by study authors:**

The abstract did not note any limitations.

**Study limitations noted by abstractor:**

The abstract lacked details of methodology and results, in particular the number of records retrieved through the various approaches.

**Key messages:**

Hand-searching is time-consuming and yields more poor quality articles than other approaches, but can identify references not retrieved through electronic database searches.

The specificity of the research question and access to different resources may influence the degree and completeness of retrieval.

**Study reference:**

Helmer D, Savoie I, Green C, Kazanjian A. Evidence-based practice: extending the search to find material for the systematic review. *Bulletin of the Medical Library Association*, 2001;89(4):346-352.

**Study objectives:**

Some of the research described in this paper has been published elsewhere [Savoie I, Helmer D, Green C J, Kazanjian A. Beyond Medline: reducing bias through extended systematic review search. *International Journal of Technology Assessment in Health Care*, 2003;19(1):168–178.]: a structured abstract for this reference is also available.

To investigate the effectiveness of different systematic search methods, beyond searches of mainstream databases, used to identify randomized controlled trials for systematic reviews.

**Study methods:**

The authors prospectively monitored the search methods used to identify relevant trials in two different systematic review projects. Searches were conducted in four major databases (MEDLINE, Embase/Excerpta Medica (Embase), HealthStar, and Current Contents), databases focusing on complementary medicine (for the acupuncture review), and a variety of specialized databases including commercial databases, Web library catalogues, trials registries and Internet databases with free access. Other approaches used to identify additional relevant material and unpublished trials were hand-searching key journals (indexed and unindexed) and specialized-subject journals not indexed in MEDLINE, checking the reference lists of included studies, and personal communication with organizations and researchers.

**Study results:**

Overall, a total of 1,034 items were retrieved for the two systematic reviews. The extended systematic search methods yielded an additional 302 items (29.2%) to the 732 items (70.8%) identified from the major databases. The most effective of the extended methods was searching specialized databases, which yielded 96 citations (31.8%), followed by reference list checks (76 citations; 25.2%), personal communication (72 citations; 23.8%) and hand-searching (58 citations; 19.2%). The two review topics differed in some retrieval rates and types of document identified. Reference list scanning and hand-searching were equally effective in both projects.

**Study limitations as noted by study authors:**

Difficulties in acquiring the literature may have led to an underestimation of the effectiveness of extended search methods. Relative effectiveness of these methods is dependent on the



quality of the major database searches, which has not been formally evaluated. Overlap between the extended methods was not examined. The absence of abstracts for some items made it difficult to assess their relevance.

**Study limitations noted by abstractor:**

It was unclear whether the availability of the major databases, which governed the timeframe searched, would have impacted on the number of additional items recovered by the extended methods. The response rate for personal communication with organizations/researchers was not reported.

**Key messages:**

Extended approaches, in particular searching specialized databases, reference checks and personal communication, are effective tools for identifying unique published/unpublished items not found in major databases. There is a need to assess the impact of the quality of retrieved articles on the conclusions of systematic reviews.

**Study reference:**

Hemminki E. Study of information submitted by drug companies to licensing authorities. *BMJ*, 1980;280:833-836.

**Study objectives:**

To study the information submitted by drug companies to the Finnish and Swedish drug licensing authorities, in particular the overall number of clinical trials included, the proportion of unpublished trials and their value in comparison with published trials, and the use of such information in studying adverse effects.

**Study methods:**

The authors reviewed a random selection of licensing applications for psychotropic drugs in Finland and Sweden for the years 1965, 1970, 1974 and 1975, and for non-psychotropic drugs in Finland alone. All licensing applications were included, except those for changes in strength or formulation, or synonym preparations (for Sweden only). The analysis included all reports of clinical trials studying drug efficacy which were submitted before the final decision on licensing, subject to availability and time constraints (111 short summaries were excluded for Sweden). A report was defined as published if it had been published or accepted for publication in a journal article or book, or was a report of a meeting.

**Study results:**

Using data from all 4 years, the mean number of trials per application for psychotropic drugs was 8.7 in Finland (100 applications) and 23.1 in Sweden (32 applications). Of the 342 controlled trials in Finnish psychotropic drug applications, 177 (52%) had been published in a journal, 24 (7%) published elsewhere, 116 (34%) were unpublished, and 24 (7%) only had a summary available. The corresponding breakdown of the 225 controlled trials in Swedish applications was 88 (39%) published in journals, 16 (7%) published elsewhere, 99 (44%) unpublished and 23 (10%) with only a summary available. Unpublished reports of psychotropic drug trials typically provided more information on study methodology, patient exclusions and adverse effects than published reports.

**Study limitations as noted by study authors:**

The authors did not note any study limitations.

**Study limitations noted by abstractor:**

The authors appear to have categorized the publication status of the trials based only on information provided in the licensing application. Checks for trial publication following the licensing application were not mentioned. The authors commented that the results of this

study raise questions about the waste of clinical and research resources used since many of the trials were unlikely to supply valuable information given their design.

**Key messages:**

There is a considerable amount of valuable, unpublished data on the files of Finnish and Swedish licensing authorities, which appears comparable in quality to published data. Even more information may be undisclosed in countries where licensing authorities require more documentation. Public disclosure of trial reports submitted in licensing applications is needed.

**Study reference:**

Hersh, W., & Price, S. Identifying randomized controlled trials in conference proceedings abstracts [abstract]. Sixth International Cochrane Colloquium; 1998 Oct 22-26; Baltimore, MD, USA.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To identify search strategies for identifying randomized controlled trials (RCTs) from conference proceedings abstracts.

**Study methods:**

The authors used various search strategies to retrieve potential RCTs from conference abstracts, using a database they had created from the titles and abstracts of records obtained from the US National Library of Medicine (1991 to 1996) for a gold standard series of conference abstracts. The retrieved abstracts were reviewed to identify RCTs.

The gold standard comprised a subset of the AIDSLINE database with citations from the International Conference on AIDS, which had been coded for RCT status.

The search strategies were based on those known to be effective in past investigations. Recall and precision were measured for each search strategy.

**Study results:**

The subset of records contained a total of 21,575 citations, of which 345 were coded as an RCT. Only 274 (79.4%) of these were likely RCTs. A review of 240 retrieved citations that were not classified as RCTs showed only one to be an RCT. The authors took this to indicate that indexers were more likely to assign an RCT code for a non-RCT than they were to not assign the RCT code when it was warranted.

The identification of RCTs was hampered by inaccurate descriptions of the study design and poor reporting in the abstracts.

There was a trade-off between recall and precision for the various search strategies.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

The abstract lacked clarity and interpretation of the results was hampered by their presentation in the downloaded version.

**Key messages:**

Conference abstracts are a potentially important source of RCTs but often suffer from poor or inaccurate descriptions of study design. Strategies developed to identify RCTs from conference abstracts may offer very high recall at the expense of low precision.

**Study reference:**

Hetherington J, Dickersin K, Chalmers I, Meinert C L. Retrospective and prospective identification of unpublished controlled trials: lessons from a survey of obstetricians and pediatricians. *Pediatrics*, 1989;84(2):374–380.

**Study objectives:**

Some of the research described in this paper has been published elsewhere [Enkin M, Hetherington J. (1996). Collecting the evidence systematically. Ensuring that it is complete and up-to-date. *International Journal of Technology Assessment in Health Care*, 1996;12(2):276–279.]: a structured abstract for this reference is also available.

To elicit information about unpublished trials in perinatal medicine through a formal survey of obstetricians and paediatricians, and thus establish the basis for identifying publication bias where it exists.

**Study methods:**

The authors surveyed 42,000 obstetricians and paediatricians in 18 countries, from the second half of 1986 to early 1987. These countries had been responsible for more than 90% of the published reports of perinatal trials registered in the Oxford Database of Perinatal Trials. Depending on the country, the survey was either comprehensive (i.e. directed at both retired and active clinicians) or targeted at those known to be involved in clinical research.

An initial letter outlining the survey, with a tear-off reply section to indicate willingness to participate, was sent either directly to the clinician or included in a regular mailing to organization members. Attempts to maximize response included publicizing the survey in a newsletter. Respondents were sent a questionnaire and letter requesting unpublished trial information. The authors searched the Oxford Database of Perinatal Trials for any published trials the respondent had co-authored, and either sent a list of these with the letter or mentioned if none had been found. A second letter and questionnaire were sent in the absence of reply within 6 months. Investigators in the USA and Canada who did not respond to the second mailing were contacted by telephone, and the questionnaire completed over the phone.

**Study results:**

Clinicians in 17 countries were willing to provide details of 481 unpublished studies. The yield per 100 letters was less for comprehensive surveys (0 to 5.5) than for targeted surveys (5.8 to 51.6). Of the 481 follow-up questionnaires, 453 were completed and returned (response rate 94.1%). Fifty-eight responses did not meet the definition of a controlled trial, thus 395 questionnaires were analysed.

The response rates for completed questionnaires ranged from 0% in two countries to 100% in seven countries. More than 80% of the unpublished trials were notified by respondents in the UK and Ireland (n=146), the USA (n=137), and Canada (n=43). Of the 395 trials, 143 (36.2%) were completed, 193 (48.9%) were ongoing and 59 (14.9%) were expecting to recruit in the near future.

The authors commented that the unpublished trials appear to have yielded results considered disappointing by the investigators.

**Study limitations as noted by study authors:**

The authors recognized that their ratio of unpublished to published trials between 1940 and the end of 1984 was most likely a substantial underestimate. They were also aware of methodologically sound trials that had not been notified to them.

**Study limitations noted by abstractor:**

The authors did not comment on the overall response to the initial mailings, how many letters had reached the recipient or had been returned undelivered, or whether any negative responses had been received.

**Key messages:**

Obtaining details of unpublished trials through contact with trial investigators relies heavily on their willingness to share results. Prospective trial registration is needed to address this and also publication bias arising from non-publication of results considered 'disappointing' or 'unmemorable.'

**Study reference:**

Honest H, Bachmann L M, Khan K. Electronic searching of the literature for systematic reviews of screening and diagnostic tests for preterm birth. *European Journal of Obstetrics, Gynecology, & Reproductive Biology*, 2003;107:19-23.

**Study objectives:**

To describe a case study of electronic searching for a systematic review of accuracy studies evaluating all tests for predicting preterm birth.

**Study methods:**

BIOSIS, EMBASE, MEDLINE, Pascal, SciSearch, DARE, Conference Papers, Medion, the National Research Register, the Cochrane Controlled Trials Register and the Cochrane Database of Systematic Reviews were searched electronically for potentially relevant studies. The reference lists of review articles were checked for additional citations. No language restrictions were applied.

**Study results:**

All stages of the search process, including development, and information management were described. Only 3333 of the deduplicated 21,221 citations were considered potentially relevant to the review question. These reported on 19 different diagnostic tests. The National Research Register yielded 6 potentially relevant records out of 107 records identified (90 excluding duplicates). Eight conference papers were identified, all of which were relevant and not duplicated elsewhere.

**Study limitations as noted by study authors:**

The authors did not note any limitations of their study.

**Study limitations noted by abstractor:**

Attempts to identify unpublished studies and grey literature were limited.

**Key messages:**

Searching databases of current research and conference papers and checking reference lists may uncover relevant unpublished studies and grey literature not detected through other electronic database searches. It is feasible to conduct broad and thorough searches for systematic reviews with multiple questions by careful consideration of the search process and information management.



**Study reference:**

Hooft, L., Van Enst, W. A., & Scholten, R. Extending the search to find ongoing and unpublished trials - a survey of methods and results of Cochrane reviews. Oral presentation at the Joint Cochrane and Campbell Colloquium; 2010 Oct 18-22; Keystone, Colorado, USA [abstract].

**Study objectives:**

This abstract is based on the abstract of a conference presentation.

Some of the research described in this paper has been published elsewhere [Van Enst W A, Scholten R J, Hooft L. Identification of additional trials in prospective trial registers for Cochrane systematic reviews. PLoS ONE [Electronic Resource], 2012;7(8):e42812.]; a structured abstract for this reference is also available.

To explore the extent to which Cochrane reviewers search online clinical trial registries for ongoing and unpublished studies, how they report the search results, and the potential impact these have on the results of the review.

**Study methods:**

The authors retrieved all reviews for which the protocol was first published in The Cochrane Database of Systematic Reviews 2008. Data relevant to searches for ongoing studies, and the reporting and impact of the results on the author's conclusion, were extracted.

**Study results:**

Only Issue 4, 2008 of The Cochrane Library had been assessed at the time of this abstract. Of the 40 reviews identified, 31 (77.5%) had searched for ongoing studies. The most widely used approach was hand-searching conference abstracts (50%), followed by expert contact (42.5%) and online clinical trial registries (25%). Four reviews identified additional studies by searching for ongoing studies. Only one reviewer mentioned that not finding any unpublished studies could give rise to bias. Although the WHO ICTRP Search Portal enables 10 registries to be searched simultaneously, it was searched substantially less often than ClinicalTrials.gov (30% versus 70%).

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

Only the results of 40 of all 179 identified reviews were reported in this abstract.

**Key messages:**

Conference abstracts and expert contact are used most often to identify ongoing studies. The value of ongoing trials registries, in particular for reducing publication bias, has yet to be fully recognised; the majority of Cochrane reviews did not search this resource for ongoing and unpublished trials. More guidance in identifying and addressing ongoing and unpublished trials is needed.

**Study reference:**

Hooft, L., Weber, E., Hamelinck, V., & Offringa, M. Access to ongoing paediatric drug trials in the Netherlands. Poster presentation at the 19th Cochrane Colloquium; 2011 Oct 19-22; Madrid, Spain [abstract].

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To determine the accessibility and ease of searching for ongoing paediatric trial data, and to determine how many retrospective clinical trial registers include paediatric drug trials.

**Study methods:**

Paediatricians and Medical-Ethical Review Boards of all eight paediatric University Medical Centres in the Netherlands were asked to provide a list of all known paediatric drug trials that were planned or ongoing between September 2005 and December 2008. In addition, prospective trial registers were searched through the WHO Search Portal of the International Clinical Trial Registry Platform (ICTRP) for Dutch paediatric drug trials.

**Study results:**

Contacts in the field yielded 172 paediatric drug trials, 97 (56%) of which had been registered prospectively. The WHO Search Portal yielded 299 Dutch paediatric drug trials, with a low number needed to screen (1.2). The majority of these trials (70%) were registered in ClinicalTrials.gov, followed by the Netherlands Trial Register (25%) and ISRCTN.org (5%). However, 17% of trials registered in the Netherlands Trial Register were not identified through the WHO Search Portal.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

There are insufficient details in the abstract to comment on any likely limitations of the study.

**Key messages:**

Many ongoing paediatric drug trials are not in the public domain. Current search tools for ongoing trials differ in their sensitivity. ClinicalTrials.gov is the best source of those trials that have been registered. The WHO Portal is easy to use.

**Study reference:**

Hopewell S. Assessing the impact of abstracts from the Thoracic Society of Australia and New Zealand in Cochrane reviews. *Respirology*, 2003;8:509-512.

**Study objectives:**

To assess the potential impact of including trials, reported in conference abstracts from the Thoracic Society of Australia and New Zealand, in Cochrane reviews.

**Study methods:**

Abstracts from the Thoracic Society of Australia and New Zealand, published in the Australian and New Zealand Journal of Medicine from 1980 to 1998 were hand-searched to identify all reports of randomized trials. The Cochrane Controlled Trials Register (Issue 1, 2002) and PubMed were also searched to establish whether any identified trials had been published in full. The Cochrane Database of Systematic Reviews (Issue 1, 2002) was then searched for each trial reported in a conference abstract, in order to find those Cochrane reviews in which the conference abstract could potentially be included.

**Study results:**

A total of 187 randomized trials were identified from conference abstracts, of which 101 (54%) had been published in full and 86 (46%) remained unpublished. Possible Cochrane reviews were identified for 28 published trials and 14 unpublished trials; no reviews were identified for the remaining 72 trials.

Twenty-four trials had been included in the possible Cochrane reviews, of which 22 were referenced with the full publication details and two were referenced as reported in the conference abstract. Three of the remaining 12 unpublished trials met the eligibility criteria for inclusion in a review.

The authors highlighted the poor reporting of methodological quality in trials reported in conference abstracts.

**Study limitations as noted by study authors:**

The study is based on a relatively small sample of trials within a specific area of healthcare, therefore the results of this study may not be the same across other areas of healthcare.

**Study limitations noted by abstractor:**

No other limitations noted.

**Key messages:**

Conference abstracts are a useful source of unpublished randomized trials for consideration in systematic reviews. However, improved reporting of conference abstracts is needed.

**Study reference:**

Hopewell, S., MacKinnon, L., & Clarke, M. Conference abstracts that report possible" randomized trials - are they worth finding? [abstract]. XI Cochrane Colloquium: Evidence, Health Care and Culture; 2003 Oct 26-31; Barcelona, Spain.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To assess whether conference abstracts designated as 'possible' randomized trials are truly randomized trials.

**Study methods:**

The authors read all abstracts published at the American Society of Clinical Oncology conference in 1992 to identify reports of randomized trials. The full publications of those deemed 'possible' trials were then sought by searching CENTRAL and PubMed, to assess whether they were actually randomized trials.

**Study results:**

Of the 1471 abstracts, 22 were considered 'possible' trials.

Eleven abstracts were based on a trial, which might be randomized. Full publications were identified for five of these trials, and three were found to be randomized.

Seven abstracts mentioned trials that might be randomized. However, although they contained details of 14 'possible' trials, they were not the main focus of the abstract. Full publications were identified for 11 of the 14 trials, and eight were found to be randomized. Suggestions that a trial might be randomized, was being undertaken, or should be undertaken, were made in three abstracts. No publications were identified.

One abstract used the terminology 'randomly selected', but although this trial had been published in full it was not a randomized trial.

Less than half of the trials mentioned in the abstracts were unpublished (12/29).

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

The dates of the database searches were not reported; research presented at conferences may take some time to reach full publication.

**Key messages:**

Conference abstracts often contain poor or inaccurate descriptions of their study designs. Searching conference abstracts for hints to randomized trials is difficult, but may detect unpublished trials not identified by other means.

**Study reference:**

Huynh, L., Scherer, R., Ervin, A., & Dickersin, K. Primary outcomes reported in abstracts and ClinicalTrials.gov - do they agree? Oral presentation at the 19th Cochrane Colloquium; 2011 Oct 19-22; Madrid, Spain [abstract].

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To compare primary outcomes described in conference abstracts with those reported in ClinicalTrials.gov and assess the relationship between primary outcome reporting and industry sponsorship.

**Study methods:**

Conference abstracts presented at meetings of the Association for Research in Vision and Ophthalmology from 2007 to 2009 were hand-searched for reports of randomized controlled trials with a valid ClinicalTrials.gov registration number. Data were extracted from both the abstract and the trials registry record for comparison purposes.

**Study results:**

Forty of the 152 eligible abstracts explicitly reported at least one primary outcome in the abstract and primary outcome field in the trials registry record. Eighteen per cent (14/80) of primary outcomes were reported in both the abstract and ClinicalTrials.gov, while 34% (27/80) of primary outcomes reported in the abstract were either not reported or were considered secondary outcomes in ClinicalTrials.gov. The abstract and trials registry record differed in the information reported in 49% (39/80).

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

It was unclear whether any of the trials had been published in full and whether this could have impacted on the level of detail reported in the trials registry record.

**Key messages:**

Systematic reviewers should obtain outcome information from both conference abstracts and trials registry records since they may not contain the same information.



**Study reference:**

Jefferson T O, Demicheli V. Is vaccination against Hepatitis B efficient? A review of world literature. *Health Economics*, 1994;3:25-37.

**Study objectives:**

To identify, retrieve and analyse the available published and unpublished studies on the efficiency of the introduction of programmes of vaccination against hepatitis B.

**Study methods:**

Relevant studies were located through searches of MEDLINE and private databases, and contact with institutions known to be active in the field of vaccination economics. The bibliographies of retrieved articles were checked for additional studies. The first or corresponding authors of all studies included in the review were asked to identify any further published or unpublished material of relevance, and to say what effect their studies had on modifying policy decisions.

The authors chose to ignore abstracts and instead pay to retrieve the studies directly.

**Study results:**

The authors found that about 10% of studies contained an economic analysis that was not mentioned in the title, abstract or keywords. Ninety of the 116 papers retrieved were included in the review. A further four studies identified through correspondence were being completed and were unobtainable.

The included studies comprised 6 (6.6%) unpublished studies, 8 studies (8.8%) published in a congress booklet, and 76 studies (84.4%) published in 64 different journals or publications. The majority of the studies were found using MEDLINE (n=46) and a private database (n=40). The remaining four studies were identified through hand-searches of journals and correspondence with authors. Two of the unpublished studies were being submitted for publication.

The response rate was 31% (28/75) for letters sent to authors asking about the impact of their study on policy decisions. Forty-one studies were conducted with the aim to inform decision-making on whether or not to vaccinate, but only six of those authors who replied reported an impact of their study on some aspect of policy.

The authors commented that there did not appear to be any significant differences in the key variables between published and unpublished studies.

**Study limitations as noted by study authors:**

Attempts to pool the data were restricted to basic manipulations given the variation between the studies. The authors commented that the presence of a large number of unsolicited studies could explain the low decision-making impact of such studies, and that unpublished well-resourced studies with a high decision-making impact – potentially the most important studies - may exist.

**Study limitations noted by abstractor:**

Although the authors report that they found little evidence of publication bias, they did not search extensively for unpublished material. However, they did acknowledge the possible existence of unpublished studies with a high decision-making impact.

**Key messages:**

Congress abstracts and personal communication yielded further unpublished research, but there was a low response to specific requests for further details. Abstracts alone may be insufficient to identify economic analyses.

**Study reference:**

Jefferson T, Jones M, Doshi P, Del Mar C. Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis. *BMJ*, 2009;339:b5106.

**Study objectives:**

To update a 2005 Cochrane review that assessed the effects of neuraminidase inhibitors in preventing or ameliorating the symptoms of influenza, the transmission of influenza, and complications from influenza in healthy adults, and to estimate the frequency of adverse effects.

The authors are also responsible for a related review [Jefferson et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database of Systematic Reviews* 2012, Issue 1. Art. No.: CD008965. DOI: 10.1002/14651858.CD008965.pub3], for which a structured abstract is available.

**Study methods:**

The Cochrane Central Register of Controlled Trials (which contains the Acute Respiratory Infections Group's specialised register), MEDLINE and EMBASE were searched for relevant trials of the effectiveness and adverse effects of neuraminidase inhibitors, reported in any language, using different search dates and strategies for the two reviews. The references of other systematic reviews were checked. In addition, the authors also sought evidence on adverse effects by searching for pharmacovigilance data, submitting a Freedom of Information Act request to the US Food and Drug Administration (FDA) and accessing the websites of regulatory authorities. Authors and manufacturers were contacted in attempts to disentangle summarised or conflated data.

**Study results:**

Overall, 20 studies reported in 19 publications were included. These all appear to have been retrieved through database searches. Additional safety data were identified from the FDA adverse events reporting system, through a Freedom of Information Act request and directly from the FDA websites, and from the website of the Japanese Pharmaceuticals and Medical Devices Agency. Data from the European Medical Agency could not be accessed. Only three of five authors of studies on oseltamivir treatment who were contacted for additional data responded. None had original data and referred the reviewers to the manufacturer, who was unable to provide the data unconditionally in time for this reviews. The authors commented that they knew of eight unpublished studies on complications for which the data were inaccessible.

**Study limitations as noted by study authors:**

The authors commented that they were obliged to exclude a previous meta-analysis of published and unpublished studies because of 'unacceptable' conditions relating to the provision of the necessary unpublished data. Thus, there were insufficient studies to assess the presence of publication bias. The results from the meta-analyses involving hazard ratios should be viewed with caution because of the approximate methods used to extract estimates for each study.

**Study limitations noted by abstractor:**

Specific attempts to locate unpublished trials were not reported.

**Key messages:**

Regulatory authorities are useful sources of pharmacovigilance data, but access may be restricted. Manufacturers and authors may be unwilling to allow unconditional release of data.

**Study reference:**

Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database of Systematic Reviews* 2012, Issue 1. Art. No.:CD008965. DOI: 10.1002/14651858.CD008965.pub3.

**Study objectives:**

The authors are responsible for a related study: Jefferson T, Jones M, Doshi P, Del Mar C. Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis. *BMJ*, 2009;339:b5106, for which a structured abstract is also available.

To review clinical study reports of placebo-controlled randomised trials, regulatory comments and reviews ('regulatory information') of the effects of the neuroaminidase inhibitors, oseltamivir and zanamivir, for influenza in all age groups and appraise trial programmes, rather than single studies.

**Study methods:**

The authors attempted to construct a definitive list of all clinical studies of neuraminidase inhibitors for influenza within all relevant trials programmes.

The sources accessed included manufacturer submissions to regulators, drug product information sheets, published reviews, Health Technology Assessment documents, and public and manufacturers' registers (e.g. [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) and [www.roche-trials.com](http://www.roche-trials.com)). Regulatory documentation from the websites of the US Food and Drug Administration (FDA), European Medicines Agency (EMA), Roche, Japanese Pharmaceuticals and Medical Devices Agency, and the National Institute for Clinical Excellence (NICE) were also searched, and manufacturers, study authors and regulators were contacted for additional information. Traditional databases (the Cochrane Library, MEDLINE and EMBASE) and grey literature were searched for previously unknown trials. No publication or language restrictions were applied.

**Study results:**

A total of 185 studies were identified from unpublished sources; there were no additional studies from published sources. Clinical study reports provided sufficient information to assess 25 included studies. There were a further 42 studies with insufficient information in the clinical study, or unresolved discrepancies in their data.

Thousands of pages of regulatory documentation were obtained from the FDA and NICE. Eight clinical study reports were obtained from EMA in response to a freedom of information

request. Additional material (14,700 pages of further clinical study reports and 33 pages of regulators' comments) arrived after the search deadline.

The analysis of zanamivir evidence was postponed because the manufacturer had promised individual patient data. The manufacturer of oseltamivir supplied only partial clinical study reports and failed to respond to five requests (over 8 to 9 months) for the full reports and verification of the data.

The Japanese regulatory body (JHMLW) refused a request to disclose all documentation relating to the approval of oseltamivir, and the required clinical study reports were not forthcoming from the manufacturers. The ruling of a petition filed to the Osaka (Japan) District court to overturn the JMLW decision is awaited.

The authors commented that many of the clinical study reports used in the review were obtained via Freedom of Information requests, and that there were substantial problems with the design, conduct and availability of information from many trials.

#### **Study limitations as noted by study authors:**

None of the review authors had any experience of reviewing regulatory information. The conclusions drawn were limited by the incomplete data set. The authors had reservations about whether evidence from reviewing trial programmes is applicable to clinical practice.

#### **Study limitations noted by abstractor:**

It is difficult to ascertain the yield of clinical trials from each source, and any overlap between sources, given the vast quantity of information presented; a summarising table would have been helpful.

#### **Key messages:**

Reviewing huge quantities of complicated data and linked comments obtained from regulatory authorities is a complex and extremely time-consuming task. Manufacturers and regulatory bodies are not forthcoming in disclosing information and Freedom of Information requests are invariably needed to gain access. It is essential that all trials are registered on public trial registries, and that regulators disclose all information on a drug shortly after making a decision.

**Study reference:**

Jefferson T, Tyrrell D. Antivirals for the common cold. Cochrane Database of Systematic Reviews 2001, Issue 3. Art. No.: CD002743. DOI: 10.1002/14651858.CD002743.pub2.

**Study objectives:**

To identify, assemble, evaluate and (if possible) synthesise the results of published and unpublished randomised controlled trials of the effects of antivirals to prevent or minimise the impact of the common cold.

The editorial group responsible for this Cochrane review have since withdrawn it from publication (Issue 3, 2004), citing a lack of funding to update the review and that unpublished data used in the original review were inaccessible to both reviewers.

**Study methods:**

The Cochrane Library was searched for randomized controlled trials and published reviews from the Specialist Registers of the Cochrane Acute Respiratory Infections Group and the Cochrane Airways Group. Searches were also conducted in MEDLINE, OLDMEDLINE, EMBASE, Biological Abstracts, SCI and AMED. The bibliographies of all relevant reports and reviews were screened for additional studies. Studies reported in any language were eligible for inclusion.

The authors also systematically checked administrative records and trial results from the Medical Research Council's Common Cold Unit (CCU) for published and unpublished material, interviewed former scientific staff about missing data, read existing correspondence between CCU investigators and manufacturers, and reviewed the complete bibliography of the Unit's published research by the Unit's last director (DAJ Tyrrell). Principal investigators, researchers in the field and relevant manufacturers were also contacted to identify unpublished trials.

**Study results:**

The review included 241 studies, described in 230 reports, assessing the effects of, interferons, interferon-inducers and other antivirals. Only the unscreened yield of the electronic searches was presented. The manual search of 1006 CCU trial records yielded 243 studies, of which 192 were summary reports of antiviral trials (129 of antivirals and 63 of interferons). These mainly contributed unpublished data to the review. Correspondence with four authors resulted in the identification of a complete set of trial reports conducted by the relevant researchers, all of which had been published.

The authors noted in their discussion that attempts were currently underway to contact the trialists involved in three subtrials of the same study, to ascertain whether more data are available and the reason for not developing the assessment further.

**Study limitations as noted by study authors:**

The authors did not note any study limitations.

**Study limitations noted by abstractor:**

There was no summary of the number of published and unpublished studies contributing to the overall review and for each individual intervention. The authors did not comment on the ease or difficulty in obtaining information from the CCU.

**Key messages:**

The Medical Research Council's CCU appears to have considerable unpublished material buried within a vast amount of documentation, but access to it may be difficult and is not guaranteed. Contacting authors did not yield any unpublished data.



**Study reference:**

Johansen H K, Gotzsche P C. Problems in the design and reporting of trials of antifungal agents encountered during meta-analysis. JAMA, 1999;282(18):1752-1759.

**Study objectives:**

To describe the problems encountered whilst collecting data for a meta-analysis comparing fluconazole with amphotericin B in cancer patients with neutropenia.

**Study methods:**

MEDLINE (1966 to March 1998) and the Cochrane Library were searched for randomized trials. Letters, abstracts and unpublished trials were also reviewed to reduce the influence of publication bias. Additional published and unpublished trials were located by checking the reference lists of articles and reviews, scanning selected conference proceedings, and through contact with authors and drug manufacturers. The authors of the included trials were also contacted for additional or clarifying information about studies of antifungal agents.

**Study results:**

Eighteen relevant trials were identified. The authors of the 15 included trials (16 reports tabulated) were contacted predominantly by letter, but also by telephone, e-mail and in person at meetings. There were unexpected difficulties in obtaining responses to requests for information, and the response was less successful than in a previous study. Two authors responded to the first letter, one author answered questions after a second letter, and a fourth author responded on personal contact. In terms of identifying unpublished studies, one author commented that their trial was old and the data were with the drug manufacturer. However, it had in fact been published in French, as a response from another author highlighted, although it was not indexed by MEDLINE. It was not possible to obtain information on issues such as overlap between trials and it was possible that results from single-centre trials were included in multi-centre trial reports.

**Study limitations as noted by study authors:**

The authors acknowledged that bias in favour of fluconazole could be greater than what they found, and that readers should be sceptical about meta-analyses that contain unpublished data to which only the sponsor has access.

**Study limitations noted by abstractor:**

The overall number of unpublished trials identified was not reported.

**Key messages:**

Investigators, institutions and pharmaceutical companies were not forthcoming in providing information to researchers conducting meta-analyses.

**Study reference:**

Jorgensen, A. W., Tendal, B., & Gotzsche, P. C. The robustness of results on weight loss in trials on sibutramine - a comparison of results from unpublished study reports with the corresponding published reports. Oral presentation at the Joint Cochrane and Campbell Colloquium; 2010 Oct 18-22; Keystone,, Colorado.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To explore the robustness of the results in trials on weight loss by comparing results from unpublished reports submitted to the Danish Medicines Agency (DMA) and their corresponding published reports.

**Study methods:**

Published reports were obtained through electronic searches and by contacting the manufacturer. Unpublished reports were obtained from the DMA.

**Study results:**

Published reports were only identified for 9 (43%) of the 21 DMA reports included. The median number of datasets analysed was higher in the unpublished DMA reports than in the published reports, 4.5 versus 1. The DMA reports potentially contain more in-depth analyses. Final results were to be presented at the colloquium.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

The abstract lacked details of search methodology and also results, and only approximately half of the reports had been data extracted at the time of this abstract.

**Key messages:**

Less than half of the reports submitted to the DMA are published, often in less detail than in the original report.

**Study reference:**

Jull A, Wills M, Scoggins B, Rodgers A. Clinical trials in New Zealand - Treading water in the knowledge wave? *New Zealand Medical Journal*, 2005;118(1221).

**Study objectives:**

To quantify and describe the clinical trials in New Zealand between 1998 and 2003, and to identify those trials seeking approval in 2003 that were listed in trial registries.

**Study methods:**

Annual reports from the regional ethics committees for the years 1998-2003 were hand-searched for applications to conduct phase I, II or III clinical trials. Identification was based predominantly on key descriptors in the application title. Trials were excluded if the application had been withdrawn. Where necessary, trial eligibility was confirmed by either a search using Google or through communication with the principal investigator. In addition, the following were searched for current registrations of trials submitted for ethical review in 2003: ClinicalTrials.gov, Cancer.gov, Current Controlled Trials (ISRCTN), National Cancer Research Network, NHMRC Clinical Trials Centre Register, International Society of Paediatric Oncology, Trans-Tasman Radiation Oncology Group, CenterWatch, and GlaxoSmithKline. Industry websites were searched in cases where the industry sponsor was identifiable, and Google was searched with keywords from the trial title.

**Study results:**

Between January 1998 and December 2003, ethical approval was sought for 665 clinical trials. Of these, 581 (87%) applications were for phase III trials, 53 (8%) were for phase II trials and 31 (5%) were for phase I trials. Only 45 (32%) of the 141 trials submitted for review in 2003 were listed on trial registers in the public domain: 25 (55%) on ClinicalTrials.gov, 10 (22%) on ISRCTN, and 10 unspecified.

**Study limitations as noted by study authors:**

The number of trials seeking ethical approval was likely to have been underestimated since identification was based predominantly on keywords present in the title. It was not possible to determine the actual number of trials conducted as the reports gave no indication of whether approved trials had progressed to completion.

**Study limitations noted by abstractor:**

Details of registers listing trials that sought approval in 2003 were not fully reported. The proportion of retrieved trials that had been published was not assessed.

**Key messages:**

Ethics committees in New Zealand are a valuable source of information on clinical trials that are not published or listed in a trials register. Such information could support a publicly accessible national register of trials.

**Study reference:**

Jureidini J N, McHenry L B, Mansfield P R. Clinical trials and drug promotion: selective reporting of study 329. *International Journal of Risk and Safety in Medicine*, 2008;20:73-81.

**Study objectives:**

To expose selective reporting that would not be apparent without access to internal company documents that only emerged through litigation. The original published report of study 329 in 2001 made claims about the efficacy and safety of paroxetine in adolescents which have since been called into question.

**Study methods:**

In June 2004, a law firm made allegations against GlaxoSmithKline (GSK) over misrepresentations about efficacy and safety, necessitating the release of all relevant documentation during the litigation process. One of the authors of this study was asked to conduct an independent psychiatric review of the data contained within these internal documents, all of which was initially deemed confidential. The law firm challenged the confidentiality of the evidence on the grounds that certain documents did not reveal trade secrets to competitors.

**Study results:**

During a class action lawsuit (*Beverly Smith vs. SmithKline Beecham*) approximately 10,000 pages of internal company documents were provided by GSK. The law firm were successful in their challenge relating to confidentiality and some documents were released into the public domain. This paper is based solely on those documents that were made publicly available. The authors assert that no document withheld because of confidentiality constraints imposed by GSK contradicts any of the documents cited in this article.

Paroxetine appears to have been promoted through memorandums sent to company neuroscience sales representatives and a series of *Med Query Letters* aimed at doctors who had requested further information from sales representatives. There was no publicly available information to clarify who (doctors/sales reps) had initiated this request for information. *Letters* characteristically started and ended with disclaimers, and were selective in the results they provided. Other academic publications and presentations frequently did not disclose the results.

The documents obtained through litigation revealed that the published conclusions of study 329 and information provided by GSK to health professionals understated adverse effect rates and emphasised post-hoc measures that were not consistent with the unpublished, protocol-defined primary and secondary outcomes.

**Study limitations as noted by study authors:**

This was a case study investigating the impact of selective reporting and the withholding of material from publication.

**Study limitations noted by abstractor:**

This study investigated selective reporting in a particular case, study 329, and was not a formal study with methods and results.

**Key messages:**

Flaws in industry-funded research can be severe and difficult to detect, potentially requiring legal action to release documentation necessary for proof of existence. Even then, confidentiality rulings may need to be challenged to release information into the public domain. Published conclusions about drug efficacy and safety may not be consistent with the unpublished data contained within company documents.

**Study reference:**

Kaiser, T., & Wieseler, B. Impact of unpublished data from industry sponsored trials on drug assessments [abstract]. XIV Cochrane Colloquium; 2006 October 23-26; Dublin, Ireland.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To evaluate the impact of including unpublished studies or unpublished information from published studies in systematic reviews.

**Study methods:**

The impact of including unpublished industry data in assessments of rapid-acting insulin analogues for the treatment of Type II diabetes and of montelukast for the treatment of persistent asthma was investigated. The criteria evaluated were the number of relevant studies, the quality of published studies, and study results.

**Study results:**

Three (43%) of the 7 included studies of insulin analogues had either not been published in journals or only partially published. Only one (7%) of the 15 included studies of montelukast had not been published in a journal. The incorporation of unpublished data had an inconsistent effect on the quality ratings of published studies of insulin analogues, but improved those of montelukast. There were inconsistencies between unpublished and published data on insulin analogues. Additional data on published and unpublished endpoints in montelukast studies were obtained from information supplied by the industry.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

It was unclear whether the analysis included only those studies retrieved from the industry or whether searches had also been conducted. There were no details of how the unpublished information was obtained, or the number of studies contributing additional information.

**Key messages:**

Unpublished information may have a substantial effect on the results and conclusion of a drug assessment.



**Study reference:**

Kaiser, T., Kerekes, M. F., & Wiesler, B. Industry clinical trials registries as a data source for systematic reviews. Oral presentation at the 17th Cochrane Colloquium; 2009 Oct 11-14, Singapore [abstract].

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To assess whether pharmaceutical industry (PI) registers are regularly used as data sources in systematic reviews, and whether the non-inclusion of registry data affects the review's conclusion.

**Study methods:**

PubMed was searched for systematic reviews of drugs. The reviews were checked to see whether PI registries had been searched and whether registry data had been considered. In the absence of such searches, [www.clinicalstudyresults.org](http://www.clinicalstudyresults.org) and manufacturers' registries were searched for documents published within the search period of each systematic review. The results were categorized as either additional studies, or additional data for eligible studies. The primary outcomes of the systematic reviews were re-analysed with the additional data incorporated.

**Study results:**

PI registries were not searched in 44 (88%) of the 50 systematic reviews identified. Of the six reviews with a registry search, four were Cochrane reviews. For the 44 reviews without a registry search, the supplemental searches provided additional relevant data in nine cases (20%). This data concerned patented drugs in eight cases. PI registries did not yield any additional data for 35 drugs, of which the majority (29; 83%) were out of patent.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

The searches and study selection process were not described. Further details of the drugs or disease areas considered may be useful. This abstract did not report the impact of registry data on the results and conclusions of each systematic review.

**Key messages:**

PI registries may provide additional relevant data, especially on patented drugs, but are rarely accessed in systematic reviews. Systematic reviews of patented drugs that ignore these registries may be biased.

**Study reference:**

Kober, T. Obtaining information on clinical trials: a challenging dilemma for Cochrane reviewers [abstract]. XI Cochrane Colloquium: Evidence, Health Care and Culture; 2003 Oct 26-31; Barcelona, Spain.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To access published and unpublished data for a Cochrane review on monoclonal antibody therapy for haematological malignancies.

**Study methods:**

A sensitive search was conducted to identify closed and open phase III randomized controlled trials (RCTs) comparing the efficacy of rituximab plus poly-chemotherapy versus poly-chemotherapy alone for B-cell lymphoma. In addition, formal and personal communication with trial investigators was used to clarify, substantiate and elicit additional information.

**Study results:**

Twelve RCTs were identified: one full publication, three abstracts reporting preliminary data, and eight ongoing trials. Enquiries made to 11 principal investigators were of mixed success. Three investigators did not respond, four responded but neither supplied nor offered information, while the remaining four provided or offered further details. Additional information ranged from trial protocols to individual patient data following journal publication.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

There were no details of the search conducted or the degree of effort made to contact trial authors/investigators.

**Key messages:**

Patience and tenacity is needed to obtain additional information on published and unpublished trials from trial investigators. The authors commented that direct communication with investigators is often characterized by suspicion and reluctance to share information. Information on industry-sponsored trials remains particularly problematic.

**Study reference:**

Krzyzanowska, M K, Pintilie M, Tannock I F. Factors associated with failure to publish large randomized trials presented at an oncology meeting. *JAMA*, 2003;290(4):495-501.

**Study objectives:**

To determine the rate of full publication of trials presented at annual meetings of the American Society of Clinical Oncology (ASCO), to quantify publication bias, and to identify factors affecting time to publication.

**Study methods:**

The proceedings of annual ASCO meetings from 1989 through 1998 were searched for abstracts reporting results for phase 3 randomized controlled trials with a sample size  $\geq 200$ . Electronic searches were conducted in PubMed, MEDLINE and EMBASE to identify full publications of these trials. The searches were completed in November 2001 and updated by searching the Cochrane Register of Controlled Trials in November 2002. Retrieved citations were compared with the original meeting abstracts to ensure they represented the same study. In cases where a published article was not found, the abstract authors were contacted by e-mail or letter and requested to provide details of any publication, or to confirm nonpublication and give reasons for this action (a checklist of potential reasons was provided). Any trials for which a response was not received by June 2002 were assumed to be unpublished.

**Study results:**

A total of 539 abstracts met the inclusion criteria. The literature search identified publications for 402 of these abstracts and 28 duplicates. For the 109 abstracts where no publication could be found, 101 authors were contactable and 8 authors could not be located. Responses were obtained from 54 authors: 40 studies were not published, 13 studies were published, and one study had an ineligible study design. The most common reason for lack of publication, cited by 34 of the 40 authors who confirmed nonpublication, was a lack of time, funds, or other resources (14%). The rate of nonpublication was highest for breast cancer (36%) and lowest for lung cancer (16%). The 13 studies found to be published studies were missed because they were in press (n=2), had been published since the last search (n=2), were published in a non peer-reviewed journal (n=1), or for an unknown reason (n=7).

The overall search strategy did not find publications for 95 (19%) of the 510 abstracts meeting the inclusion criteria.

The authors also reported that, taking censored observations into account, overall, 26% of eligible trials were not published in full within 5 years of presentation at the meeting. Trials described in 491 abstracts (96%) had either been published or had a follow-up of  $\geq 5$  years. Studies with significant results were more likely to have been published within 5 years than

those with nonsignificant results (81% versus 68%). The median time to publication (2.7 years) was sooner for studies with oral or plenary presentation and those sponsored by the pharmaceutical industry.

The authors commented that non-publication breaks the contract that investigators make with trial participants, funding agencies and ethics boards.

**Study limitations as noted by study authors:**

The authors noted potential limitations as being the use of conference abstracts, which are also subject to publication bias, to identify relevant trials; only approximately 50% of the authors responded to requests to confirm the publication status of their studies; and difficulties in controlling for study quality.

**Study limitations noted by abstractor:**

'Full publication' appears to relate to articles published in journals indexed in three main databases.

**Key messages:**

A long delay in publication exists for some large trials and a substantial amount of trials remain unpublished 5 years after conference presentation. Researchers should be aware that publication may be delayed for reasons such as long follow-up, non significant results, size of the trial, type of research, and role of sponsor. Conference abstracts are no substitute for full reports. Only about half of abstract authors respond to requests for further or clarifying information.

**Study reference:**

LaValley, M., Lo, G., Hunter, D., & Felson, D. Use of the USA Food and Drug Administration web site for clinical trial information from approved therapies [abstract]. 12th Cochrane Colloquium: Bridging the Gaps; 2004 Oct 2-6; Ottawa, Ontario, Canada.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To evaluate whether efficacy data from premarket approval documents on the US Food and Drug Administration (FDA) website would be a useful supplement to a meta-analysis.

**Study methods:**

Premarket approval documents for two groups of therapies, hyaluronic acid and cyclooxygenase-2 inhibitors, for pain relief in osteoarthritis were retrieved from the FDA website and examined for controlled clinical trials of patients with osteoarthritis. The reporting of the trials in these documents was evaluated on the basis of the Jadad scale for quality, the number of primary and secondary outcomes presented, and items relating to the analysis.

**Study results:**

Twenty-three reports were retrieved for the six therapies. Reporting of the trials was variable, in particular details of the methods of randomization and blinding were lacking. Approximately 25% of the clinical trials scored 3 or more on the Jadad scale, used intention-to-treat analysis, and presented adequate measures of variability. Most trials reported several outcomes.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

Details of searching the FDA website, for example the strategy and ease of searching, were not provided.

Key messages

The FDA website is a valuable source of sponsor-provided clinical trials data that may not be publicly available and is of potential use to meta-analytic research.

**Study reference:**

Leclercq, E., Kremer, L. C. M., & Van Dalen, E. C. Electronic searching versus hand-searching of conference abstracts. Poster presentation at the Joint Cochrane and Campbell Colloquium; 2010 Oct 18-22; Keystone, Colorado, USA [abstract].

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To compare the results of electronic searches and hand-searches of conference abstracts.

**Study methods:**

The 2008 conference abstracts of the International Society of Paediatric Oncology (SIOP) meeting were searched electronically, with a separate search performed for each keyword. The printed version of the 2008 SIOP conference abstract book was hand-searched.

**Study results:**

The electronic searches identified 40 relevant abstracts, none of which were detected using the keyword 'CCT'. The hand-searches did not detect any additional abstracts.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

The number of identified abstracts that were missed by the hand-searches was not reported. The time involved in conducting the electronic searches and hand-searches does not appear to have been assessed.

**Key messages:**

Hand-searches are not as efficient as electronic searches when searching printed and electronic versions of conference proceedings. A larger study involving more conference abstracts is needed to confirm these results.

**Study reference:**

Lee, K., Ong, C., Bacchetti, P., Jeng, S., & Sim, I. Publication of clinical trials supporting approved new drug applications in the United States [abstract]. XV Cochrane Colloquium; 2007 Oct 23-27; Sao Paulo, Brazil.

**Study objectives:**

This abstract is based on an abstract of a conference presentation. The research it describes has subsequently been published as: Lee K, Bacchetti P, Sim I. Publication of clinical trials supporting successful new drug applications: a literature analysis. PLoS Medicine, 2008;5(9):e191, for which a structured abstract is also available.

To determine the proportions of trials supporting successful new drug applications to the US Food and Drug Administration (FDA) that are published in the medical literature, and to identify predictors of publication.

**Study methods:**

This was a cohort study of all trials submitted to the FDA in support of all new molecular entities (NMEs) approved between 1998 and 2000. Full publications of these trials were identified by searching PubMed, the Cochrane Library and CINAHL, conducted to 1 August 1996. Trial characteristics associated with full publication in the literature were evaluated. Pivotal trials were those described in the 'clinical studies' section of the FDA-approved label.

**Study results:**

Between 1998 and 2000, 909 trials were submitted to the FDA in support of 90 approved NMEs. Of these, 383 (42%) were published in full by 1 August 2006 (the final follow-up date). The publication rate for pivotal trials, which comprised 34% of the submitted trials (309/909), was 73% (226/309). Thus, by the final follow-up date, over half of the supporting trials and nearly a third of the pivotal trials remained unpublished.

Factors likely to reduce time to publication were statistically significant results, larger sample sizes, double-blinding, randomization and pivotal status.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

The authors do not appear to have contacted trial investigators, searched trials registries, or accessed company websites for further information.



**Key messages:**

Over half of the trials supporting approved NMEs in the USA remain unpublished at least 5 years following FDA approval. Pivotal trials, statistically significant results and larger sample sizes increase the likelihood of publication. Incomplete publication of trials supporting newly approved drugs is evident. The findings of this study support the need for mandatory reporting of trial results in full to ensure an unbiased public evidence base.

**Study reference:**

Lee K, Bacchetti P, Sim I. Publication of clinical trials supporting successful new drug applications: a literature analysis. *PLoS Medicine*, 2008;5(9):e191. <http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.0050191>

**Study objectives:**

This study has also been published as a conference abstract: Lee, K., Ong, C., Bacchetti, P., Jeng, S., & Sim, I. (2007). Publication of clinical trials supporting approved new drug applications in the United States [abstract]. *XV Cochrane Colloquium; 2007 Oct 23-27; Sao Paulo, Brazil*, for which a structured abstract is also available.

To determine the proportion of trials submitted to the US Food and Drug Administration (FDA) for a variety of approved drugs that are published in biomedical journals that a typical US-based clinician, consumer, or policy maker would reasonably search.

**Study methods:**

All new drugs approved by the FDA between January 1998 and December 2000 were identified from the Center for Drug Evaluation and Research website. For each new drug, documents contained within the FDA Summary Basis for Approval were searched for clinical trials submitted by the sponsor in support of their application. PubMed, the Cochrane Library and CINAHL were then searched for full English-language publications of these trials. The Medical Letter was reviewed for additional trial publications, and the pharmaceutical industry's Clinical Study Results database, was searched for all outstanding trials without a matching publication. Abstracts or review articles were not considered matching publications as the details they contain are inherently incomplete. The literature search was completed in Aug 2006.

**Study results:**

Between January 1998 and December 2000, the FDA approved 89 new drug applications submitted by pharmaceutical companies and one by the military. FDA review documents revealed 909 supporting trials, of which 515 (57%) appeared to be unpublished. Summaries for 22 (4%) of these trials were identified through the Clinical Study Results database. Only one of the new drugs had none of its supporting trials published.

Within subset analyses according to trial classification, 24% (83/340) of 'pivotal trials' (phase II/III trials described in the FDA-approved drug label) and 76% (432/569) of 'non-pivotal trials' (all other trials) were not published.

The majority of published trials (92%) were published within 3 years of FDA approval. Statistically significant results, larger sample sizes, double-blinding, randomization and pivotal status were likely to reduce time to publication.

The authors expressed concerns about the reporting of clinical trials in FDA review documents and drug labels, and commented that review documents sometimes contained sections of redacted information.

**Study limitations as noted by study authors:**

The overall publication rate may have been underestimated as some published trials may have been misclassified as unpublished, due to insufficient detail in the FDA documents for matching purposes, other databases (e.g. European EMBASE) were not searched, and investigators/sponsors were not contacted to determine or confirm publication status. The follow-up time following approval may have been inadequate, and dates used to determine time-to-publication may not be reliable. The study focused on the medical literature and did not explore trial results made publicly available on company websites. The statistical significance of many results could not be determined. The findings of this study cannot be generalized to any specific product, company, institution, organization, or investigator.

**Study limitations noted by abstractor:**

No other limitations noted.

**Key messages:**

FDA approval documents contain details of many clinical trials, more than half of which remain unpublished at 5 years following approval. Incomplete and selective publication of trials supporting newly approved drugs is apparent in the years immediately following FDA approval. The findings of this study provide a baseline for monitoring the effects of the FDA Amendments Act 2007, which aims to improve the accuracy and completeness of trial reporting.

**Study reference:**

Lemeshow A R, Blum R E, Berlin J A, Stoto M A, Colditz G A. Searching one or two databases was insufficient for meta-analysis of observational studies. *Journal of Clinical Epidemiology*, 2005;58:867-873.

**Study objectives:**

To address methodologic issues in searching for observational studies, in particular the sensitivity of various bibliographic databases and search strategies.

**Study methods:**

The authors compared two literature searches for observational studies exploring the relationship between alcohol consumption and breast and large bowel cancer, respectively. For each cancer site, they searched multiple electronic databases (BIOSIS, Dissertation Abstracts Online, EMBASE, ETOH (the US National Institute on Alcohol Abuse and Alcoholism (NIAAA) Alcohol and Alcohol Problems Science Database), MEDLINE, NIH CRISP, NTIS, Pre-MEDLINE and SCI-EXPANDED-SSCI) and reviewed the reference lists in recent meta-analyses and pertinent reviews. Published and unpublished material was sought. The sensitivity of each database was estimated against the total number of eligible publications identified.

**Study results:**

The searches identified 79 relevant reports on alcohol consumption and breast cancer and 58 on alcohol consumption and large bowel cancer. Of these, 2 and 3 reports, respectively, were found through hand-searching. The sensitivity of the individual databases ranged from 0 to 82% in breast cancer studies and from 0 to 66% in large bowel cancer studies.

Grey literature was mainly sourced through Dissertation Abstracts Online (which does not provide any keywords), NIH CRISP and NTIS. Dissertation Abstracts Online identified 44 dissertations for breast cancer, none of which were relevant (sensitivity 0%), and 20 dissertations for large bowel cancer, of which 3 were relevant (sensitivity 5%) and 3 were considered unique. Neither NIH CRISP nor NTIS identified any relevant reports from the 35 and 42 reports retrieved, respectively, for breast cancer, and the 20 and 3 reports found for large bowel cancer (0% sensitivity). The authors noted that only one of the relevant dissertations reported statistically significant results, and that the published report associated with one dissertation was excluded as it did not present relevant results.

**Study limitations as noted by study authors:**

The sensitivity of each database was based on what was found in each search given the chosen search terms and not on the publications to which the database had access. In the absence of an ideal complete list of publications, the sensitivity estimates are likely biased upwards. The publications found during the hand-search of reference lists might have been

accessible through the electronic databases. Publication bias may determine the sensitivity of each database.

**Study limitations noted by abstractor:**

The authors referred only to publications throughout the text of their study, despite unpublished manuscripts being eligible for inclusion. Attempts to locate unpublished studies and grey literature were minimal.

**Key messages:**

Minimal attempts to locate unpublished material were not very fruitful. A broad search strategy incorporating electronic and manual approaches is essential for identifying observational studies for inclusion in a meta-analysis or systematic review.

**Study reference:**

Lexchin J, Holbrook A. Methodologic quality and relevance of references in pharmaceutical advertisements in a Canadian medical journal. *Canadian Medical Association Journal*, 1994;151(1):47-54.

**Study objectives:**

To evaluate the methodologic quality and relevance of references in pharmaceutical advertisements in the *Canadian Medical Association Journal (CMAJ)*, the most widely read peer-reviewed Canadian general medical journal.

**Study methods:**

The first two issues of volume 146 of the *CMAJ* were screened for all distinct pharmaceutical advertisements that quoted references. Where companies advertised more than one product, only the advertisement appearing earliest in the journal was selected. The medical director of each company was contacted by letter, signed by a local general practitioner not involved in the study, requesting a copy of all references cited. A second letter was sent if no reply had been received after 5 or 6 weeks, but no further attempts were made thereafter.

**Study results:**

Copies of 114 references cited in the first 22 distinct pharmaceutical advertisements were requested; the median number of references cited per advertisement was 4. Twenty companies responded within a median of 20 days (range: 7-87), sending 78 (90%) of the 87 references requested. Seven of these companies had needed a reminder, although two claimed not to have received the initial letter. One company telephoned the signatory to explain that references could not be sent because of copyright issues, but then proceeded to supply them. Two missing references referred to in the covering letter were not enclosed. The references requested from those companies that had responded comprised articles published in journal issues/supplements (65), data on file (10), product monographs (4) and other (8). All monographs and the majority of journal articles (96-100%) were received compared with only 60% of data on file requests and 62% of other articles. One company responded that the data on file were not in the public domain and could not, therefore, be sent. Some companies sent additional references beyond those requested, and one company provided a summary of the findings from both requested and unrequested material. Where the publication date was stated (74 references), 73% were published within the previous 5 years. Fifty of the references received related to clinical trials, 20 were review articles, and 8 were product monographs, books, monographs in the *Compendium of Pharmaceuticals and Specialties (CPS)* - a collection of monographs written by pharmaceutical companies and published by the Canadian Pharmacists Association, or government documents.

The authors expressed concerns with the methodological quality of the references, and the overall accuracy of the advertisements in terms of misleading information and non-information.

**Study limitations as noted by study authors:**

Rating scales for clinical trials and review articles did not consider key elements of trial design and statistical analysis, and the scale for assessing relevance was untested. Specific methodologic quality rating scales were not developed for other sources of information, which may have influenced the scores that these references received (none got more than the minimum). A different group of advertisements might have produced different results.

**Study limitations noted by abstractor:**

The authors did not comment on the quality of reporting in unpublished material.

**Key messages:**

Pharmaceutical companies responding to requests for literature cited in product advertisements are more likely to send published material than unpublished material; more than one request may be needed. The methodologic quality of the cited articles is of concern, as well as the accuracy of the advertisements citing them.

**Study reference:**

MacLean, C., Morton, S., Straus, W., Ofman, J., Roth, E., & Shekelle, P. Unpublished data from United States Food and Drug Administration New Drug Application Reviews: How do they compare to published data when assessing Nonsteroidal Antiinflammatory Drug (NSAid) associated dyspepsia? [abstract]. 7th Annual Cochrane Colloquium; 1999 Oct 5-9; Rome, Italy.

**Study objectives:**

This abstract is based on an abstract of a conference presentation. The authors subsequently published this study as: MacLean C H, Morton S C, Ofman J J, Roth E A, Shekelle P G. How useful are unpublished data from the Food and Drug Administration in meta-analysis? *Journal Of Clinical Epidemiology*, 2003;56:44-51, for which a structured abstract also exists.

To compare US Food and Drug Administration (FDA) Reviews and published reports on the quantity and quality of data available for a meta-analysis on the risk of dyspepsia from nonsteroidal anti-inflammatory drugs (NSAIDs).

**Study methods:**

MEDLINE, EMBASE, HEALTHSTAR and BIOSIS were searched from 1966 to 1997 for randomized controlled trials of NSAIDs; no restrictions were applied. The authors also hand-searched all FDA New Drug Application Reviews for the five NSAIDs with the largest market in the USA, to identify unpublished studies with identical inclusion criteria to those used in the published reports. All studies were assessed for quality using the Jadad scale.

**Study results:**

Electronic searches yielded 37 published studies for inclusion in the meta-analysis. The 27 FDA Reviews contained 141 studies, 11 of which met the inclusion criteria. The published studies and FDA reports were of comparable quality. However, the two sources of information reached different conclusions: the use of NSAIDs was not associated with dyspepsia when using data obtained through FDA Reviews, but was associated with dyspepsia when using published data

**Study limitations as noted by study authors:**

The abstract did not note any limitations.

**Study limitations noted by abstractor:**

There was insufficient detail provided in this abstract to establish whether sufficient measures had been taken to ensure the data solicited from the FDA Reviews was indeed unpublished and had not been published in any study retrieved by the electronic searches.



**Key messages:**

FDA Reviews contain a substantial amount of unpublished information that is of comparable quality to published material and may warrant inclusion in meta-analyses.

**Study reference:**

MacLean C H, Morton S C, Ofman J J, Roth E A, Shekelle P G. How useful are unpublished data from the Food and Drug Administration in meta-analysis? *Journal Of Clinical Epidemiology*, 2003;56:44-51.

**Study objectives:**

This study was previously published as a conference abstract: MacLean, C., Morton, S., Straus, W., Ofman, J., Roth, E., & Shekelle, P. (1999). Unpublished data from United States Food and Drug Administration New Drug Application Reviews: How do they compare to published data when assessing Nonsteroidal Antiinflammatory Drug (NSAID) associated dyspepsia? [abstract]. *7th Annual Cochrane Colloquium; 1999 Oct 5-9; Rome, Italy*, for which a structured abstract is also available.

To ascertain whether studies of nonsteroidal anti-inflammatory drugs (NSAIDs) summarized in US Food and Drug Administration (FDA) reviews are ultimately published; to compare the methodologic and population characteristics of these studies with those reported in peer-reviewed literature; and to compare the pooled relative risk of dyspepsia from NSAIDs in each data source.

**Study methods:**

MEDLINE, EMBASE, HEALTHSTAR and BIOSIS were searched from 1966 to 1997 for randomized controlled trials of NSAIDs; no restrictions were applied.

The authors obtained FDA reviews through the Freedom of Information Act. All FDA New Drug Applications (NDAs) were hand-searched for the five NSAIDs with the largest market in the USA, to identify unpublished RCTs with identical eligibility criteria to those used in the published reports.

Matching published studies and FDA studies were hand-reviewed to ensure they represented the same trial. The methodological quality of the studies was assessed using the Jadad scale.

**Study results:**

Electronic searches yielded 15 relevant published studies. Hand-searches of FDA reviews yielded 12 relevant reviews summarizing 141 studies, of which 11 were relevant. Only one study was described in both an FDA review and the published literature, but there were inconsistencies in some of the information reported.

Methodological details such as randomization and allocation concealment were lacking in FDA studies. However, the authors reported that they found no meaningful difference in

overall quality between published studies, the majority of which were industry-sponsored, and industry-sponsored unpublished studies (FDA data).

The authors noted that searching FDA reviews was time-consuming due to the large volume of material and the need to assess every individual page given problems inherent with the report presentation (e.g. copy quality, missing pages).

**Study limitations as noted by study authors:**

The study was limited to one drug class and one common adverse effect and its findings may not be generalizable to other drug classes and rare adverse effects or efficacy estimates. NDA summaries obtained from the FDA through the Freedom of Information Act may not be an accurate representation of the original data submitted by the manufacturer. The method used to assess methodological quality has not been validated for unpublished material. The methodological quality of published, nonindustry-sponsored research and unpublished industry-sponsored research could not be compared because the majority of published trials were sponsored by the pharmaceutical industry.

**Study limitations noted by abstractor:**

The dates to which the FDA reviews related were not reported. It is possible that some FDA studies might have been published since 1997 (end data for database searches).

**Key messages:**

Hand-searching of FDA reviews is time-consuming and hampered by report presentation issues. A large proportion of clinical trials contained in FDA reviews are unpublished. FDA data should be considered for systematic reviews and meta-analysis when there is a lack of published data or there is an a priori reason to suspect the FDA data may be systematically different from published data.

**Study reference:**

Mallet, S., Hopewell, S., & Clarke, M. The use of grey literature in the first 1000 Cochrane reviews. 4th Symposium on Systematic Reviews: Pushing the Boundaries; 2002 Jul 2-4; Oxford, UK.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To assess the number of Cochrane reviews which include information from grey literature and, within these reviews, the proportion of studies containing 'grey' information and the sources from which it were obtained.

**Study methods:**

For the purpose of this report, grey literature sources were considered to be all those other than journal publication. The first 1000 reviews in The Cochrane Library, Issue 1, 2001 were selected for analysis. Studies containing 'grey' information (ranging from details of a study's design to unpublished patient data) were identified from the reference lists and details provided in each review.

**Study results:**

Twelve reviews were not available for analysis. The remaining 988 reviews contained 9723 studies which met the eligibility criteria for the relevant review and contributed information (i.e. were included studies). Fifty-six percent of reviews included studies with 'grey' information, with a median of 33% of such studies within each review. In 66 reviews more than 95% of studies provided 'grey' information. The sources of 'grey' information in the 2141 studies containing it were personal communication (59%), conference abstracts (48%), unpublished reports (6%), and dissertations or theses (3%); 16% of studies referenced more than one source.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

Further details of the types of 'grey' information reported might be useful.

**Key messages:**

Personal communication and conference abstracts, in particular, are important sources of 'grey' information. Such information provides a valuable addition to the content of Cochrane reviews.

**Study reference:**

Malouf R, Noel-Storr A, Collins H, McShane R, Schneider L S. Alois: Alzheimer's and cognitive improvement studies register, a free, on-line register of dementia and cognitive enhancement trials (<http://www.medicine.ox.ac.uk/alois/>). *Alzheimer's and Dementia*, 2009;1:251–252. doi:<http://dx.doi.org/10.1016/j.jalz.2009.04.264>

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To create and maintain a comprehensive, up-to-date study-based registry of all trials of dementia and cognitive enhancement (ALOIS), and to make this register freely available on-line.

**Study methods:**

This abstract provides very brief details of the ALOIS trials register created by the Cochrane Dementia and Cognitive Improvement Group.

The register was populated with randomized controlled trials of treatment, prevention and cognitive enhancement that were retrieved through searches of major databases, trial registers and grey literature sources. Monthly searches are conducted to identify completed, ongoing and aborted studies.

**Study results:**

The ALOIS trials register contains records of 2525 randomized controlled trials and 495 controlled clinical trials. Details of all completed, ongoing and aborted studies have been included since 1st April 2009.

The register was due to be launched online in June 2009

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

This was a brief overview of a newly developed trials register.

**Key messages:**

ALOIS is an up-to-date source of all published and unpublished trials in the area of dementia and cognitive enhancement.

**Study reference:**

Manheimer E, Anderson D. Survey of public information about ongoing clinical trials funded by industry: Evaluation of completeness and accessibility. *BMJ*, 2002;325(7363):528–531.

**Study objectives:**

To evaluate the completeness and accessibility of public information about US clinical trials of drugs in development, in particular, experimental drugs for prostate and colon cancer.

**Study methods:**

Three drug industry sources (NDA Pipeline, PhRMA 1999 Survey and What's in the Pipeline) were searched for drugs in development for prostate and colon cancer, using the most up-to-date versions of these available. To eliminate duplicate listings of the same drug, company websites were checked for correct spellings of drug names and all alternatives names (chemical, trade, generic), and also for any additional drugs.

Phase III trials (and phase II-III) testing the identified drugs were then sought in US-based online trials registers: CancerNet.gov (now named Cancer.gov), CenterWatch.com, ClinicalTrials.gov, and the trials registers for the 37 'Comprehensive Cancer Centers' designated by the National Cancer Institute. The registers were searched using either a visual scan for trials listed under the cancer site, each register's search dialogue box, or the browser's 'find in page' function. Searches for each drug were conducted using all possible synonyms of a drug name. Drug developers were contacted directly to confirm the conduct of a US phase III trial when no such trial was identified through a trials register.

**Study results:**

Industry data sources identified a total of 32 experimental drugs (12 for prostate cancer and 20 for colon cancer) that were undergoing phase III trials. Up to five different names were used to describe the same drug. About half of the drugs were listed in one source, and only one or two listed in all three sources.

None of the online trials registers contained trial details for all of the drugs identified. Only four drugs had trials listed on all trials registers, and six drugs had trials listed on only one register. ClinicalTrials.gov was the most comprehensive register, with trials listed for approximately half of the drugs (17/32), whereas CenterWatch.com was the least comprehensive (4/32 listed).

Eleven drugs did not have trials registered on any of the registers searched. Of these, confirmation of a phase III US trial was obtained for seven drugs, the company contact explicitly stated that no phase III trials had been conducted (2 drugs), and the contact was unable to locate any information on any US-based phase III trial (2 drugs). The conduct of a phase III trial outside of the US was not referred to in any of these cases.

The authors commented that searching for both the experimental drugs and trials was hampered by non-standardised language, incomplete or unclear information, and limitations associated with web-based searches. In addition, information obtained through the industry sources sometimes contradicted that obtained directly from the company.

**Study limitations as noted by study authors:**

The authors noted that there may be other drugs in phase III trials that were not listed in their 'pipeline' sources (i.e. industry data sources).

**Study limitations noted by abstractor:**

It is unclear why the study focused on phase III trials conducted in the USA and listed in US online trials registers, given that many drug companies are multinationals and trials conducted across multiple sites may be registered in other countries.

**Key messages:**

Searching online registers is time-consuming and difficult because of limitations in the websites and the non-standardised language used to describe trials. Few ongoing trials appeared on all online registers searched, and many were not listed at all. There is a clear need for a comprehensive clinical trials register encompassing all ongoing trials, including those sponsored by industry. However, the authors commented that drug companies may not be willing to register their trials if they believe it will compromise their commercial interests.

**Study reference:**

Matthews E J, Edwards A G, Barker J, Bloor M, Covey J, Hood K, et al. Efficient literature searching in diffuse topics: lessons from a systematic review of research on communicating risk to patients in primary care. *Health Libraries Review*, 1999;16:112-120.

**Study objectives:**

To demonstrate an efficient approach to locating the maximum amount of primary research on a diverse subject for a systematic review.

The example presented was the development and evaluation of a search strategy for communication about risk in primary care.

**Study methods:**

The full search was conducted from 1985 to 1996 using six electronic databases (MEDLINE, EMBASE, PsycLIT, CancerLIT, CINAHL and SSCI). In addition, all issues of the four most frequently encountered journals were hand-searched from 1990 to 1996, and the most frequently cited authors were contacted for CVs outlining details of their publications and



ongoing research. The authors also conducted citation searches in the Science Citation Index and SSCI for accepted papers, and reviewed the reference lists of review articles.

### **Study results:**

Overall, 168 references, relating to 99 unique studies, were retrieved by the various approaches. The majority of references were identified through electronic searches. Supplementary approaches made little contribution, with only 11 papers identified: four by hand-searching, four by reference searching, two by citation index and one through a CV search. However, five of these references were papers indexed on MEDLINE but missed by the MEDLINE search, and a further five references were considered unique (defined as not indexed on MEDLINE).

No references were found using CancerLIT, which is a subset of MEDLINE with the inclusion of conference proceedings and other grey literature.

### **Study limitations as noted by study authors:**

The authors did not note any study limitations since this was a report of experiences in developing an efficient search strategy for a diverse subject.

### **Study limitations noted by abstractor:**

There is the potential for overlap between the other search approaches in terms of the number of references retrieved. It is unclear how many of the references obtained by manual approaches were truly unique. It would have been interesting to know how many authors responded to requests for their CVs.

### **Key messages:**

Supplementary approaches such as hand-searching and reference checking yield few studies, but may detect those not identified through electronic searches.

**Study reference:**

McAuley, L. M., Moher, D., & Tugwell, P. The role of grey literature in meta-analysis [abstract]. Third International Congress on Biomedical Peer Review and Global Communications; 1997 Sept 18-20; Prague, Czech Republic.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To estimate the frequency of citations of 'data on file' in drug advertisements, to survey how companies respond to requests for them, and to ascertain the nature of the data.

**Study methods:**

The authors conducted a survey of all drug advertisements in nine consecutive issues of Hospital Doctor and five issues of Prescriber (aimed at UK General Practitioners) published in the last quarter of 1996. All companies citing 'data on file' or other unpublished material in any of these advertisements were contacted for these data. Eleven further advertisements from recent issues of other journals were investigated similarly.

**Study results:**

The 14 issues contained 95 different full drug advertisements, of which 25 referred to unpublished material (mostly 'data on file'). Thirty-eight different advertisements, corresponding to 28 companies, were investigated further. Within these 38 advertisements, 'data on file' was referenced once in 25 advertisements, twice in 10 advertisements, and three times in 3 advertisements. Twenty advertisements supplied a code number or identified the nature of the documents, whilst 18 referred to unidentifiable documents. One advertisement cited a paper that had been 'submitted for publication'.

Half of the 38 requests for information were responded to within 10 days, but the material supplied was mainly incomplete and further correspondence was needed. Companies typically supplied abstracts or summaries with insufficient detail for critical evaluation. Three companies marked their material as 'Confidential'.

The authors commented that the documentation referred to as 'data on file' is generally inadequate to support promotional claims.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

There was no description of the content of the material supplied (e.g. ongoing research, completed clinical trials). It was unclear whether repeated requests for information were made to non-responding companies, or how successful further correspondence with the company was.

**Key messages:**

Contacting companies for unpublished material referred to in promotional drug advertisements meets with mixed response and may not yield any information of value.

**Study reference:**

McDonald S. Improving access to the international coverage of reports of controlled trials in electronic databases: a search of the Australasian Medical Index. *Health Information Library Journal*, 2002;19(1):14-20.

Also presented as: McDonald, S., & Middleton, P. Improving the international coverage of controlled trials: a story from Australia [abstract]. Eighth International Congress on Medical Librarianship; 2000 Jul 2-5; London, UK.

**Study objectives:**

To identify reports of randomized controlled trials (RCTs) and controlled clinical trials (CCTs) from the Australasian Medical Index (AMI), and to measure the quality of indexing of trials in this database.

**Study methods:**

The AMI was searched from 1966 to 2000 for controlled trials. Trials meeting the relevant criteria were submitted for inclusion in the Cochrane Controlled Trials Register (CCTR).

**Study results:**

The full search strategy retrieved 7414 records of human studies, of which 512 were reports of controlled trials (317 RCTs and 195 CCTs). All 512 trials were reported in English, with the majority (94%) published in Australian journals. The trials were reported in 114 different sources: 76 separate journals and 38 other publications (e.g. proceedings of conferences and society meetings). Approximately half (258/512) of the identified trials were reported as a conference paper, either published in a journal or in separate conference proceedings. The majority of the trials (88%) were not previously available through searches of the CCTR. The authors highlighted problems with the retrieval of controlled trials, such as insufficient information in the title and/or abstract, and poor and inadequate indexing, although tagging records with the appropriate publication type term will help.

**Study limitations as noted by study authors:**

The authors did not note any limitations of their study.

**Study limitations noted by abstractor:**

No limitations noted by the abstractor.

**Key messages:**

The Australasian Medical Index is a valuable source of research published in Australian and New Zealand journals which are not indexed in MEDLINE.

**Study reference:**

McGrath J D, Soares K. Writing to authors of systematic reviews elicited further data in 17% of cases. *BMJ*, 1998;316:631.

**Study objectives:**

This abstract is based on a letter describing experiences in contacting study authors for additional information.

**Study methods:**

Letters were written to study authors in North America, Europe and other countries during the course of nine systematic reviews relating to the treatment of tardive dyskinesia. The letters requested clarification of design issues or additional data. The nine reviews have since been completed and are available in the Cochrane Library.

**Study results:**

In addition to the 49 trials with data suitable for the reviews, a further 72 potentially relevant trials were identified. A total of 133 letters were sent to authors in North America (n=72), Europe (n=44) and other countries (n=17). After an interval of 10 to 18 months, 51 replies had been received and another 12 were returned to sender (current location of author unknown). There had been no response to 70 letters. Twenty-three responding authors had changed their address, suggesting that the letters had been forwarded on. There was no indication that authors of older publications (1970-79 and 1980-89) were less likely to reply than authors of more recent publications (1990-97).

The authors stated that responses to over a third of the letters helped with completion of the reviews. Twenty-three study authors (17%) supplied data suitable for meta-analysis and 26 authors indicated that relevant data could not be extracted. The data extraction was pending in the remaining two cases.

The authors commented that it was not surprising that so many letters were returned to sender given the mobility of the research community. They expect the probability of locating authors to improve given the increased use of e-mail.

**Study limitations as noted by study authors:**

The authors did not note any limitations of their study.

**Study limitations noted by abstractor:**

This was a report of experiences and not a formal evaluation of writing to authors to solicit information on their studies.

**Key messages:**

Contacting study authors by letter yielded useful data for completion of the reviews, but less than half of the authors responded.

**Study reference:**

McManus R J, Wilson S, Delaney B C, Fitzmaurice D A, Hyde C J, Tobias R S, et al. Review of the usefulness of contacting other experts when conducting a literature search for systematic reviews. *BMJ*, 1998;317:1562-1563.

**Study objectives:**

To examine the usefulness of expert contact to identify relevant references for a systematic review of a field that does not have a specialist focus.

**Study methods:**

The authors report the literature search undertaken as part of a systematic review on near patient testing in primary care. Electronic searches were conducted in MEDLINE, EMBASE, CINAHL, BIDS SCI, BIDS Index to Conference Proceedings, GPLit, DHSS and PsycLIT. The bibliographies of identified publications were checked and published abstracts from international primary care conferences were hand-searched. A questionnaire requesting key journal references, unpublished data, and names of other workers in the field was sent to 194 selected academics in the UK and 152 commercial companies with an interest in near patient testing. Only articles in English were eligible for the review.

**Study results:**

Overall, 156 (45%) of the 346 questionnaires sent were returned completed. The response rate was greater from academics (53%) than commercial companies (35%). No unpublished data were offered.

The searches yielded 1057 unique references of potential relevance to the review, of which 102 were eligible for inclusion when excluding overlap between the three search methods. Fifty (49%) of the 102 unique references were identified by one of the databases, 40 (39%) through people working in the field and 31 (39%) through hand-searches. Contact with people working in the field yielded 24 articles that would otherwise have been missed, and hand-searching yielded 21 articles. The authors commented that each of the sources provided a similar proportion of high quality papers.

**Study limitations as noted by study authors:**

The authors did not note any limitations of their study.

**Study limitations noted by abstractor:**

The varying use of 'unique articles' and 'unique references' in the table presented hampers interpretation of the search results reported.



**Key messages:**

Expert contact is essential when sourcing references for a systematic review, in particular in developing fields that do not have a clearly defined specialist literature.

**Study reference:**

Milton J, Logan S, Gilbert R. Well-known signatory does not affect response to a request for information from authors of clinical trials: a randomised controlled trial [abstract]. 9th Annual Cochrane Colloquium; 2001 Oct 9-13; Lyon, France.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To compare the response of clinical trial investigators to requests for information signed by either Richard Smith (RS), editor of the British Medical Journal, or an unknown researcher (Julie Milton; JM) in a randomized study.

**Study methods:**

Authors of 144 RCTs published since 1996, and eligible for a methodological systematic review of interventions in hypertension, were randomised (2:1) to receive a mailed questionnaire addressing unpublished details of study methodology with a covering letter signed by either RS or JM. Non-respondents were re-sent the questionnaire, with the same signatory, by recorded mail 3 weeks later. In the absence of a response after a further 5 weeks, JM telephoned the authors either as herself or on the behalf of RS. Baseline data for 80 studies were requested from authors who responded to the questionnaire, using the original signatory. As before, repeat requests were sent to non-respondents by recorded mail after 3 weeks, and attempts made to telephone them after a further 3 weeks.

**Study results:**

There were no significant differences between signatory groups in response rates. Approximately one third of authors in each group had responded by 3 weeks: 32/96 in the RS group and 13/48 in the JM group. By the end of the study (17 weeks), responses had been received from 71 authors in the RS group and 32 authors in the JM group. None of the 80 authors contacted for baseline data had responded by 3 weeks. By the end of the study, responses had been received for 16 of the 53 studies in the RS group and 5 of the 27 studies in the JM group. The overall response for baseline data was 26%.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

It is unclear whether authors who failed to respond had received the questionnaire and not replied, or they were not contactable.

**Key messages:**

Increased contact with authors is more likely to improve the yield of unpublished trial information. There is no significant advantage of having a well-known person within the medical profession sign the request for information.

**Study reference:**

Minozzi, S., Vecchi, S., Amato, L., & Davoli, M. Systematic search for unpublished trials and assessment of publication bias in the reviews of the Drugs and Alcohol Group [abstract]. XV Cochrane Colloquium; 2007 Oct 23-27; Sao Paulo, Brazil.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To assess how many systematic reviews and protocols published by the Cochrane Drugs and Alcohol Group (CDAG) searched for unpublished studies, found them, and analyzed the possibility of publication bias through a funnel plot.

**Study methods:**

The authors examined all reviews and protocols published by the CDAG in the Cochrane Library, Issue 2, 2007.

**Study results:**

Fifty-two articles (37 reviews and 15 protocols) were available for analysis. Of these, 69% (21 reviews and 15 protocols) reported contacting authors and pharmaceutical companies, and 61% (21 reviews and 11 protocols) searched conference proceedings. However, only 31% (6/21 reviews and 4/11 protocols) described the conference proceedings they searched. Only 19% (4/21) of reviews seeking unpublished studies found them, with each review finding one unpublished study, but 43% (9/21) of reviews incorporated unpublished data for published studies.

The authors commented that, over time, all the protocols stated their intention to search for unpublished studies compared with only 57% of the reviews.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

The results for some 'questions' were not based on the full data set. The authors do not comment on the generalizability of their findings to other Cochrane review groups.

**Key messages:**

Cochrane review groups commonly seek unpublished information from conference proceedings and through contact with authors and pharmaceutical companies, but the retrieval rate is low.

**Study reference:**

Mullan R J, Flynn D N, Carlberg B, Tleyjeh I M, Kamath C C, LaBella M L, et al. Systematic reviewers commonly contact study authors but do so with limited rigor. *Journal of Clinical Epidemiology*, 2009;62(2):138-142.

**Study objectives:**

To characterize the prevalence, quality and results of author contact in recently published systematic reviews in leading medical journals and the Cochrane Library, by way of a systematic review.

**Study methods:**

MEDLINE, EMBASE and the Cochrane Library were searched for systematic reviews of treatment efficacy published in 2005-2006 in either the 25 journals with the highest impact factor publishing systematic reviews in clinical medicine or the Cochrane Database of Systematic Reviews.

Review authors were contacted by e-mail and asked to complete an online survey on their practices of contacting authors of eligible studies. A reminder e-mail was sent out to nonresponders after 1 week.

**Study results:**

Over half (92) of the 147 systematic reviews identified made some mention of author contact, with greater frequency noted in Cochrane reviews (85%) than in journal reviews (50%). Where described (n=85), reasons for author contact related to study eligibility for the systematic review (n=29), requests for incomplete data (n=76) and verification of abstracted data (n=9). Only nine reviews reported the response rate.

The response to the e-mail survey was 74%: 109 of the 147 reviewers completed the survey, although 111 reviewers actually responded. Most of the reviewers (n=89) contacted at least one study author, with greater frequency reported by Cochrane reviewers (93%) than journal reviewers (74%). The majority of reviewers (n=63) contacted one to nine study authors, with a high response rate attained. Contact with study authors was more frequent than that indicated in the published articles. Reasons for author contact related to study eligibility (n=33), additional data (n=77) and verification of abstracted data (n=31). The main reasons given for not contacting authors were that all the information needed was already present in the published report (n=30) and the articles were too old (n=20).

The authors commented that both Cochrane and journal systematic reviews infrequently and incompletely report the results of author contact.

**Study limitations as noted by study authors:**

Details of how reviewers contacted authors, and whether they had assessed the impact of additional data on the review results, were not requested.

**Study limitations noted by abstractor:**

The table presenting the results of the survey lacks clarity, in particular how some of the percentages were calculated, and the number of authors who were contacted and responded for Cochrane reviewers.

**Key messages:**

Author contact is an important step in systematic review methodology, but is costly, time-consuming and meets with varying degrees of success. Nonresponse from study authors seemed to discourage future attempts at author contact.

**Study reference:**

O'Connor A B. The need for improved access to FDA reviews. JAMA, 2009;302(2):191–193.

**Study objectives:**

This was a commentary on the value of US Food and Drug Administration (FDA) reviews and the difficulties in trying to locate them.

**Study methods:**

The author highlighted some obstacles and difficulties in accessing FDA reviews, using the medical reviews of pregabalin for pain associated with diabetic neuropathy and Fentora for chronic non-cancer pain in opioid-tolerant patients as examples.

**Study results:**

The authors stated that legal barriers to the release of research data considered proprietary by the sponsors into the public domain may prevent or delay some FDA reviews becoming publicly available.

To find the pregabalin medical review within the FDA's website required successful navigation of six screens. Links within the site were poorly named, with applications listed by number and not the specific indication. The Drugs@FDA search engine, the second of the six screens, identifies a drug by either its generic or brand name. However, to increase the specificity of the review (e.g. by searching for 'pregabalin review' or 'Lyrica approval') consistently yielded a response of 'no results'. The search window on the FDA homepage also failed to find the review of interest when searching 'pregabalin review' and 'Lyrica approval', despite yielding 79 and 37 hits, respectively. Attempts to access the Fentora review were equally unsuccessful. The review did not appear under any of the Drugs@FDA Fentora links and could not be found using the application number on the FDA.gov search engine. However, the review was identified using the Google search strategy.

Reviews were difficult to navigate once found: the table of contents for pregabalin, which was on page 17 of 390, listed incorrect page numbers and the indication was not mentioned until page 19. The authors commented that locating specific information within the pdf file was challenging and time-consuming.

**Study limitations as noted by study authors:**

The authors did not note any limitations.

**Study limitations noted by abstractor:**

This was not a formal evaluation of success in the access of FDA reviews.



**Key messages:**

FDA reviews are challenging to find through the FDA website resources; more success may be achieved with Google. The accuracy of tables of contents, labelling and hyperlinks needs improvement.

**Study reference:**

Ogilvie D, Hamilton V, Egan M, Petticrew M. Systematic reviews of health effects of social interventions: 1. Finding the evidence: how far should you go? *Journal of Epidemiology & Community Health*, 2005;59:804-808.

**Study objectives:**

To assess the value of different ways of finding information about the health effects of social interventions, for a systematic review of the effectiveness of interventions in promoting a population shift from using cars towards walking and cycling.

**Study methods:**

Full details of the search strategy had been reported in a previous paper.

Twenty electronic databases that had provided the greatest yields for a systematic review on a related topic were searched for studies of any design. The authors also compiled a purposive list of 16 websites for their Internet searches, which contained bibliographies or searchable databases of documents covering a range of organisations, countries of origin and language of publication.

The review protocol was posted online along with a list of references, and experts and relevant electronic mail groups were invited to review the list and suggest additional studies. The reference lists of all documents were searched.

**Study results:**

Approximately half of the 69 relevant studies were identified through the Transport database. First-line health and science databases yielded a total of 12 relevant studies, while specialist databases such as Dissertation Abstracts and Geobase contributed eight relevant references and the purposive search of websites contributed nine. A further seven studies were found by chance, one through 'surfing' the web and the others from a book of conference proceedings that was ordered for a particular article. Reference list checking revealed comparatively few studies, mainly those that had already been identified. The reviewers' own collections and experts' recommendations did not reveal any relevant studies beyond those already identified. The majority (16) of the 22 studies included in the review were not indexed in first-line health and science databases.

**Study limitations as noted by study authors:**

The authors did not note any limitations of their retrospective analysis.

**Study limitations noted by abstractor:**

This was a retrospective analysis of the sources of studies for one systematic review, not a formal evaluation of the methods used to identify published and unpublished studies.

**Key messages:**

Topic-specific databases, Internet searches and chance discoveries may identify unpublished or grey literature not otherwise indexed in mainstream health literature databases. Comprehensive searching across multiple resources is very labour intensive but may provide unique evidence.

**Study reference:**

O’Kelly M, Julious S A, Pyke S, Day S, Todd S, Seldrup J, et al. Making available information from studies sponsored by the pharmaceutical industry: some current practices. *Pharmaceutical Statistics*, 2011;10(1):60–69. doi:<http://dx.doi.org/10.1002/pst.430>

**Study objectives:**

This article described the development of publicly available sources of study registry and results information, and examined the completeness of the available study details.

**Study methods:**

The article drew upon information from 11 large pharmaceutical companies and 5 smaller companies, which had been selected from a published list of pharmaceutical companies on the basis of region and market capitalization. Privately owned companies were not included. Examples of searches conducted at the websites of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), National Library of Medicine (NLM), and Pharmaceutical Researchers and Manufacturers of America (PhRMA) were reported, to gauge the level of study information being made publicly available.

**Study results:**

Various government bodies, editors of medical journals, the pharmaceutical industry and the World Health Organization have issued guidance or standards for the registering of clinical trials and reporting of the results. Attempts have been made to define the type of study information that should be published, and its format.

Characteristics of the websites of the 11 larger pharmaceutical companies (8 US and 3 European) were described. Ten companies published a policy statement about how they intend to make study information available. These policy pages tended to link to a registry and a source of study results, the most important of which are the NLM site [ClinicalTrials.gov](http://ClinicalTrials.gov) (10/11 companies), the PhRMA site [clinicalstudyresults.org](http://clinicalstudyresults.org) (9/11 companies) and the IFPMA site [clinicaltrials.ifpma.org](http://clinicaltrials.ifpma.org) (8/11 sites), which contains information from both the NLM and PhRMA sites. There is overlap among the sources of study information. Two companies provided a company search engine linking to an external trials registry and one a search engine linking to an external results database; three companies confirmed that neither of these facilities were available. Four companies had their own registry of studies and five their own results database.

A study of a sample of papers published in 2008 found that studies reported in the selected general medical journals (113/114) were more likely to have been registered than studies reported in speciality journals (123/209).

Searches on the three major web sources found reasonable consistency between the IFPMA and either NLM or PhRMA sites, with somewhat more studies available via the IFPMA portal. There was considerable variation in the type of information (category, quantity and detail of results published) that was actually made available.

The authors noted that differing levels of voluntary disclosure and differences in legal requirements must affect the amount of study information made publically available, depending upon the study type, class of information and sponsoring company.

**Study limitations as noted by study authors:**

The authors did not note any limitations.

**Study limitations noted by abstractor:**

No limitations noted since this was an account of the availability of study information from a number of specific web sites. It should be noted, however, that the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal was not assessed.

**Key messages:**

There is no single route to accessing information about study results. The best approach is to search the IFPMA portal, then check ClinicalTrials.gov and individual company websites. The quantity of publically available information is variable, and reports may be incomplete.

**Study reference:**

Pandolfini C, Bonati M. Children's presence in research. A review of online registers. *European Journal of Clinical Pharmacology*, 2009;65(9):873–880.

**Study objectives:**

To determine how many online clinical trial registers include paediatric trial data, how much information is provided, the ease of searching for paediatric trials, and the accessibility of paediatric trial data in general.

**Study methods:**

MEDLINE and Google were searched in July 2008 for any mention of clinical trial registers. The websites of identified registers were searched for links to additional registers. Trial registers were eligible if they were freely accessible, involved multiple drugs or therapeutic areas, and contained data on ongoing clinical trials. Websites or registers that only listed a few trials were excluded.

Each register was evaluated in terms of the search options available, the total number of trials included, the number of paediatric trials, and the information provided. To assess the presence of paediatric trials in the World Health Organization's ICTRP, it was searched for trials present in the six registers that were not at that time directly searchable through the ICTRP.

**Study results:**

The majority of the 108 online trials registers found were excluded, some because they were not searchable registers: the user was required to insert personal health information and was then informed of any trials in which they could participate. Three registers were excluded because they had stopped (National Research Register), not been updated (DEC-net), or were inaccessible (DrugsOnTrial).

The 12 online registers reviewed comprised two pharmaceutical company registers, the Association of the British Pharmaceutical Industries' (ABPI) register, and nine public service registers. None required registration. All but one provided detailed trial data; the National Organization for Rare Disorders Register (NORD) gave a brief description only but specified an e-mail or website for obtaining additional information. The ABPI register often had incomplete or outdated trial records.

The different registers offered a variety of search options, of which seven provided free-text searching. The Netherlands Trial Register did not provide any instructions in English. Only three registers facilitated searching for paediatric trials: AMGEN, ClinicalTrials.gov and Australian New Zealand Clinical Trials Registry. It was not possible to identify paediatric trials in the ABPI, Roche and Sri Lanka Clinical Trials registries, and records in NORD had to

be checked individually. Details of the search options provided and the strategies used in each register were tabulated

The authors commented that it is probable that many trials were not published, thus it is difficult to draw a conclusion on how representative trials registers are in relation to the actual number of paediatric studies performed. Of the 210 paediatric trials sought in the ICTRP, 71 (34%) were not found.

**Study limitations as noted by study authors:**

This study relied on the limited search facilities of the different registers, which meant it was not possible to guarantee a precise result.

**Study limitations noted by abstractor:**

No other limitations noted.

**Key messages:**

There are numerous trials registers online, but few are open to trials involving any therapeutic area, few are easily searchable and few provide detailed trial information.

**Study reference:**

Parekh-Bhurke S, Kwok C S, Pang C, Hooper L, Loke Y K, Ryder J J, et al. Uptake of methods to deal with publication bias in systematic reviews has increased over time, but there is still much scope for improvement. *Journal of Clinical Epidemiology*, 2011;64(4):349–357.

**Study objectives:**

To evaluate the measures taken to deal with publication bias across different categories of systematic reviews published in 2006 and to compare these with reviews published in 1996.

**Study methods:**

PubMed was searched for systematic reviews published in 2006. The random sample for assessment comprised 100 treatment effect, 50 diagnostic accuracy, 100 risk factor, and 50 gene-disease association reviews. Methods used to identify, prevent, or reduce publication and related biases were examined within each category of systematic review. The results were compared with those reported in a Health Technology Assessment (HTA) published in 2000, which assessed 193 systematic reviews published in 1996.

**Study results:**

Overall, unpublished studies were explicitly sought in 27% of reviews published in 2006, ranging from 10% (genetic reviews) to 49% (treatment effect reviews) across categories. Contacting study authors, experts and pharmaceutical companies were the most common methods used. Only 8% of reviews included unpublished studies.

Grey literature was explicitly sought in 34% of reviews, ranging from 8% (genetic reviews) to 50% (treatment effect reviews) across categories. Conference abstracts, meeting proceedings, and grey literature-specific databases such as LILACS and SIGLE, were the main approaches used. Only 13% of reviews included grey literature.

Across review categories, non-English language studies were explicitly sought in 22% (genetic) to 52% (diagnostic) of reviews and were included in 10 to 28%.

A total of 23 reviews searched prospective trials registers such as the UK National Research Register (57%), ClinicalTrials.gov (39%), Current Controlled Trials (13%) and Physician Data Query (7%).

The use of MEDLINE, EMBASE, the Cochrane Library and bibliographies increased considerably from 1996 to 2006. There was also a substantial increase in explicit searches for or inclusion of unpublished studies and grey literature: from 35% to 61% in treatment reviews. The overall increase in searches for or inclusion of non-English language studies was 13% since 1996.



**Study limitations as noted by study authors:**

The design of the data extraction form (assessment based on 'yes', 'no', or 'unclear') meant that information might have been lost, for example, the extent to which non-English language studies were sought.

**Study limitations noted by abstractor:**

The original HTA report did not assess effectiveness and diagnostic reviews separately, so the authors have compared overall data for 1996 with data for separate review categories in 2006. It was unclear whether it would have been feasible to have categorised reviews from 1996, thus enabling direct comparison.

**Key messages:**

Searching for grey literature and unpublished studies is becoming increasingly more common. The most popular approaches used are contact with study authors, experts and pharmaceutical companies for unpublished studies, and conference abstracts/proceedings and specialist databases for grey literature.

**Study reference:**

Parkhill A, Hill K. Identifying the effective evidence sources to use in developing Clinical Guidelines for Acute Stroke Management: lived experiences of the search specialist and project manager. *Health Information and Libraries Journal*, 2009; 26:47-55.

**Study objectives:**

To identify the relative effectiveness of differing evidence sources for the update of the Australian National Stroke Foundation's (NSF) *Clinical Guidelines for Acute Stroke Management*.

**Study methods:**

The authors developed a series of 89 clinical and economic questions to address interventions relevant to acute stroke care. Various approaches were used to identify literature pertinent to these questions. Nine electronic databases were searched. References lists in three guideline documents (previous version 2003, NSF Rehabilitation 2005, Royal College of Physicians 2004) and key articles ('snowball' approach) were checked for relevant articles. Four journals (*Stroke*, *Cerebrovascular Disease*, *Lancet*, and *Archives of Physical Medicine and Rehabilitation*) were hand-searched and e-mailed tables of contents were screened for other key journals. In addition, national and international experts, as well as experts suggested by the working group, were contacted for relevant studies.

**Study results:**

Previous knowledge and sources made a greater contribution than electronic databases in identifying evidence for the clinical portion of the guidelines document. Of the 153 references used to support the guideline recommendations, 60 (35.3%) were from electronic databases, 54 (39.2%) were known from the previous documents, and 39 (25.5%) were from other approaches, such as 'snowballing' from reference lists, expert contact, hand-searches and serendipitous discovery. Only one reference appears to have been identified through expert contact.

Electronic databases made a greater contribution to identifying economic evidence. Of the 39 references used for the recommendations, 30 (76%) were found through electronic searches and 9 (24%) through expert contact.

**Study limitations as noted by study authors:**

The categories of source were loose and grey in their definition; the 'previous' sources may well have been in the electronic database searches as well.

**Study limitations noted by abstractor:**

Within the abstract the authors specified the Internet/grey literature as one of the valid evidence sources they searched. However, there were no specific details of this approach and it is unclear whether it was actually used.

**Key messages:**

Although online databases remain the best source of information, researchers should use many different media and sources, such as expert contact, to identify the best available evidence.

**Study reference:**

Peinemann, F., Sauerland, S., & Lange, S. Identification of unpublished studies contribute to a systematic review on negative pressure wound therapy [abstract]. XIV Cochrane Colloquium; 2006 October 23-26; Dublin, Ireland.

**Study objectives:**

This abstract is based on an abstract of a conference presentation. It is related to a study by the same author group: Peinemann F, McGauran N, Sauerland S, Lange S. Negative pressure wound therapy: potential publication bias caused by lack of access to unpublished study results data. BMC Medical Research Methodology, 2008;8:4, for which a structured abstract is also available.

**Study objectives:**

To identify unpublished studies for a systematic review on negative pressure wound therapy (NPWT). The full systematic review has subsequently been published [Peinemann et al. BMC Medical Research Methodology 2008;8:4], and a structured abstract is available.

**Study methods:**

Preliminary searches were conducted in MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials. Publications identified from the electronic searches, such as congress abstracts, online trial registers and systematic reviews, were further analysed for details of unpublished studies. Authors and sponsors were contacted for further information.

**Study results:**

The electronic searches identified six small randomized controlled trials (RCTs) of poor quality.

Nineteen unpublished studies were identified. Three trials had been completed, seven were ongoing, four were of unclear status, and five had been discontinued. Eleven trials were sponsored by a manufacturer. Responses to requests for additional information generally did not resolve the original issues but raised new unanswered questions. One ongoing relevant RCT was identified; following completion of the trial, the results were added to the body of evidence.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

There was no breakdown of the sources of the unpublished studies.

**Key messages:**

Additional searches for unpublished studies may reveal recently completed trials.

**Study reference:**

Peinemann F, McGauran N, Sauerland S, Lange S. Negative pressure wound therapy: potential publication bias caused by lack of access to unpublished study results data. *BMC Medical Research Methodology*, 2008;8:4.

**Study objectives:**

This study is related to study by the same author group published as a conference abstract: Peinemann, F., Sauerland, S., & Lange, S. (2006). Identification of unpublished studies contribute to a systematic review on negative pressure wound therapy [abstract]. XIV Cochrane Colloquium; 2006 October 23-26; Dublin, Ireland, for which a structured abstract is also available.

To identify unpublished randomized controlled trials (RCTs) on negative pressure wound therapy (NPWT) within the framework of a systematic review.

**Study methods:**

MEDLINE, EMBASE, CINAHL and The Cochrane Library were searched (from inception to 2005) for RCTs comparing NPWT with conventional wound therapy; the search was updated in December 2006. Further information was sought in online trials registers (ClinicalTrials.gov and National Research Register (NRR)), through a search of the US Food and Drug Administration website, and through contact with German authorities. Congress proceedings and the reference lists of retrieved articles and systematic reviews were hand-searched for clues to unpublished studies. Manufacturers of NPWT devices and authors of conference abstracts were contacted for study information. Studies reported in any language were included, provided an English title was available.

Retrieved RCTs were classified as 'completed', 'discontinued', 'ongoing' or 'unclear'. Completed or discontinued RCTs were considered 'unpublished' if a full-text paper on final or interim study results was not available.

**Study results:**

A total of 28 RCTs on NPWT were identified: 12 published and 16 unpublished.

The main sources of conference abstracts and unpublished information on these were a manufacturer (n=19), the Cochrane Library (n=18), a systematic review (n=15), and congress proceedings (n=14).

Of the 16 unpublished RCTs, four had been completed, five had been discontinued, four were ongoing, and three were of unclear status. All four completed RCTs had been identified through online trials registers (three in the NRR and one in ClinicalTrials.gov). RCTs classified as discontinued, ongoing or unclear status were predominantly identified

through congress proceedings (n=9), followed by ClinicalTrials.gov (n=1), the Cochrane Library (n=1) and a manufacturer (n=1).

Overall, 10 (59%) of the 17 authors contacted and both manufacturers responded to requests for information. One manufacturer readily provided details on methodological issues and study and publication status, while the other could only provide information on case reports since it did not sponsor RCTs. One author stated that an ongoing trial had recently been completed and the manuscript submitted to The Lancet. In terms of the unpublished trials, only one author responded to enquiries about a completed trial, while the manufacturer and/or the study author responded to enquiries for eight of the discontinued or ongoing trials. No response was obtained for one ongoing trial and three of unclear status. Results data were either not available or requests for results data were not answered.

**Study limitations as noted by study authors:**

This investigation was conducted during a systematic review and was not a formal evaluation of searching for unpublished studies.

**Study limitations noted by abstractor:**

No limitations noted.

**Key messages:**

Manufacturers, the Cochrane Library, systematic reviews and congress proceedings are good sources of conference abstracts and information relating to unpublished trials.

**Study reference:**

Prentice, V. J., Sayers, M. K., & Milan, S. Accessibility of trial data to EBM reviews - lessons for systematic reviewers and the pharmaceutical industry. First Symposium on Systematic Reviews: beyond the basics; 1998 Jan 8-9; Oxford, UK.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

The paper considers how much data should be reviewed in order to capture a high proportion of the relevant evidence for a systematic review.

**Study methods:**

The authors report that systematic reviewers do not always search for grey literature ('unpublished' data such as abstracts and posters), relying instead on searches of online databases such as MEDLINE. By way of example, they drew on a review undertaken by the pharmaceutical company, Allen & Hanburys, of their respiratory publication strategy.

**Study results:**

This publication strategy review identified that 51% of the clinical trials relating to their respiratory products had been published in journals indexed in MEDLINE, Embase or CINAHL; 3% had been published in journals not indexed in these databases; 46% were in the grey literature. Published data may be several years old given the long lead times in many peer-reviewed journals.

The authors commented that the Cochrane Collaboration recommends searching at least one online mainstream database and the grey literature, and also suggests contacting pharmaceutical companies. Pharmaceutical companies are encouraged to publish trials in journals indexed in MEDLINE.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

This was an analysis of publication patterns of a pharmaceutical company, not an empirical study.



**Key messages:**

Systematic reviewers should make more effort to search grey literature, which is a valuable source of published and unpublished research. Registering grey literature on the Cochrane Controlled Trials Register would make it more readily accessible.

**Study reference:**

Reveiz, L., Andres Felipe, C., & Egdar Guillermo, O. Using e-mail for identifying unpublished and ongoing clinical trials and those published in non-indexed journals [abstract]. 12th Cochrane Colloquium: Bridging the Gaps; 2004 Oct 2-6; Ottawa, Ontario, Canada.

**Study objectives:**

This abstract is based on an abstract of a conference presentation. The research it describes has subsequently been published as: Reveiz, L., Cardona A F, Ospina E G, de Agular S. An e-mail survey identified unpublished studies for systematic reviews. *Journal of Clinical Epidemiology*, 2006;56:755-758, for which a structured abstract is available.

To determine the usefulness of e-mailing authors of clinical trials and literature reviews found in MEDLINE in detecting relevant ongoing or unpublished trials or those published in non-indexed journals for systematic review.

**Study methods:**

Following a structured search on the OVID platform from 1999 to 2003, a random sample of clinical trials (any phase) and reviews on a variety of topics was selected for each year. A questionnaire was sent to the e-mail addresses of corresponding authors on two occasions. Randomized controlled trials (RCTs) identified through the questionnaire responses were sought on MEDLINE (1966-2003), EMBASE (1974-2003), the Cochrane Controlled Trials Register, LILACS and ClinicalTrials.gov.

**Study results:**

Responses were monitored during the 4 weeks after the e-mails had been sent. Of the 525 e-mails sent, 40 replies (7.6%) were received and 105 (20%) did not reach their destination. Forty per cent of responding authors were involved in 28 ongoing RCTs; five authors had registered their trial in an ongoing trials registry. A further 12 RCTs were identified that were either unpublished or published in a non-indexed journal; two of these were in the Cochrane Controlled Trials Register.

The main reasons for nonpublication were insufficient time for analysis and manuscript preparation, contractual obligations with the pharmaceutical sponsor, research that was the topic of an undergraduate thesis, methodological errors, editorial rejection, and loss of data. Approximately half of the authors (53%) expressed a willingness to send information on unpublished studies. Authors involved in systematic reviews (29.6%) were less willing to send data concerning ongoing studies than those involved in a clinical trial (65%). The inclination to send such data was reduced by half in authors who had received a previous e-mailed request for information.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

It was unclear how many separate authors were initially contacted by e-mail and how many were contacted a second time.

**Key messages:**

E-mailing authors of studies identified through database searches can yield ongoing and unpublished RCTs of potential relevance to systematic reviews, but the response rate was poor.

**Study reference:**

Reveiz, L., Cardona A F, Ospina E G, de Agular S. An e-mail survey identified unpublished studies for systematic reviews. *Journal of Clinical Epidemiology*, 2006;56:755-758.

**Study objectives:**

This study was also published as a conference abstract: Reveiz, L., Andres Felipe, C., & Egdar Guillermo, O. (2004). Using e-mail for identifying unpublished and ongoing clinical trials and those published in non-indexed journals [abstract]. 12th Cochrane Colloquium: Bridging the Gaps; 2004 Oct 2-6; Ottawa, Ontario, Canada, for which a structured abstract is also available.

To determine the usefulness of making e-mail contact with authors of clinical trials and literature reviews found in MEDLINE to identify unpublished or difficult to locate randomized controlled trials (RCTs).

**Study methods:**

MEDLINE was searched from 1999 to 2003 for human controlled clinical trials reported in any language, from which a random sample of RCTs was selected. The 525 corresponding authors of these RCTs were e-mailed a questionnaire relating to their publication practices and unpublished information. The survey was sent twice, with 4 weeks allowed for a response after the second mailing. MEDLINE (1966-2003), EMBASE (1974-2003), the Cochrane Controlled Trials Register, LILACS and ClinicalTrials.gov were then searched for clinical trials identified through the survey and referred to as either unpublished or published in unindexed journals,

**Study results:**

The proportion of references citing an e-mail address for correspondence increased over time.

There were 40 replies (7.6%) to the 525 e-mails sent and 380 nonresponses (72.4%); 105 e-mails (20%) did not reach their destination. Responses were mainly received from authors in England (25%) and the USA (15%), followed by France, Germany and Sweden. Previous e-mailed requests for information concerning unpublished clinical trials were reported by 25% of authors completing the survey.

The survey revealed that 60% of responding authors had at least one unpublished or ongoing RCT. There were 28 ongoing RCTs, involving 41.5% of authors. Five authors had registered their trials in a trials registry: ClinicalTrials.gov, Glaxo Wellcome Register of Clinical Trials, Current Clinical Trials and NCI PDQ trials Register. A further 12 RCTs were identified that were either unpublished or published in a non-indexed journal, of which two were in the Cochrane Controlled Trials Register. The majority of authors (75%) expressed a willingness to send information on unpublished studies, but less than half of authors would

be inclined to send such data if they had received a previous e-mailed request for information. The survey found that 13 e-mails must be sent to find one RCT.

The main reasons for non-publication were insufficient time for analysis and manuscript preparation, contractual obligations with the pharmaceutical sponsor, research that was the topic of an undergraduate thesis, methodological errors, editorial rejection, and loss of data. The authors noted that e-mails sent to inaccurate e-mail addresses may not bounce.

**Study limitations as noted by study authors:**

There was a large amount of selection bias, due to “less than half of the authors having e-mail” and the response rate was low. No attempt was made to obtain the results of each trial to evaluate whether they modified the result of published meta-analysis.

**Study limitations noted by abstractor:**

Response rates were reported overall and not after each mailing.

**Key messages:**

Ongoing and unpublished RCTs may be identified by e-mailing authors of relevant studies, but the response is poor. The authors of this study consider that, despite the low hit rate, the effort is justified given the low cost and time involved.

**Study reference:**

Reyes M M, Panza K E, Martin A, Bloch M H. Time-lag bias in trials of pediatric antidepressants: a systematic review and meta-analysis. *Journal of the American Academy of Child and Adolescent Psychiatry*, 2011;50(1):63-72.

**Study objectives:**

To determine whether there is evidence of a time-lag bias in the publication of paediatric antidepressant trials, in particular those of serotonin reuptake inhibitors for the treatment of major depressive disorder in children and adolescents.

**Study methods:**

Electronic searches were conducted in PubMed. In addition, the references lists of included articles, reviews and meta-analyses were checked for citations of relevant published and unpublished research. Eligible trials were also sought through searches of online databases: the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research online database on approved drug products ('Approval History, Letters, Reviews, and Related Documents') and ClinicalTrials.gov trials register.

Time to publication was the time elapsed from study completion to manuscript publication. The date of study completion was identified from the date reported from (in order of preference) the published manuscript, the FDA report, ClinicalTrials.gov trials register, FDA Center for Drug Evaluation and Research online database, company website, correspondence with the primary author or principal investigator.

**Study results:**

The searches identified 15 randomized placebo-controlled trials eligible for inclusion: 14 published and one unpublished. The results of the unpublished trial had not been formally published, although they had been discussed in a longitudinal follow-up of study participants and several review articles. This study was not included in the meta-analysis.

The authors commented that safety factors had put pharmaceutical companies under pressure to publish paediatric antidepressant trials with negative findings that would have otherwise remained suppressed. However, there may be other psychiatry and medical fields where such trials remain unpublished or are delayed.

**Study limitations as noted by study authors:**

The small number of trials included in the analysis limited the power to detect significant differences, and to examine the effect of potential confounders. The primary outcome measure chosen for analysis (treatment response) differed from the primary outcome

reported in the published article in many cases. Trial investigators were not surveyed to determine the factors that influenced time to publication.

Study limitations noted by abstractor

It would be interesting to know where the completion date was obtained from for each individual study.

**Key messages:**

Delayed publications add to the wealth of information existing outside of the public domain. More effort should be made to ensure the timely publication of all trials, positive or negative, to minimize the risk of bias which, ultimately, can impact on expert opinion, meta-analyses, practice guidelines, and clinical practice.

**Study reference:**

Roberts I, Po A L, Chalmers I. Intellectual property, drug licensing, freedom of information, and public health. *Lancet*, 1998;352:726-729.

**Study objectives:**

This article examines the barriers imposed by pharmaceutical companies and licensing authorities to disclosing information from clinical trials, and the concerns it gives rise to. Reasons why publishing all evidence may be beneficial to manufacturers, researchers, health care organizations and patients alike, are proposed. A case study, documenting the experiences of one particular group of researchers in trying to obtain unpublished trial information, is used to illustrate the challenges in getting pharmaceutical companies and licensing authorities to disclose information.

**Study methods:**

The authors report a case where the results of a systematic review of randomized controlled trials comparing albumin with crystalloid had given considerable cause for concern. Researchers in the Cochrane Injuries Group, who had conducted the review, contacted the medical directors of three UK-based albumin manufacturers in April 1998, expressing their concerns and requesting access to the trials used in the licensing applications, to enable re-analysis of the data. The Group also sent requests for information to the Medicines Control Agency (MCA) and to the US Food and Drug Administration (FDA) in April 1998, pointing out that it was not in the public interest to withhold this information. In further correspondence, the Cochrane Injuries Group indicated its intention to take the matter up with the Ombudsman (June 1998).

**Study results:**

Approximately one week after their original request for data, one of the companies sent the published papers they had used in support of their application to the MCA. The application included only 10 of the 18 trials that were available at that time, all of which had been published. The application lacked methodological details (no search strategy, no quality assessment) and there was no quantitative synthesis of the results. Another manufacturer responded that their application had been based on an earlier US application, and that no specific clinical studies were required as it was viewed as an abridged application. The third company responded with only a promotion portfolio of 'Albumin clinical papers', which referred to just one of the 32 randomized trials included in the Cochrane review.

The MCA's initial response was to request copies of and ask questions about the Cochrane review. Subsequently (May 1998), the MCA explained that they didn't believe they held any unpublished information and considered it an unreasonable amount of work to actively search for it, although they might reconsider if justification was provided. Further correspondence resulted in a meeting in which it was agreed that the MCA would write to the



companies that manufacture albumin and other colloids, urging them to provide all published and unpublished trials.

The FDA responded in June 1998 saying that they had undertaken a search but found no relevant information.

**Study limitations as noted by study authors:**

The author did not note any limitations, as this was not a formal study with methods and results.

**Study limitations noted by abstractor:**

It was unclear whether and to what extent the Cochrane Injuries Group's attempts to obtain unpublished information were successful.

**Key messages:**

Determined efforts are needed to release documents from manufacturers and licensing agencies unwilling to disclose unpublished information about clinical trials. Changes in attitudes and legislation are necessary to ensure all relevant information is made publicly available, and patients remain the priority.

**Study reference:**

Robertson-Malt S, Afrane B, Elbarbary M. Prophylactic steroids for pediatric open heart surgery. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD005550. DOI: 10.1002/14651858.CD005550.pub2.

**Study objectives:**

To systematically review the beneficial and harmful effects of the prophylactic administration of corticosteroids, compared with placebo, in paediatric open heart surgery.

This research has been published elsewhere as: Robertson-Malt S, El Barbary M. Prophylactic steroids for paediatric open-heart surgery: a systematic review. *International Journal of Evidence-Based Healthcare*, 2008;6(4):391–395. doi:<http://dx.doi.org/10.1111/j.1744-1609.2008.00112.x>, for which a structured abstract is also available.

**Study methods:**

Electronic searches were conducted in the Cochrane Heart Group's trials registry, the Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 4, 2006), MEDLINE (1966 to January 2007) and EMBASE (1980 to January 2007). The EMRO (Eastern Mediterranean Regional Office) database of the World Health Organization was hand-searched for Arabic literature. The National Research Register and the controlled-trials.com website were searched for ongoing trials, and SIGLE and Conference Papers Index were searched for grey literature. In addition, the reference lists of included trials were hand-searched, and authors and experts in the field were contacted for details of any current research, or completed but unpublished studies. No language restrictions were applied. Principal investigators were contacted for relevant data not available in the trial reports.

**Study results:**

Hand-searches, trials registries, grey literature sources, and personal communications did not reveal any additional trials to those identified by the electronic searches.

Seventeen reports of potentially relevant trials were identified, of which five published trials (6 reports) were eligible for inclusion. One of the five trials was awaiting further assessment following translation. The remaining four trials were included in this review. Six authors were contacted; two responded with no additional information to give.

All-cause mortality could not be assessed as the data reports were incomplete.

**Study limitations as noted by study authors:**

Publication bias could not be formally assessed because of the small number of studies identified.

**Study limitations noted by abstractor:**

No other limitations noted.

**Key messages:**

Attempts to identify grey literature and unpublished studies were unsuccessful. Contacting key investigators in the field did not yield any additional unpublished data.

**Study reference:**

Robertson-Malt S, El Barbary M. Prophylactic steroids for paediatric open-heart surgery: a systematic review. *International Journal of Evidence-Based Healthcare*, 2008;6(4):391–395. doi:<http://dx.doi.org/10.1111/j.1744-1609.2008.00112.x>

**Study objectives:**

To systematically review the beneficial and harmful effects of the prophylactic administration of corticosteroids, compared with placebo, in paediatric open-heart surgery.

This research is the subject of a Cochrane review [Robertson-Malt S, Afrane B, Elbarbary M. Prophylactic steroids for pediatric open heart surgery. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD005550. DOI: 10.1002/14651858.CD005550.pub2.], for which a structured abstract is also available.

**Study methods:**

The Cochrane Heart Group's trials registry, the Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 4, 2006), MEDLINE (1966 to January 2007) and EMBASE (1980 to January 2007) were searched for relevant studies. In addition, bibliographies were checked, key journals were hand-searched, and experts were contacted. No language restrictions were applied.

Study authors were e-mailed requests for missing information on methodology and results, and to elicit details of any current work in the area.

**Study results:**

Seventeen reports of potentially relevant trials were identified, of which five published trials (6 reports) were eligible for inclusion. One of the five trials was awaiting further assessment following translation. The remaining four trials were included in this review. All four principal authors were contacted for further information, but only three responded. No additional unpublished data were provided.

All-cause mortality could not be assessed as the data reports were incomplete.

**Study limitations as noted by study authors:**

Publication bias could not be formally assessed because of the small number of studies identified.

**Study limitations noted by abstractor:**

There were discrepancies between the search strategies described in the abstract and the main text of the article. The authors appear to have sought unpublished research but only published trials were considered in the review.

**Key messages:**

Contacting key investigators in the field did not yield any unpublished data.

**Study reference:**

Roderick, P., Ferris, G., Baigent, C., & Collins, R. Impact of methodology on the quality and findings of a systematic review of thromboprophylaxis. Second Symposium on Systematic Reviews: Beyond the Basics; 1999 Jan 5-7; Oxford, UK.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To assess the impact of using original data from trialists, non-English language trials and multiple data sources on a systematic review of mechanical and pharmacological agents for the prevention of venous thromboembolism in surgical and medical patients.

**Study methods:**

Electronic databases (including MEDLINE, EMBASE, BIOSIS, Derwent, the Cochrane Library) were searched for randomized controlled trials reported in any language. In addition, references from the PVD Cochrane group were searched, leading manufacturers were contacted for unpublished trials, and review bibliographies were cross-checked for eligible trials. All trialists (n=290) with potentially eligible trials were contacted for their original tabular data and clarification of trial design.

**Study results:**

The abstract does not report any results.

The authors intended to examine response rates, resource implications, the methodological impact of using original data obtained from trialists, and the contribution of non-English language trials. Details of the sources of robust data used in the final review were to be provided.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

The abstract lacked results.

**Key messages:**

Contact with leading manufacturers and trialists may yield unpublished trials and original data.

## **Study reference**

:

Royle P, Bain L, Waugh N. Systematic reviews of epidemiology in diabetes: finding the evidence. *BMC Medical Research Methodology*, 2005;5:2.

[Also presented as: Royle, P., Bain, L., Payne, L., Hill, M., & Waugh, N. The value of literature searching beyond Medline and Embase for systematic reviews of interventions and epidemiology in diabetes [abstract]. In: Proceedings of the First Annual Meeting of the Health Technology Assessment International (HTAi); 2004 May 30 - June 2; Krakow, Poland.]

## **Study objectives:**

To determine how many databases it is necessary to search to ensure a comprehensive coverage of the literature in diabetes epidemiology, and to examine the efficiency of searching when conducting systematic reviews on this topic.

## **Study methods:**

The authors searched for journal articles and grey literature on diabetes epidemiology, in any language, in databases other than MEDLINE and EMBASE. The databases searched were: AMED, ASSIA, BIOSIS (abstracts only), BNI, CINAHL, Conference Papers Index, Dissertation Abstracts US, HMIC, Index to Theses UK, ISI Proceedings, PsycINFO, NLM Gateway, LILACS, National Research Register (NRR), SIGLE, SCI (abstracts only), SSCI, and Zetoc.

Grey literature was defined as any literature not published in a peer-reviewed journal.

## **Study results:**

A search of LILACS retrieved 23 Spanish and Portuguese language articles reporting studies conducted in Latin America.

Searches of Dissertation Abstracts US, Index to Theses UK and SIGLE identified 51 dissertations. The majority of these (92%) had associated publications in journals indexed in MEDLINE or EMBASE. SIGLE did not reveal any grey literature other than dissertations. The NRR provided brief details of 18 ongoing projects that would otherwise have not been identified. The authors commented that the NRR might be a useful source if unpublished results could be included in the review.

None of the 25 articles identified through the Conference Proceedings Index appeared to have been published as journal articles after five years. Articles found in Zetoc Conference Search (n=8), SCI (n=171) and BIOSIS (abstracts only) (n=71) had been published in full to varying degrees (BIOSIS 11%, SCI 30%, Zetoc 50%), typically within three years where the time to publication was reported.

**Study limitations as noted by study authors:**

The search to identify diabetes journal articles was restricted to English language journals only. The quality of the articles identified from databases other than MEDLINE and EMBASE was not assessed. Searches were restricted to the range of available databases. Additional databases, inaccessible or unknown, that cover foreign language and regional journals not indexed in MEDLINE and EMBASE may exist.

**Study limitations noted by abstractor:**

Only databases searches were used to identify grey literature. Other approaches, such as contacting experts in the field and searching trials registers, may have yielded further studies.

**Key messages:**

The NRR and meeting abstracts are valuable sources of unpublished research, but quality and bias issues need consideration. Research reported in dissertations is largely published. MEDLINE and EMBASE do not provide comprehensive coverage of foreign language journals.



**Study reference:**

Royle P L, Bain L, Waugh N R. Sources of evidence for systematic reviews of interventions in diabetes. *Diabetic Medicine*, 2005;22:1386-1393.

[Also presented as: Royle, P., Bain, L., Payne, L., Hill, M., & Waugh, N. The value of literature searching beyond Medline and Embase for systematic reviews of interventions and epidemiology in diabetes [abstract]. In: Proceedings of the First Annual Meeting of the Health Technology Assessment International (HTAi); 2004 May 30 - June 2; Krakow, Poland.]

**Study objectives:**

To analyse the effect on systematic reviews in diabetes interventions of including only trials that are indexed in MEDLINE, and to assess the impact of adding trials from other databases and the grey literature.

**Study methods:**

MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews (in the Cochrane Library, 2004, Issue 2) were searched for all systematic reviews of diabetes interventions which included a meta-analysis of randomized controlled trials, and were published since 1996. Reviews had to have searched more than one source for trials. MEDLINE, Cochrane CENTRAL and EMBASE were checked for the included trials.

Details of the sources searched for each meta-analysis were recorded. The meta-analyses in Cochrane reviews were re-done to assess the impact of including only those trials indexed in MEDLINE, and the effect of then adding trials from other sources.

**Study results:**

Forty-four reviews including a total of 643 trials (695 articles) were included. Of the 695 articles, the majority (93%) were published in peer-reviewed journals and the remainder (7%) came from grey literature sources such as conference abstracts, unpublished data, dissertations, reports, and articles in press. The reviews mainly searched MEDLINE (93%), followed by CENTRAL (55%) and EMBASE (48%).

MEDLINE yielded 575 articles (83%).

The 120 articles (17%) not indexed in MEDLINE comprised journal articles (62%) and grey literature (38%), and were spread across 23 reviews. However, a high proportion (43%) came from one review on Chinese herbs. The reviews retrieved the non-MEDLINE articles from journals (n=14), meeting abstracts or conference proceedings (n=9), drug manufacturers (n=2), dissertations (n=1), and unspecified unpublished sources (n=2). Two meta-analyses were based largely on unpublished studies (8/9 studies) or 'data on file' (8/8

articles) from the drug manufacturer. Sources of non- MEDLINE data which had the biggest effect on the meta-analyses were journal articles from CENTRAL and EMBASE and unpublished data (mainly from industry).

**Study limitations as noted by study authors:**

It was assumed that the review authors had found all relevant studies.

**Study limitations noted by abstractor:**

This study was not a formal evaluation of the sources used to find non-MEDLINE indexed articles in published reviews. The authors drew conclusions from re-analysed meta-analyses of Cochrane reviews but qualitative estimates for meta-analyses published in journals.

**Key messages:**

Searching MEDLINE alone is not sufficient, but exhaustive searching of many databases is not worthwhile. Meeting abstracts and contact with authors and drug manufacturers are useful sources of unpublished data, especially for new interventions. The authors commented that, in their experience, they had found drug companies willing to help.

**Study reference:**

Royle P, Milne R. Literature searching for randomized controlled trials used in Cochrane reviews: rapid versus exhaustive searches. *International Journal of Technology Assessment in Health Care*, 2003;19(4):591–603.

**Study objectives:**

To analyze sources searched in Cochrane reviews, to determine the proportion of trials included in reviews that are indexed in major databases, and to compare the quality of these trials with those from other sources.

**Study methods:**

The authors retrieved all new systematic reviews in the Cochrane Library (Issue1 2001) that included only randomized controlled trials (RCTs) or quasi-RCTs. The Cochrane Controlled Trials Register (CCTR), MEDLINE, EMBASE, and the Science Citation Index/Social Sciences Citation Index were checked for the included trials. Any trials not indexed in these databases were sought in a further 25 databases indexing published and grey literature.

Information on the search strategy used for each review was extracted: publication status, publication format and language. Publication status was categorized as published data only, unpublished data only, a mixture of published plus unpublished data, or unpublished data sought but not used. The quality of the included trials was assessed in terms of allocation concealment and number of patients.

**Study results:**

Sixty-six reviews of potential relevance were identified. Their search strategies involved a total of 79 sources, of which the most frequently used were MEDLINE (81.8%), contact with authors, expert or manufacturers (82%), reference lists/bibliographies (80.3%), CCTR (74.2%), EMBASE (68.2%), Collaborative Review Groups Trials Registers (60.6%), and hand-searches of journals and conference papers (56.1%). CINAHL, SCI, PsycLIT and SSCI were used in 10 to 27% of reviews, and AMED, BIOSIS, Dissertation Abstracts, NRR, HealthSTAR, websites, the Cochrane Library and Current Contents in less than 10%. The mean number of sources searched per review was 8 (range: 2 to 30).

The various publication formats included English-language journal article, foreign language journal article, drug company report, meeting abstract, manuscript in press or preparation, dissertation, book chapter, ongoing trial, and other unspecified formats.

The 57 reviews finding at least one trial reported a total of 781 trials, of which CCTR identified 78.5%. Sixty-two trials indexed in CCTR were not in MEDLINE or EMBASE, of which 36 were conference proceedings/meeting abstracts. A total of 136 trials not indexed in the major databases: CCTR, MEDLINE and Embase (non-CME trials) were found in 29 reviews. Over half (56%) of these were classified as unpublished; insufficient details of these were provided in the original reviews.

The authors commented that there was no evidence that non-CME trials were of poorer quality than CME trials. The vast majority of the higher quality non-CME trials were either unpublished or published in Chinese complementary medicine journals.

**Study limitations as noted by study authors:**

It was a retrospective study, and it only analyzed a small number of reviews. It was assumed that Cochrane reviewers fully and accurately reported their search strategies. There may have been inconsistencies between reviewers in classifying publication status and allocation concealment. The outcome of searching was measured in terms of the number of unique studies identified and not the information added. The study did not consider the time costs of the scientists and reviewers.

**Study limitations noted by abstractor:**

The included trials were not summarized according to publication format (e.g. ongoing trial, drug company report, manuscript in press). Publication categories were not specifically defined.

**Key messages:**

Hand-searching meeting abstracts and communication with experts and drug manufacturers is important to ensure a comprehensive search. Contacting authors and manufacturers to find unpublished trials appeared to be a more effective method of obtaining additional better quality trials.

**Study reference:**

Royle P, Waugh N. Literature searching for clinical and cost-effectiveness studies used in health technology assessment reports carried out for the National Institute for Clinical Excellence appraisal system. *Health Technology Assessment*, 2003;7(34).

**Study objectives:**

To contribute to making searching for Technology Assessment Reports (TARs) more cost-effective by suggesting an optimum literature retrieval strategy, based on empirical data. Two of the main objectives were to survey the frequency with which different sources have been searched in recent TARs, and to determine which sources, other than the major databases, indexed studies included in TARs.

**Study methods:**

The authors reviewed a sample of 20 recent TARs (December 2000 to 2002) and recorded details of all sources searched for clinical and cost-effectiveness studies. Each of the included databases was then checked to see if it was indexed in any of the following databases: initially, MEDLINE, EMBASE and either the Cochrane Controlled Trials Register (CCTR) or NHS EED, then the Science Citation Index and BIOSIS, followed by various subject-specific and grey literature databases.

**Study results:**

The 20 TARs used 67 different sources: 48 were electronic databases and the remainder were non-database sources such as sponsor or industry submissions, consulting reference lists, web searching, and contact with manufacturers and experts. A mean of 20 sources were searched per review. Trials registries were used in 5 to 20 TARs. Sponsor/industry submissions, web searches and reference lists were each used in 10 to 20 reviews, and other sources of unpublished and grey literature typically in fewer than 10.

Meeting abstracts and unpublished material accounted for 48 and 37 studies, respectively, of the 424 clinical effectiveness studies. Thirty-one of the 130 cost-effectiveness studies were classified as unpublished, 2 as abstracts and 2 as grey literature. Abstracts (n=6), reference sources (n=21), unpublished (n=21) and grey literature (n=12) also contributed to the 121 articles used in the economic modelling.

The 37 unpublished clinical effectiveness studies comprised 26 confidential industry submissions, one dissertation, two posters, five unpublished papers, and three NICE documents. All but one of the unpublished cost-effectiveness studies were company submissions. Unpublished studies used in the economic modelling were predominantly obtained through personal communication and contact with experts. Grey literature sources included websites, NICE guidance and DEC reports.

**Study limitations as noted by study authors:**

The number of TARs studied was small and there is the potential for bias given the high number of cancer topics in the NICE programme. Many of the key measurement decisions were made by one reviewer. It was assumed that the study designs and sources searched were accurately and completely reported. The impact of removing difficult to find studies from the review was not explored, and the search terms used and costs of searching were not evaluated. The design of search filters required some subjective judgement in relation to study design. Not all details of the included studies were available to reviewers.

**Study limitations noted by abstractor:**

Tables summarising the yield of individual grey literature or non-database sources would have been helpful.

**Key messages:**

Searching beyond a small number of major databases gives marginal returns for the costs and time involved. Non-database sources such as manufacturers' submissions, recent meeting abstracts, contact with experts, and checking reference lists offer a productive means of identifying further studies.

**Study reference:**

Savoie I, Helmer D, Green C J, Kazanjian A. Beyond Medline: reducing bias through extended systematic review search. *International Journal of Technology Assessment in Health Care*, 2003;19(1):168–178.

**Study objectives:**

Some of the research described in this paper has been published as: Helmer D, Savoie I, Green C, Kazanjian A. Evidence-based practice: extending the search to find material for the systematic review. *Bulletin of the Medical Library Association*, 2001;89(4):346-352, for which a structured abstract s also available.

**Study objectives:**

To evaluate the sensitivity and precision of various extended search methods in identifying randomized controlled trials (RCTs) for two systematic reviews (the use of acupuncture for addiction and lipid-lowering therapy for coronary heart disease).

**Study methods:**

The authors undertook a prospective analysis of major databases and extended search strategies. The major databases searched were MEDLINE, EMBASE, HealthSTAR and Current Contents in both reviews; additional databases were searched for acupuncture.

The extended search strategies differed between the two reviews but, essentially, comprised: searches of subject-specific databases, trials registries, library web catalogues and in-house databases; hand-searches of key indexed and nonindexed journals located either through the local academic health sciences library or through Uncover Reveal Table of Contents; screening the reference lists of retrieved articles; Internet searches for peer-reviewed material and contact details of relevant organizations and researchers; personal communication with organizations and researchers.

Sensitivity and precision were evaluated. Sensitivity reflected the proportion of RCTs uncovered by any extended search method, of the total number of known RCTs from the gold standard (major databases plus extended search). Precision reflected the proportion of RCTs identified by any extended search method, of all items uncovered by that method.

**Study results:**

The extended search yielded 94 additional RCTs for inclusion. The nine trials identified for acupuncture and 85 trials for lipid-lowering therapies represented 42.9% and 23.5%, respectively, of the RCTs included in the two reviews. The overall precision of the extended search strategies in identifying RCTs was 8.9% for acupuncture and 31.8% for the lipid-lowering project. A posthoc analysis found that the major database search had missed 75 of the 94 RCTs, partly due to timing and indexing issues.

For acupuncture, specialized databases/trials registries and reference lists each identified three RCTs (33.3%), personal communication revealed two RCTs (22.3%) and hand-searching one RCT (11.1%). Internet searches did not reveal any RCTs. Specialized databases/trial registries and reference lists had the highest sensitivity (both 14.2%) and precision (17.6% and 8.3%, respectively).

The majority of RCTs for lipid-lowering therapies were identified from specialized databases/trials registries (n=49; 57.6%), followed by reference lists (n=26; 30.6%). Hand-searching contributed six RCTs (7.1%), personal communication three RCTs (3.5%), and Internet searches one RCT (1.2%). Specialized databases/trial registries had the highest sensitivity and precision (13.6% and 52.7%, respectively), followed by reference lists (7.2% and 41.9%).

**Study limitations as noted by study authors:**

The effectiveness of extended searches may have been underestimated given difficulties in acquiring grey literature (e.g. locating it and cost). Not all personal communication produced a response. The extended search methods were not conducted in sequence and overlap was not considered when coding retrieved items; these issues could affect the total number of articles uncovered by the various extended search methods. Indexing problems may have impacted on the results.

**Study limitations noted by abstractor:**

It was unclear how many of the identified RCTs were actually unpublished, and whether any were ongoing trials. Response rates for personal communication would have been useful.

**Key messages:**

Searches of specialized databases, trials registries and references lists were the most effective methods of identifying additional RCTs to those found in major databases. Hand-searching journals, personal communication and Internet searches yield little additional relevant material.



**Study reference:**

Scherer R W, Ervin A and Dickersin K. Where are authors registering clinical trials? [abstract]. *Clinical Trials*, 2008;5(4):393

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To examine where authors of abstracts presented at the Association for Research in Vision and Ophthalmology (ARVO) meeting 2007 registered their studies, and to determine the actual design of registered studies.

**Study methods:**

Organizers of the 2007 ARVO meeting were contacted for a list of abstracts for which authors had entered information about trial registration. Each abstract was classified in terms of study design and type of information on trial registration.

**Study results:**

Authors of 256 (4.2%) of 6044 abstracts provided information on trial registration. The majority (75%) had registered their trials at either ClinicalTrials.gov (166/256) or another international trials registry (25/256). Other information the authors reported included registration at local institutions (19/256), ethics committees (14/256) and regulatory or government agencies (10/256), a reason for not registering the study (5/256), an intention to register (3/256), or other (14/256).

The 256 abstracts described randomized controlled trials (105), controlled trials (18), uncontrolled trials (96), case-control studies (22) and other studies (12) (animal studies, laboratory experiments, image evaluation with no humans, simulation experiment). Within each type of study design, instances of registration in a publically available trial registry were found.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

From the numbers reported for each study type, the total number of studies was 253. The number of correctly registered trials was not reported overall, or according to study design.

**Key messages:**

Authors' misconceptions about trial registration need rectifying, in particular what types of trial and where they should be registered. This could increase the number of trials registered.

**Study reference:**

Shadish W R, Doherty M, Montgomery L M. How many studies are in the file drawer? An estimate from the family/marital psychotherapy literature. *Clinical Psychology Review*, 1989;9:589-603.

**Study objectives:**

To provide an empirical estimate of the number of unpublished studies in the file drawer, by way of a random sample survey conducted during an ongoing meta-analysis of the effects of family/marital psychotherapies with distressed clients.

**Study methods:**

The authors conducted a random sample survey of 519 members of five relevant professional organizations (AAMFT, 1985; AFTA, 1986; AABT, 1984; Divisions 37 and 43 of the APA, 1985) (total membership 14,002) that might have unpublished studies filed away. Each individual was mailed a cover letter describing the purpose of the survey, a one-page questionnaire, and a stamped addressed envelope for return. The instructions provided were broad in order to avoid the loss of relevant unpublished studies. The questionnaire sought to establish whether individuals had conducted relevant research and produced any reports, and to obtain copies of such reports.

When letters were returned as not deliverable to the address, the addressee was replaced by the next name listed in the relevant directory. Four waves of mailings to responders and subsequent nonresponders, including replacements, were sent out.

A file drawer study was defined as one that met the inclusion criteria, was accessible directly by the respondent, and was not a dissertation, an ongoing study or currently being analysed. The definition included convention papers and final grant reports.

**Study results:**

The original searches located 165 randomized controlled studies for the meta-analysis, of which about 50 were unpublished dissertations. Search procedures had involved electronic searches, checking the bibliographies of published reviews, screening journal tables of contents and abstracts, and specialist advice.

About 15% of the mailings were returned as not deliverable to the address. Overall, 375 (72%) individuals responded. Of these, 27 (7%) gave a positive response to having been engaged in a relevant study, and were contacted by telephone if necessary. Five respondents (1.3%) had conducted a study but no longer had access to the written report, four (1.1%) enclosed a written report, and nine (2.4%) requested to be contacted for copies of their written report. Only three of the 13 available reports met the criteria for a file drawer study and would otherwise have qualified for inclusion in the meta-analysis.

The authors commented that presently available evidence suggests that there might be roughly one unpublished file drawer study for every published study.

**Study limitations as noted by study authors:**

Methodological features of the study probably resulted in underestimates of both the number and proportion of file drawer studies. The proportion of file drawer studies to published studies may be an overestimate if the original sample of included studies was not exhaustive. Estimates of the prevalence of file drawer studies are dependent on the inclusion criteria for the meta-analysis. The results may not be generalizable to other substantive areas.

**Study limitations noted by abstractor:**

There is no standard definition of a file drawer study. However, the authors acknowledged this and gave the reasoning behind the definition they used. The period of time over which the survey was carried out was unclear.

**Key messages:**

The potential existence of a large number of file drawer studies, possibly as many as there are published studies and dissertations, is a cause for concern. However, attempts at retrieval will incur substantial costs for little return.

**Study reference:**

Shukla, V. The challenge of obtaining unpublished information from the drug industry [abstract]. XI Cochrane Colloquium: Evidence, Health Care and Culture; 2003 Oct 26-31; Barcelona, Spain.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To compare the success of two methods used to obtain unpublished information from the drug industry.

**Study methods:**

The author used two different approaches to elicit unpublished information from the pharmaceutical industry for each of five systematic reviews of drugs. The first approach entailed sending out a general request letter. The second approach identified unpublished studies in advance through electronic searches of BIOSIS Previews and hand-searches of conference abstracts, review articles and the bibliographies of included studies. Google was also searched. The drug industry was asked to provide specific details of the unpublished studies identified.

**Study results:**

No unpublished information was obtained through the first approach.

The second approach yielded relevant unpublished information for four of the five systematic reviews. The information was supplied as either manuscripts or oral/poster presentations. This had a major impact on the findings of a Canadian Co-ordinating Office for Health Technology Assessment (CCOHTA) report in several cases.

**Study limitations as noted by study authors:**

The abstract does not note any limitations, but does mention the sample was small.

**Study limitations noted by abstractor:**

The abstract did not report the proportion of studies for which unpublished information was received, or describe the level of response achieved.

**Key messages:**

Identifying unpublished studies in advance of contacting industry for specific unpublished information was more fruitful than sending them a general request.

**Study reference:**

Siegfried, N. L., Pienaar, E. D., & Abrams, A. L. More needle, less haystack - identifying ongoing trials with the Pan African Clinical Trials Registry. Oral presentation at the Joint Cochrane and Campbell Colloquium; 2010 Oct 18-22; Keystone, Colorado, USA [abstract].

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To categorise interventions in trials registered on the Pan African Clinical Trials Registry ([www.pactr.org](http://www.pactr.org)) and map these to published Cochrane reviews or protocols.

To demonstrate the use of searching [www.pactr.org](http://www.pactr.org) for review authors.

**Study methods:**

The authors downloaded details of trials registered on [www.pactr.org](http://www.pactr.org) on 23 March 2010, then searched the Cochrane Database of Systematic Reviews (CDSR) 2010, Issue 2 for published reviews or protocols evaluating the interventions reported in these trials.

**Study results:**

Twenty-five trials were registered on [www.pactr.org](http://www.pactr.org), of which 13 were randomized controlled trials of efficacy that met Cochrane review criteria. The CDSR search yielded nine reviews and one protocol where data from eight of the ongoing trials identified would be eligible for inclusion. None of the reviews reported these.

The authors commented that access to [www.pactr.org](http://www.pactr.org) is free and researchers should search it using the disease field. Sensitivity may be greatest for topics prevalent in resource-poor settings.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

Further details of searching [www.pactr.org](http://www.pactr.org) may be helpful.

**Key messages:**

The Pan African Clinical Trials Registry ([www.pactr.org](http://www.pactr.org)) is a valuable source of ongoing clinical trials in Africa; access is free. Cochrane reviewers should include such trials in any review updates.

**Study reference:**

Silagy C, Gray S, Fowler G, Lancaster T. Development of a prospective register of smoking cessation trials. *Controlled Clinical Trials*, 1996;17(3):235–241.

**Study objectives:**

This abstract is based on a report of the development of a register of planned and ongoing randomized controlled trials (RCTs) of smoking cessation interventions. The objective of the registry is to compile and maintain lists of trials, but not to collect any results or participant information.

**Study methods:**

Potential sources of trials for the register were obtained from four in-house databases containing details of journals, principal authors and public health organizations that had published or promoted smoking cessation research, and pharmaceutical companies with smoking cessation products in their portfolio.

Principal authors were contacted by letter, inviting them to register any relevant planned or ongoing trials and requesting them to forward registration forms to researchers whom they knew were currently involved in eligible studies. Editors of journals that had published at least three RCTs of smoking cessation interventions were asked to publish a letter that outlined the register and invited contributions. Medical directors of pharmaceutical companies were asked to forward trial registration forms to the principal investigators of any relevant research they were currently funding, but not to release project details directly. The heads of public health organizations were requested to advertise and promote the registry within their networks. In the absence of a reply, follow-up letters were sent after 4 months. Any letters 'returned to sender' were resent if a more recent address for the researcher could be found on MEDLINE.

**Study results:**

Seventy-eight of the 389 letters sent generated a response, of which 38 resulted in trial registration. Fifteen of the remaining 40 forms related to completed trials. Fifty-nine of the 333 researchers replied. Three of the 22 journals approached agreed to publish a letter to the editor, and two publicized the register through a brief announcement in a notes or news section.

The majority (n=27) of the 38 planned or ongoing trials that had been registered as of 20 September 1994 arose from researchers in the database. The remainder were obtained through referrals/suggestions from other researchers (n=4), the pharmaceutical companies' database (n=1), were prompted by members of the advisory committee (n=3), or the contact source was not known (n=3). Neither the journals nor public health bodies' databases resulted in the registration of any trials.

The authors outlined their intentions to contact researchers annually for details of any new trials and for their publication plans if the study results have not been published within 12 months of the projected completion date.

**Study limitations as noted by study authors:**

The authors acknowledge that, despite substantial progress, the register is far from being comprehensive.

**Study limitations noted by abstractor:**

This paper described the sources used to populate a registry with planned and ongoing trials; it was not a formal evaluation of the sources used.

**Key messages:**

Mailing researchers in the field was the most useful method of obtaining details of relevant trials, but the response was very low. Attempts to publicize the register and directly approach relevant public health organizations and pharmaceutical companies yielded few trials.



**Study reference:**

Simes R J. Confronting publication bias: a cohort design for meta-analysis. *Statistics in Medicine*, 1987;6(1):1–29.

**Study objectives:**

To develop a model for pooling the results of clinical trials, which is free from publication bias, based on an international registry of all clinical trials from which a cohort of trials may be selected independently from the trial results.

To illustrate the approach by using the International Cancer Research Data Bank (ICRDB) registry of cancer clinical trials to evaluate the effect of chemotherapy on survival in advanced ovarian cancer.

**Study methods:**

Clinical trials published by October 1983 were identified through an electronic search of MEDLINE, and hand-searches of reference lists in pertinent articles and also abstracts from two relevant organizations. Registered clinical trials were selected from protocols registered with the ICRDB by October 1983 and contained in the Compilation of Experimental Cancer Therapy Protocol Summaries or its associated computer database CLINPROT. The principal investigators of all published trials and registered trials were contacted by letter for further information. In the absence of a response, investigators were sent a second letter; where possible, letters were also sent to an alternative address. Pooled analyses were conducted separately for registered trials and published trials in advanced ovarian cancer. Follow-up and publication details were also reported for trials in multiple myeloma.

**Study results:**

Investigators generally replied positively to requests for information, although much had been published already. Updates of trial data beyond the last publication were rarely obtained, and none of the investigators provided new data on published, unregistered trials. The ICRDB yielded a total of 27 protocols for ovarian cancer (n=16) and multiple myeloma (n=11). Eight letters (30%) were returned because they had the wrong address. Seventeen investigators (63%) responded to the letters sent, of which 11 (41%) provided new or additional information. Follow-up data for three protocols (11%) could not be obtained from either the principal investigators or the literature.

Overall, 29 ovarian cancer trials were identified: 13 trials had been published but not registered by October 1983, 8 trials were published and registered, and 8 trials were registered only (and had not been identified through literature searches). The pooled analyses based on published and registered trials gave different conclusions. Problems in implementing the model were discussed.

**Study limitations as noted by study authors:**

Assumptions had to be made because of missing data for some studies. The choice of statistics used to pool the trial results was governed mainly by the data available rather than what might be optimal.

**Study limitations noted by abstractor:**

The results of investigator follow-up were not reported for published trials.

**Key messages:**

Information in current trial registers may be incomplete or inaccurate; there is a need to establish and maintain an international registry of all clinical trials. Attempts to contact principal investigators for further trial details may not be fruitful.

**Study reference:**

Slobogean G P, Verma A, Giustini D, Slobogean B L, Mulpuri K. MEDLINE, EMBASE, and Cochrane index most primary studies but not abstracts included in orthopedic meta-analyses. *Journal of Clinical Epidemiology*, 2009;62(12):1261–1267.

**Study objectives:**

To test the hypothesis that all primary studies used in orthopaedic meta-analyses are indexed in MEDLINE or EMBASE.

**Study methods:**

MEDLINE was searched for all meta-analyses of orthopaedic surgical interventions published in English from 1995 to 2005. The authors extracted information from each meta-analysis, such as the specific databases and sources the authors used to identify the included studies.

MEDLINE and EMBASE were then searched for each of the primary studies in each meta-analysis (defined as the 'gold standard' set) and secondary searches were conducted in the Cochrane Library, Web of Science (WoS) and CINAHL.

**Study results:**

A total of 101 meta-analyses were identified, of which 39 underwent full data extraction. The meta-analyses reported 699 articles in total, which reduced to 647 when accounting for duplication. The included articles were located using 25 different sources. On average, each meta-analysis used four sources to identify trials.

All 39 meta-analyses used MEDLINE supplemented with other databases and nonelectronic approaches. The other main sources or methods were manual searches (n=25; 64%), the Cochrane Library (n=22; 56%), EMBASE (n=15; 39%) and content experts (n=10; 26%). Less frequently used sources were CINAHL (15%), SCI (15%), textbooks (10%), Grateful Med (8%), and Allied and Complementary Medicine (5%). Databases used once only included British Nursing Index, DHSS: Data, Current Contents, SIGLE, metaRegister of Controlled Trials, French Database of Theses, THA, FDA, AMED, DARE, SPORTdiscus, BIOSIS, Dissertation Abstracts, Index to UK Theses, and Lonesome Doc.

When assessing the recall rates of MEDLINE and EMBASE, 56 references were not in either database. These were primarily abstracts reported in journal supplements or conference proceedings. The Cochrane Library demonstrated the most comprehensive accumulation of evidence of the additional databases searched.

**Study limitations as noted by study authors:**

The authors did not note any limitations of their study.

**Study limitations noted by abstractor:**

The study was not an evaluation of search strategies used to identify studies for orthopaedic meta-analyses, although it did provide a general overview of the search strategies that were used. There was no particular focus on unpublished material.

**Key messages:**

Authors of orthopaedic meta-analyses use a wide variety of sources to identify studies. The Cochrane Library is particularly useful in increasing the yield of conference proceedings and abstracts, which may not be identified through MEDLINE and EMBASE.

**Study reference:**

Soares H P, Kumar A, Daniels S, Sargent D J, Buckner J C, Swann S, et al. Lack of publication bias in randomized clinical trials (RCTs) sponsored by the National Cancer Institute (NCI) and performed by Cooperative Oncology Groups (COGs) [abstract]. *Journal of Clinical Oncology*, 2004; 22(14S):6004.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To assess the publication rate of Cooperative Oncology Groups (COGs) sponsored by the US National Cancer Institute (NCI).

**Study methods:**

The authors obtained a list of all completed phase III randomized controlled trials (RCTs), along with details of their publication status, from the main protocol office of the NCI, principal investigators, and statistical offices from four of the eight NCI COGs that have conducted and completed more than 30 RCTs. The COGs included in the analysis were the Radiation Therapy Oncology Group (RTOG), the Children's Oncology Group (CsOG), the North Central Cancer Treatment Group (NCCTG) and the National Surgical Adjuvant Breast and Bowel Project (NSABP). The publication rate was determined.

Completed studies were defined by the NCI as studies that met their primary objectives, were closed to accrual and in which all patients have completed therapy.

**Study results:**

The analysis included 245 studies: 5 unpublished and 240 published. The unpublished studies had been conducted by two groups, the RTOG (3/60) and CsOG (2/74). The publication rate of individual COGs was high, ranging from 95% to 100%.

Of the 240 published studies, the majority (98%) were published as manuscripts and the remainder (2%) as abstracts only. Two groups had published some studies as abstracts, the CsOG (4/72) and NCCTG (2/81).

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

It was unclear why this study only considered four of the eight COGs with more than 30 completed RCTs.

**Key messages:**

Few completed trials conducted by NCI-sponsored COGs are unpublished.

**Study reference:**

Sodha R J, Van Amelsvoort T. Multi-database searches in biomedicine: citation duplication and novelty assessment using carbamazepine as an example. *Journal of Information Science*, 1994;20:139.

**Study objectives:**

To determine the rate of citation duplication during multi-database searches for carbamazepine adverse drug reactions, and to assess novelty of the output.

**Study methods:**

MEDLINE, EMBASE, Ringdoc and an in-house database of literature on company pharmaceutical products (CG-DOC) were searched for citations relating to carbamazepine adverse drug reactions published in 1992. Original publications were obtained for records that overlapped across at least three of the four databases.

**Study results:**

The internal database (CG-DOC) uncovered the most papers (218), followed by EMBASE (170), Ringdoc (121) and MEDLINE (76). Approximately half of those retrieved by CG-DOC (106/218) and EMBASE (85/170) were considered unique papers, less for Ringdoc (32/121) and MEDLINE (10/76). Fewer papers in the set of unique records mentioned carbamazepine in the title or abstract compared with overlapping records. CG-DOC contained the highest proportion of unique relevant records (82/106), then Ringdoc (19/32), MEDLINE (3/10) and EMBASE (7/85). Most of the relevant unique citations in CG-DOC were abstracts from meetings and proceedings, whereas those from EMBASE came from non-English journals not indexed by the other three databases. More novel items were retrieved from CG-DOC (71/106) than the other databases.

The authors commented that if all the documents retrieved were combined in a single database (n=470), the in-house database would make a considerable contribution (23%) to the overall number of records identified.

**Study limitations as noted by study authors:**

The authors did not note any limitations of their study, which was reported as a 'brief communication'.

**Study limitations noted by abstractor:**

This study focused on published work and did not aim to explore search strategies for unpublished or grey literature. Sources of unique citations were not described for Ringdoc or MEDLINE.

**Key messages:**

Company databases are an important source of unique, and often novel, citations that are not present in mainstream commercial databases.



**Study reference:**

Song F, Eastwood A J, Gilbody S, Duley L, Sutton A J. Publication and related biases. *Health Technology Assessment*, 2000;4(10).

**Study objectives:**

To identify and appraise studies that have examined methodological issues and provided empirical evidence about publication and other dissemination-related biases.

An update was published in 2010 [Song F, Parekh S, Hooper L, Loke YK, Ryder J, Sutton A J, et al. Dissemination and publication of research findings: an updated review of related biases. *Health Technology Assessment*, 2010;14(8)], for which a structured abstract is available.

**Study methods:**

The Cochrane Review Methodology Database, MEDLINE, EMBASE, BIDS, Library and Information Science Abstracts, PsycLIT, Sociofile, ERIC, Dissertation Abstracts, MathSci, British Education Index, SIGLE and ASSIA were searched in June 1997 for relevant literature on publication and related biases; update searches were conducted in September 1998. References lists of identified articles were checked and experts in the field were contacted. A sample of 193 systematic reviews published in 1996 was selected from the Database of Abstracts of Reviews of Effectiveness (DARE) for survey purposes.

**Study results:**

The authors conducted a systematic review of publication and related biases, and a survey of publication bias in published systematic reviews. The consequences, sources and prevention of publication bias are discussed.

One study showed that about 31% of meta-analyses included unpublished data. Where reported, the main sources of unpublished trials were researchers or authors, organizations, research funding agents and commercial companies. The effort needed to identify one unpublished trial varied, ranging from 1 to 5 surveys when there was no restriction on study area to 173 questionnaires for a more specific field. Response can be variable and success is not guaranteed. Concerns about the quality and completeness of unpublished data were raised.

A survey of 193 systematic reviews found that 52 (27%) had explicitly searched for unpublished studies, which were sought more often in meta-analyses than in narrative systematic reviews (33% versus 15%). Unpublished studies were mainly identified by writing to investigators/authors, research organizations and pharmaceutical companies, although trials registries were sometimes used. If conference abstracts were considered unpublished, then meeting proceedings were also searched. Overall, studies that were

unpublished, or only presented as abstracts, were explicitly searched for, or included, in 36% of meta-analyses and 30% of narrative reviews.

The authors provided a list of existing clinical trials registries in an appendix, along with details of some registries under development.

**Study limitations as noted by study authors:**

The authors noted limitations of their study in the updated review. First, systematic reviews taken from DARE may be of better quality, and thus not representative of those from general bibliographic databases. Second, reviews of the effects of health care interventions (91%) were not assessed separately from those of diagnostic accuracy (9%). Finally, reviews of epidemiological studies of association between risk factors and health outcomes, and reviews of studies gene-disease associations, were not included.

**Study limitations noted by abstractor:**

The review covered a wide range of issues and contributory factors associated with publication and related biases, hence the identification of unpublished studies was only briefly discussed.

**Key messages:**

The inclusion of unpublished studies in systematic reviews and meta-analyses may help reduce publication bias. Contact with individual investigators/authors, research organizations and pharmaceutical companies are commonly used to identify such studies.

**Study reference:**

Song F J, Fry-Smith A, Davenport C, Bayliss S, Adi Y, Wilson J S, et al. Identification and assessment of ongoing trials in health technology assessment reviews. *Health Technology Assessment*, 2004;8(44).

**Study objectives:**

To assess the importance of ongoing trials in health technology assessments (HTA) reviews for the National Institute for Clinical Excellence (NICE), and to provide practical recommendations for identifying ongoing trials and assessing their possible impact.

**Study methods:**

MEDLINE, the Cochrane Database of Methodology Reviews and the Cochrane Methodology Register were searched for relevant methodological literature. In addition, selected journals and abstracts presented at Systematic Review Symposia (1998–2002) or Society for Clinical Trials Meetings (1980–2002) were hand-searched. The authors assessed ongoing trials in HTA reviews completed by the end of August 2002, and conducted a survey and assessment of trial registers and other sources of ongoing trials. Issues related to searching ongoing trials registers were discussed with reference to two case studies.

Ongoing trials (trials in progress) were defined as any trials that have started but where the results are not yet available or only interim results are available.

**Study results**

All 32 HTA reviews surveyed searched for unpublished studies, and/or ongoing trials and/or grey literature and trial registers. Fifteen stated explicitly that they had searched for unpublished data and 11 had explicitly searched for ongoing trials. Twenty-three of the HTA reviews identified one or more ongoing trials (range: 1 to 94). The main sources of ongoing trials were general and subject-specific trials registers, conference proceedings, information on drugs in development, the Internet, journals that publish trial protocols and journal supplements. More specific examples of these were discussed in detail, and summary tables presented.

An assessment of six main registers (mRCT, ISRCTN Register, NRR, Cancer.gov, ClinicalTrials.gov and Centerwatch.com) found that all provided free public access or required registration. Some were cumbersome and inconsistent in use but all had a 'help' facility. Most registers provided abstracts or summaries of trials, and all but one (Centerwatch) included both ongoing and closed trials. However, the currency of the data was often unclear. There was variation in the search and export functionalities, and the information retrieved. Sometimes it was unclear whether ongoing trials identified from different registers were the same trials or belonged to the same multicentre trials. The ISRCTN (the International Standard Randomised Controlled Trial Number) is the most reliable system but it has not been widely adopted.

Case studies found a significant number of additional trials were identified by searching NRR and ClinicalTrials.gov separately than searching mRCT. Duplicate entries of the same trials existed within registers and were often difficult to identify. More extensive searches increased the retrieval of additional ongoing studies.

**Study limitations as noted by study authors:**

The literature search could have been more comprehensive, thus it should be considered a preliminary effort to identify relevant studies. The survey of ongoing trials in effectiveness reviews was limited to a sample of HTA reviews for NICE, although there are no reasons to believe the findings would not be relevant to other reviews of healthcare interventions. The usefulness and limitations of methods for assessing the possible impact of ongoing studies needs further evaluation.

**Study limitations noted by abstractor:**

There was no breakdown of the different sources used to identify ongoing trials in the sample of HTA reviews, or details of the overall retrieval rates according to source.

**Key messages:**

Trial registers and grey literature are important sources of information on ongoing trials. However, researchers should be aware of the scope, use and limitations of current trial registers.

**Study reference:**

Song F, Parekh S, Hooper L, Loke YK, Ryder J, Sutton A J, et al. Dissemination and publication of research findings: an updated review of related biases. *Health Technology Assessment*.2010;14(8):iii, ix-xi, 1-193. doi: 10.3310/hta14080.

**Study objectives:**

To identify and appraise empirical studies on publication and related biases published since 1998; to assess methods to deal with publication and related biases; and to examine the measures taken to prevent, reduce and detect dissemination bias in a random sample of published systematic reviews.

This is an update of a review conducted in 1998 [Song F, Eastwood A J, Gilbody S, Duley L, Sutton A J. *Publication and related biases*. *Health Technology Assessment*, 2000;4(10)], for which a structured abstract is available.

**Study methods:**

Electronic searches for relevant literature from 1998 to August 2008 were conducted in the Cochrane Methodology Register, MEDLINE, EMBASE, AMED and CINAHL; update searches from 1998 to May 2009 were conducted in PubMed, PsycINFO and OpenSIGLE. The references lists of identified articles and citations of key studies were also examined. MEDLINE was searched for systematic reviews published in 2006. A random sample comprising 100 reviews of the effects of health care interventions, 50 reviews of diagnostic accuracy, 100 reviews of the association between risk factors and health outcomes, and 50 reviews of gene-disease associations was selected.

**Study results:**

The authors conducted a systematic review of publication and related biases, and a survey of publication bias in published systematic reviews.

The survey found that about 31% of meta-analyses included unpublished data. Where reported, the main sources of unpublished trials were researchers/authors, organizations, research funding agents and commercial companies. Other useful sources of ongoing trials and unpublished data were trial registers and grey literature, and to a lesser extent internet searches and email surveys. However, direct communication can be difficult to establish, response rates can be varied, and success is not guaranteed. Use of hand-searches of conference abstracts and review articles to target investigators may help establish more reliable contacts. Concerns about the quality and completeness of unpublished data have been raised. It may be difficult to distinguish between ongoing studies and unpublished completed studies.

In their survey of 300 systematic reviews, the authors attempted to separate grey literature from other unpublished studies. The main sources of grey literature were conference

abstracts, meeting proceedings and grey literature-specific databases (e.g. SIGLE and LILACS). Other unpublished studies were mainly identified through contact with authors, experts and pharmaceutical companies. Grey literature and unpublished studies were explicitly searched for in 34% and 27%, respectively, of reviews overall, ranging from 10% (genetic) to 58% (treatment) across review types. The use of prospective trials registers to identify unpublished or ongoing studies was also reported in 18 treatment reviews, three diagnostic reviews and two risk-factor reviews. The UK National Research Register and ClinicalTrials.gov were the most commonly searched.

**Study limitations as noted by study authors:**

The authors did not note any limitations of their study.

**Study limitations noted by abstractor:**

The review focused on publication and related biases in general; grey literature and unpublished studies were two of the many factors explored.

**Key messages:**

Abstracts, conference proceedings, specialized databases, and contact with authors, experts and pharmaceutical companies remain the most common sources of grey literature and unpublished studies. Recent developments in clinical trial registration and electronic publication of results will aid the identification of ongoing and unpublished clinical trials.

**Study reference:**

Stevinson C, Lawlor D A. Searching multiple databases for systematic reviews: added value or diminishing returns? *Complementary Therapies in Medicine*, 2004;12:228-232.

**Study objectives:**

To explore whether searching specialised bibliographic databases for a systematic review of exercise therapy identified additional relevant papers to those located by a MEDLINE search.

**Study methods:**

Electronic searches (from database inception to 2002) were conducted in three general medical databases (MEDLINE, EMBASE, the Cochrane Library) and four specialised databases (CancerLit, CINAHL, PsycINFO, SPORTDiscus) to identify controlled trials of exercise interventions for cancer patients. A table of contents search was also set up (ZETOC), with results e-mailed on a daily basis. Additional published and unpublished trials were sought through contact with 20 experts in the field, searches of existing literature files, and reference list checks of relevant reviews and identified studies.

**Study results:**

Electronic searches identified 36 potentially eligible studies, of which 18 were included in the review. All but three were retrieved through MEDLINE.

Non-database sources yielded a further 27 citations of potential relevance. These were obtained from reference lists (n=22), expert contact (n=1), own files (n=2) and the ZETOC alert service (n=2). Seven studies were included in the review, of which six had been identified from reference lists and one from expert contact.

Three of the 10 non-MEDLINE indexed papers that met the inclusion criteria were in MEDLINE but had been missed by the search strategy.

**Study limitations as noted by study authors:**

The authors did not note any limitations of their study. They did, however, comment that the implications of their findings are likely to be applicable to other research areas that do not directly fall within a specific conventional medical field.

**Study limitations noted by abstractor:**

Further details of expert contact (e.g. response rate) were not reported.  
Key messages

Sole reliance on MEDLINE is inadequate. Contacting experts in the field and checking reference lists of relevant articles are essential for identifying studies that may be unpublished or difficult to locate.



**Study reference:**

Sutton A J, Abrams K R, Jones D R, Sheldon T A, Song F. Systematic reviews of trials and other studies. *Health Technology Assessment*, 1998;2(19).

**Study objectives:**

To identify applications of systematic review and meta-analytical methods in Health Technology Assessments (HTA); to promote further, appropriate use of such approaches in these areas of application; and to begin to identify priorities for further methodological developments in this field.

**Study methods:**

Various methods were used to search for relevant literature. Electronic searches (typically 1991 to 1997) were conducted in MEDLINE, EMBASE, Institute of Scientific Information (ISI) Science/Social Science databases and the Cochrane methods database. Private reference collections from the study team were searched, and the reference lists of all relevant papers were checked. Grey literature and unpublished studies were sought through contact with experts in the field and Internet searches.

**Study results:**

The authors provided a brief overview of the important issues to be considered when searching the literature and identifying primary studies.

Identifying grey literature and unpublished studies is not an easy task, and there are concerns about the quality, reliability and completeness of such data. Results may have been published in sources not indexed in the main databases, such as booklets, conference proceedings, discussion papers, technical reports, or other formats. Databases covering grey literature (e.g. SIGLE, NTIS and DHSS-Data) and conference proceedings (e.g. ISTP) do exist, but the retrieval of relevant material once identified can be problematic. The best option to obtain results buried in interim reports, unsubmitted papers and manuscripts, conference presentations, rejected papers, and partial reports is likely to be through personal communication with trial investigators, although electronic networks, contact with public policy organizations and advertisements may yield further articles of relevance. Consultation with experts in the field can be fruitful in terms of identifying recent or older trials that have yet to be published, whereas pharmaceutical companies may not be willing to disclose results when contacted for information on trials. Research registers are valuable sources of planned, active or completed research studies.

**Study limitations as noted by study authors:**

The authors did not note any limitations of their study.

**Study limitations noted by abstractor:**

The aim of this report was to promote appropriate application of systematic review and meta-analytical methods; it was not a formal evaluation. However, within the section on identifying literature, there appears to have been little mention of clinical trials registers as sources of ongoing and unpublished trials. In addition, difficulties in searching electronic media and eliciting responses from investigators, organizations and companies were given little consideration, despite their importance.

**Key messages:**

No single search strategy is likely to provide adequate results. Conference proceedings, specialized databases and personal communication with trial investigators are the approaches most likely to yield grey literature and unpublished studies, but retrieval can be difficult and there are concerns about the quality and completeness of the data retrieved.

**Study reference:**

Taus, C., Pucci, E., Giuliani, G., Telaro, E., & Pistotti, V. The use of "grey literature" in a sub-set of neurological Cochrane reviews [abstract]. 7th Annual Cochrane Colloquium; 1999 Oct 5-9; Rome, Italy.

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To assess the prevalence of studies included in Cochrane systematic reviews (CSRs) that had not been retrieved through bibliographic databases.

**Study methods:**

The authors classified 814 references of 599 studies included in 75 neurological reviews from the Cochrane Library, Issue I 1999\*, according to source: papers coming from journals indexed on MEDLINE or EMBASE, papers from journals, and reports from other sources, such as books, thesis, pharmaceutical companies (data on file) and unpublished studies.

**Study results:**

The majority of the 814 references had been retrieved through bibliographic databases (79%). Journals and other sources yielded similar proportions of references, 10% and 11%, respectively. Of the 599 included studies, 84 (in 35 CSRs) were not referenced on MEDLINE or EMBASE. Just over half of these studies (52%) had been identified through references based on 'other sources'; these represented 7% of all 599 included studies.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor:**

This was a survey of literature sources cited in a sub-set of CSRs. The abstract did not provide a breakdown of the retrieval rate according to type of 'other source', which would have been informative.

**Key messages:**

References identified from sources other than main bibliographic databases make an important contribution to the overall number of studies identified.

**Editor's note:**

There is an error in the Cochrane Methodology Register (CMR) record on which this Structured Abstract is based. The CMR contains a typographical error with respect to the Issue of The Cochrane Library that was assessed for this study. The correct Issue details were retrieved from the original conference abstract record at:

<http://www.imbi.uni-freiburg.de/OJS/cca/index.php?journal=cca&page=article&op=view&path%5B%5D=4466>

**Study reference:**

Tfelt-Hansen P C. Unpublished clinical trials with sumatriptan. *Lancet*, 2009;374:1501–1502.

**Study objectives:**

This abstract is based on a letter describing how unpublished trials of sumatriptan were found in the GlaxoSmithKline (GSK) clinical trial register.

**Study methods:**

The author initially looked in the GSK trial register for details of a particular randomized clinical trial (RCT) of sumatriptan that had never been fully published. The finding of other unpublished trials prompted him to conduct a systematic search of the register for phase 3 comparative RCTs that were unpublished (indicated as 'no citation' in the short description of each trial) and met the relevant criteria (oral sumatriptan 100 mg and headache relief as the primary outcome).

**Study results:**

A total of 182 studies of sumatriptan were identified on the GSK trial register. Of these, five were unpublished comparative trials that met the relevant criteria. These trials were conducted in 1990–91, mostly in general practice in the UK. The author commented that, given the findings of the trials, it was easy to understand why these RCTs had never been published: only one of the oral trials reported more than 50% of patients had headache relief. A further trial of rectal sumatriptan that had been partially published in a review was also identified.

**Study limitations as noted by study authors:**

This letter does not note any limitations.

**Study limitations noted by abstractor:**

This letter described the chain of events following a preliminary search of the GSK trial register for the results of a particular unpublished RCT. It was not an evaluation of the trial register. However, details of access to the GSK register would have been helpful.

**Key messages:**

Pharmaceutical companies and investigators are under no obligation to publish trial data. Searching company trial registers may reveal unpublished trials, the results of which may impact adversely upon the perceived benefits of new drugs.

**Study reference:**

Tieman J J, Abernethy A P, Fazekas B S, Currow D C. CareSearch: finding and evaluating Australia's missing palliative care literature. *BMC Palliative Care*, 2005;4:4.

**Study objectives:**

To provide an overview of the CareSearch project which has three specific aims:

- To identify, collect and evaluate Australia's 'grey' palliative care literature and to identify international 'missing' published literature in palliative care;
- To make this literature publicly available through the CareSearch website;
- To promote evidence-based practice in palliative care through an electronic cyber-community.

**Study methods:**

The CareSearch Project Team and a National Reference Group of 13 clinicians and researchers identified potential sources of relevant grey literature.

The sponsoring organization of each pertinent conference held in Australia since 1980 was contacted for a copy of the conference proceedings or abstract book. Individuals in state, territory and federal departments with responsibility for palliative care activities were contacted in writing and by follow-up phone call for reports and other literature; national organizations with palliative interests and Australian universities were contacted similarly. Academic institutions offering higher degrees in fields associated with palliative care were asked to put forward theses and treatises of potential relevance. To identify non-indexed journal articles, 12 key journals, selected from a list of 51 journals, were hand-searched (from first publication to July 2002) for original research articles and significant reviews. The identified articles were then sought in MEDLINE, EMBASE, CINAHL and PsycINFO.

Where necessary, permission was sought to include relevant abstracts in the CareSearch database.

**Study results:**

Twenty-five conference organizations were approached and all supplied books of conference proceedings. A total of 111 books were reviewed, yielding 1,690 relevant abstracts. The database is updated annually and when other conferences are identified. Government departments and relevant organizations provided 100 documents for inclusion in the database. There were also 78 theses from 14 Australian universities. Non-indexed articles comprised 10% (n=841) of the items identified through hand-searches of key journals. Approximately half of these (n=410) were included in the CareSearch database.

The authors stated that, in total, over 2,500 items that were missing from the formally indexed palliative care literature had been located, evaluated, catalogued and combined into the CareSearch database.

**Study limitations as noted by study authors:**

The authors did not note any limitations as this was an overview of the CareSearch Project, in particular, the specialised repository for grey literature in palliative care.

**Study limitations noted by abstractor:**

This paper described the implementation, maintenance and development of a specialised repository for grey literature in palliative care. It did not aim to evaluate specific search strategies, but the relative success of the difference approaches would have been informative.

**Key messages:**

CareSearch is a new evidence resource which provides the palliative community with access to relevant grey literature via a publicly available website.

**Study reference:**

Till J E, Phillips R A, Jadad A R. Finding Canadian cancer clinical trials on the Internet: an exploratory evaluation of online resources. *CMAJ Canadian Medical Association Journal*, 2003;168(9):1127–1129.

**Study objectives:**

To assess the completeness of online databases of breast cancer clinical trials available in Canada, and to promote awareness of the need for better online databases about clinical trials in general.

**Study methods:**

Various approaches were used to identify websites providing free access to searchable online databases that contained information about individual cancer clinical trials (phase 1 to phase IV) available in Canada. Searches were conducted in MEDLINE (for articles published from 1966 to January 2002), the first 200 websites identified using Google, and websites of major organizations that promote or support cancer care. In addition, the authors reviewed a list of websites that provide links to other relevant websites, including those already known to them and those recommended by members of the planning group for a new clinical trials information network, to be supported by the Ontario Cancer Research Network.

Reviewers logged onto eligible websites and extracted details such as the organization, focus of the website, and the numbers of clinical trials and breast cancer trials currently in progress in Canada.

**Study results:**

Eight of the 30 websites identified were eligible for inclusion. Of these, three were based in Canada and five in the USA. Three yielded unique breast cancer trials: Physician Data Query (PDQ) Clinical Trials Database, National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) and CenterWatch Clinical Trials Listing Service. The total number of breast cancer trials identified as being available in Canada was 28, of which 24 (86%) were identified by PDQ, eight (29%) by NCIC CTG and one (4%) by CenterWatch; five studies were in both PDQ and NCIC CTG. The authors noted that information on all of the trials included in PDQ was also available in [ClinicalTrials.gov](http://ClinicalTrials.gov).

Other websites that listed breast cancer trials but did not reveal any unique Canadian trials included Current Controlled Trials and Cancer411.org. It was not possible to search for trials at a particular location in the [bettercancercare.com](http://bettercancercare.com) website and the [MediStudy.com](http://MediStudy.com) website, which is supposed to provide information on trials in Canada, had no clinical trials registered.

**Study limitations as noted by study authors:**

The authors regarded their study as a case study on the diffusion of innovations. They considered it limited by its exploratory nature, its focus on breast cancer, and the lack of a comprehensive list of Canadian breast cancer clinical trials against which the online databases could have been compared.

**Study limitations noted by abstractor:**

No other limitations noted.

**Key messages:**

The PDQ database is the best source of breast cancer clinical trials available in Canada. Online cancer data sources should improve access to clinical trials, particularly for residents of the country where the trial is to be conducted.



**Study reference:**

Turer A T, Mahaffey K W, Compton K L, Califf R M, Schulman K A. Publication or presentation of results from multicenter clinical trials: evidence from an academic medical center. *American Heart Journal*, 2007;153:674-680.

**Study objectives:**

To examine rates of publication or presentation of research findings from multicentre clinical trials and determine what factors are associated with dissemination of results.

**Study methods:**

The electronic database of the institutional review board (IRB) of the Duke University Health System was searched for protocols submitted for approval in 1998. The authors then conducted a follow-up study of all prospective, multicentre clinical trials of treatment that were not ongoing or in active follow-up as follows: attempts were made to determine the publication status of each study by searching for them in PubMed and MEDLINE (January to April 2005, and September 2005); ClinicalTrials.gov, the online registry of the National Cancer Institute and the websites of industry sponsors were searched for public disseminations; Internet searches were conducted using Google and Google Scholar; principal investigators were contacted by telephone and e-mail, followed by off-site investigators and sponsors listed in the protocol if the principal investigator could not be contacted or was unable to provide details of publications or presentations.

**Study results:**

Of the 197 protocols eligible for the analysis, 145 trials (74%) were published or presented as manuscripts (101), abstracts (40) and internet presentations (4). There was no evidence of publication or presentation for 52 trials (26%). Follow-up with investigators and sponsors confirmed that 33 of these unpublished studies had begun enrolment. The enrolment status of the remaining 19 trials could not be ascertained because the principal investigator or sponsor could not be contacted (n=3), the investigator/sponsor was contacted but the trial information was missing (n=5), there was no response from the investigator/sponsor (n=6), and the investigator/sponsor confirmed the trial had 'ended' but was unable to confirm whether the trial ever enrolled (n=5).

Studies were more likely to have been published if they were phase 3 trials, had medium or low risk of an adverse outcome, involved investigational therapies, or were sponsored by independent trial groups or government.

The authors commented that the ethical conduct of research relies in part on a commitment to disseminate the results and thus contribute to scientific knowledge. Failure to make public the data obtained from human experimentation violates the informed consent contract, which offers the potential of research results helping future patients if not the participants directly.  
Study limitations as noted by study authors

The data are from a single centre and may not reflect the experiences of other institutions. Some protocols of potential relevance could not be reviewed as they were not present in the IRB database. The small sample size limited the statistical relationships that could be explored. It was assumed that the 19 studies for which a final disposition could not be confirmed by follow-up with investigators and sponsors had begun enrolment and never completed.

**Study limitations noted by abstractor:**

No other limitations noted.

**Key messages:**

A large proportion of clinical research is not disseminated. Attempts to elicit further details through contact with principal investigators and sponsors met with mixed success. Mechanisms to ensure public dissemination of clinical trial results are needed.

**Study reference:**

Turner H, Boruch R, Petrosino A, Lavenberg J, De Moya D, Rothstein H. Populating an international web-based randomized trials register in the social, behavioral, crime, and education sciences. *Annals of Political and Social Science*, 2003;589:203.

**Study objectives:**

To describe the framework for populating the Campbell Collaboration's (C2) Sociological, Psychological, Educational, and Criminological Trials Register (C2-SPECTR), other prospective registers, and the practical issues of implementation.

**Study methods:**

The authors described the framework for populating a Web-based register of randomized controlled trials (RCTs), primarily C2-SPECTR, and the proposed connection between C2-SPECTR and the US Department of Education's What Works Clearinghouse (WWC).

Initial efforts to identify trials for inclusion involved hand-searches of 48 journals in relevant fields, electronic searches of ERIC, Sociological Abstracts and Crime and Justice Abstracts, and searches of published bibliographies and books on RCTs. To substantially increase the coverage of relevant published and unpublished studies, a strategy for routine surveillance and augmentation was developed based on targeting sources of completed and newly initiated trials. The authors also described the development of a register of newly initiated trials, the C2 Prospective Register of Trials (C2-PROT), which should enable the progress of such trials to be tracked.

**Study results:**

The surveillance strategy for identifying completed trials for C2-SPECTR involved hand-searches of full text of journals; sophisticated electronic searches of journals and databases; systematic reviews, syntheses and meta-analyses from the C2, the WWC, and similar sources; non-C2 reviews; C2 secretariat detection and spontaneous referrals; the Cochrane Collaboration; and C2 and emerging technologies.

Six major potential resources for uncovering newly initiated RCTs for C2-PROT were proposed: the invisible college (network of colleagues with shared research interests); research organizations and sponsors; Paper Work Reduction Act; the Foundation Grants Index (database); institutional review boards; and trialists as informants.

These individual resources were described and discussed in terms of the type of information they could provide, practical issues associated with how best to tap into, access or obtain relevant information, and some limitations. Challenges in implementing the plans were highlighted.

**Study limitations as noted by study authors:**

The authors did not note any limitations as this was an overview of historical, current and future aspects associated with implementing and maintaining a web-based randomized trials register.

**Study limitations noted by abstractor:**

This was not a formal evaluation study with methods and results, but details of the relative proportions of published and unpublished trials currently contained in C2-SPECT and C2-PROT would have been informative. There were no apparent plans to investigate the efficiency of the various resources in identifying relevant trials.

**Key messages:**

At present, the C2 relies on the C2-Secretariat, the invisible college, and trialists for spontaneous referrals of newly initiated RCTs. This strategy is set to continue until more practical and cost-effective ways of using other resources become available.

**Study reference:**

Turner E H. A taxpayer-funded clinical trials registry and results database. *PLoS Medicine / Public Library of Science*, 2004;1(3):e60.

**Study objectives:**

This abstract is based on an article describing the value of the US Food and Drug Administration (FDA) registry and results database for trials conducted in the USA.

**Study methods:**

The author provides an overview of the FDA registry and results database, with particular reference to new drug applications, database content and access, obstacles to making trial information freely available, and limitations of the database.

The value of the FDA database as a source of unpublished data was investigated in a case study of the use of paroxetine for anxiety disorder. Relevant studies were sought in a Cochrane systematic review of antidepressants for generalized anxiety disorder, PubMed and in the FDA review (accessed from Drugs@FDA).

**Study results:**

The FDA registry and results database contains details of all US industry-sponsored trials that are intended to support new drug applications. Pharmaceutical companies must provide a trial protocol as part of the registration. Also contained within the database are documents and analyses arising from the FDA review process. This process occurs entirely outside of the public domain, although new drug application (NDA) reviews for selected approved drug-indication combinations may be posted on the Drugs@FDA website. Aside from objections from the pharmaceutical industry, not all NDAs that are submitted and approved have their reviews posted online. The review documents provide more detail than package inserts, may be more detailed than any journal publication, and report both positive and negative outcomes. Simple formatting changes are necessary to make FDA review data more accessible and user-friendly.

The Cochrane systematic review listed only one double-blind placebo-controlled study of paroxetine; this was published. PubMed did not yield any additional relevant studies. The FDA review, however, revealed three pivotal double-blind placebo-controlled studies, of which two were unpublished and one was the study listed in the Cochrane review. The author also found that in a review article discussing the use of paroxetine for panic disorder with or without agoraphobia, the statement of efficacy would not have been supported by the results reported in the FDA statistical review.

The author notes that this resource does not compete with proposals for clinical trial registries, merely complements them.

**Study limitations as noted by study authors:**

The authors did not note any limitations as this was an essay-type article.

**Study limitations noted by abstractor**

This article aimed to discuss the value, and limitations, of the FDA registry and database. It was not a formal evaluation of this resource.

**Key messages:**

Despite its limitations, the FDA registry and results database is a valuable source of in-depth and unbiased information on many, if not most, of the drugs currently marketed in the USA. However, access to the information available within the database should be improved.

**Study reference:**

Turner E H, Matthews A M, Linardatos E, Tell R A, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *New England Journal of Medicine*, 2008;358:252-260.

**Study objectives:**

To address the question 'How accurately does the published literature convey data on drug efficacy to the medical community?' by comparing drug efficacy inferred from the published literature with drug efficacy according to US Food and Drug Administration (FDA) reviews.

**Study methods:**

The authors identified the phase 2 and 3 clinical-trial programmes for 12 antidepressant agents approved by the FDA between 1987 and 2004. Hard copies of statistical and medical reviews for the eight older antidepressants were obtained from colleagues who had procured them through the Freedom of Information Act. Reviews of the remaining four newer antidepressants were available on the FDA website.

PubMed and the Cochrane CENTRAL Register of Controlled Trials were searched for relevant published literature. In addition, the reference lists in review articles were checked, the drug sponsor's medical information department was contacted by telephone or email, and the same department was sent a certified letter with a deadline for response to the query about whether the trial results had been published. The study results were considered unpublished if none of these steps revealed a publication. Data disclosed in conference proceedings (including published conference abstracts), clinical trial registries, book chapters, or newspaper articles were not considered.

Trials in FDA reviews were then matched to those in journal articles on the basis of key trial information.

**Study results:**

The analysis included 74 FDA-registered studies, of which 23 (31%) appeared to be unpublished (i.e. no evidence of any publication found). The FDA considered 38 studies to be positive and 36 studies to be either negative (n=24) or questionable (n=12). One of the 38 positive studies was not published, compared with 22 of the 36 negative or questionable studies. The remaining 14 negative/questionable studies were either published as not positive (n=3) or, in the opinion of this paper's authors, as positive (n=11), which conflicted with the FDA's conclusion.

The authors commented that there may be many reasons why the results of a study are not published, and they did not know the reasons for nonpublication.

**Study limitations as noted by study authors:**

The findings are restricted to antidepressants, to industry-sponsored trials registered with the FDA, and to issues of efficacy (as opposed to 'real-world' effectiveness). Other factors that may distort the apparent risk–benefit ratio, such as selective publication of safety issues, were not considered. Articles covering multiple studies were excluded, thus some 'unpublished' studies may have technically been published.

**Study limitations noted by abstractor:**

The focus of this study was on published literature, thus unpublished literature (other than the FDA reviews) was not sought.

**Key messages:**

Nearly a third of FDA-registered studies were found not to have been published, 'not published' being defined as not published in sources other than conference proceedings (including published conference abstracts), clinical trial registries, book chapters, or newspaper articles. There was evidence of a bias towards the publication of positive results.



**Study reference:**

Van Driel M L, De Sutter A, De Maeseneer J, Christiaens T. Searching for unpublished trials in Cochrane reviews may not be worth the effort. *Journal of Clinical Epidemiology*, 2009;62(8):838–844.e3.

**Study objectives:**

To explore whether identifying unpublished data to include in Cochrane reviews contributes to the reviews and how much searching is undertaken to identify unpublished trials.

**Study methods:**

The authors retrieved all completed Cochrane reviews from issue 3 2006 of the Cochrane Library and checked the reference lists for unpublished studies. A random sample of 20% of the reviews using unpublished studies was taken. Formal publications of each of the unpublished studies were searched for in a range of databases. Truly unpublished trials were categorised by document or source type and three quality criteria were assessed: allocation concealment, blinding and withdrawals.

**Study results:**

292 (11.9%) of the Cochrane reviews included unpublished trials. 8 reviews were excluded because they contained only unpublished trials. A sample of 62 reviews was assessed in detail yielding 116 unpublished studies. The mean number of unpublished studies per review was 1.9. The reviews in the sample represent 32 of 51 review groups. 44/116 were found to have published reports. The 74 remaining unpublished studies were: the reviewer's own data (11 references), data from a manufacturer (28 references), conference abstracts (23 references), dissertations (4 references), reports (1 reference) and "not located" (7 references).

The authors conclude that searching for unpublished trials does not give a high yield and that the methodological quality of those trials is concerning. A third of unpublished trials may be formally published later. The authors express concern that data obtained from manufacturers may be biased because the manufacturer may choose what information to pass on (donation bias).

**Study limitations as noted by study authors:**

The authors note that they could only investigate a sample of reviews from the Cochrane Library, but stress the rigour of their random sample and that their mean number of studies per review conformed to the total mean. The authors did not include reviews based only on unpublished data.

**Study limitations noted by abstractor:**

The authors do not report how they categorised the data sources used to identify the trials or any uncertainties in the categorisation.

**Key messages:**

The authors urge caution in using unpublished data and recommend spending less effort identifying unpublished trials and more time on other aspects of the systematic review.

**Study reference:**

Van Enst W A, Scholten R J, Hooft L. Identification of additional trials in prospective trial registers for Cochrane systematic reviews. PLoS ONE, 2012;7(8):e42812. <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0042812>

**Study objectives:**

This abstract is based on the abstract of a conference presentation.

Some of the research described in this paper has been published elsewhere [Hooft, L., Van Enst, W. A., & Scholten, R. (2010). Extending the search to find ongoing and unpublished trials - a survey of methods and results of Cochrane reviews. Oral presentation at the Joint Cochrane and Campbell Colloquium; 2010 Oct 18-22; Keystone, Colorado, USA [abstract]]; a structured abstract for this reference is also available.

This study evaluated how the authors of Cochrane systematic reviews used trial registers, in addition to database searches, to identify potentially eligible trials.

**Study methods:**

The authors retrieved all Cochrane reviews of effects with a protocol published in 2008 that had been converted into a full Cochrane Review by February 2010. Data on study identification methods from registers were gathered from each review, along with authors' justifications for the methods and whether the searching of trials registers had yielded results.

**Study results:**

212 Cochrane reviews of effects begun in 2008 had completed by 2010. In 80 (38.1%) of these reviews at least one prospective trial register was searched. 66.3% searched the MetaRegister of Current Controlled Trials and 20% the WHO ICTRP. 60% searched ClinicalTrials.gov. In 75 reviews (93.8%) the authors searched in a portal or register approved by the ICMJE or WHO. In 35% of the reviews, these searches yielded potentially eligible trials and in 14.3% trials were included in the review. Trials were also excluded, recorded as ongoing in the review or awaiting classification. 34 reviews reported no trials as a result of the searches and in 18 reviews the fate of the searches was poorly documented. 15% of reviews involved searching of one portal only and 16.3% searched a portal and an approved register. 55% of the reviews assessed a portal overlapping with a register. Authors reported searching for the purposes of identifying ongoing trials but also to identify unpublished trials.

In 49% of the reviews authors had contacted experts for information on trials and in 5.2% reported searching the internet.

The authors conclude that Cochrane authors are trying to identify additional trials through searching trials registers but that the practice is not yet universal and seems to have a lower priority than other strategies such as contacting experts. The authors speculate about the reasons for searching overlapping resources and also encourage a consideration of non-western registers to prevent geographical bias. The authors suggest that searching trials registers identifies unique trials not identified by other methods.

**Study limitations as noted by study authors:**

The authors noted that Cochrane Reviews may represent a biased sample of reviews and suggest their findings do not apply to non-Cochrane reviews. They also speculate that reviewers may not have reported all their methods in detail and may have carried out more searches than they reported. Given the poor reporting they encountered, the authors suggest that the yield of unique trials is probably underestimated. This study was not powered to explore whether the inclusion of the trials from trials registers had an impact on the effect size of the reviews.

**Study limitations noted by abstractor:**

The authors do not provide a detailed breakdown of the success of the reviews where the authors were conducting searches to identify unpublished data.

**Key messages:**

The authors urge wider application of searching trials registers as a routine activity within the production of a systematic review and better recording of the search process.

**Study reference:**

Van Loo J. Medical and psychological effects of unemployment: a "grey" literature search. *Health Libraries Review*, 1985;2:55-62.

**Study objectives:**

To undertake a literature search of a specific health-related topic in order to quantify as much conventional and non-conventional literature as possible; to quantify and analyse the results; to identify the types and origin of 'grey' literature; and to draw conclusions on the impact of secondary sources as retrieval tools and other methods of locating literature.

**Study methods:**

Various approaches were used to locate literature on the medical and psychological effects of unemployment, published in the UK between 1975 and 1983. Thirteen secondary sources of journal articles, abstracts, reports, translations and theses were searched (2 online and 11 manually). Twenty-eight organizations that may have conducted relevant research were contacted with requests for any material they had published in the field, in particular, internal reports, working papers, pamphlets and meeting presentations. Two specialist libraries, DHSS and King's Fund, were visited to assess their ability to identify difficult to locate material. Finally, the references cited in retrieved articles were followed-up.

**Study results:**

Of the 196 British references retrieved, 111 (57%) were found in secondary sources, 17 (9%) through contact with relevant organizations, 28 (14%) by visiting specialist libraries, 31 (16%) by checking citations in retrieved articles, and 9 (4%) through more than one non-secondary source. Fifty-four articles could be categorized as 'grey' literature: 19 typed reports, 11 semi-published pamphlets, 6 journal articles, 5 transcripts of presented papers, 4 handouts, 3 theses and 6 'unseen'. The majority of these originated from either university departments (n=20) or national associations (n=20). Conferences were important sources of grey literature.

Eighty-two articles (74%) retrieved from secondary sources were unique to the source. The main sources were MEDLINE (n=23), British National Bibliography (n=17), Social Services Abstracts (n=12) and Current Literature on Health Services (n=10). Only 22% of grey literature was identified through these sources.

The 28 organizations contacted reflected a diverse range of bodies working within the field. Approximately half (n=15) responded to the requests for information. Seventeen of the 24 references identified had not been identified by the secondary sources. Only four items could be classed as conventionally published literature.

The specialist libraries revealed 94 documents in total; 28 were unique to the source.

The authors commented that the finding of 31 documents through reference checks highlights the significant role of 'invisible colleges', where researchers are exchanging documents that information professionals may be unaware of.

**Study limitations as noted by study authors:**

The authors did not note any limitations.

**Study limitations noted by abstractor:**

The topic of interest seemed fairly broad and it was unclear whether any further selection criteria, other than country and publication date, had been applied during the search process to limit the number of retrieved documents.

**Key messages:**

Specialist libraries and contact with relevant organizations are valuable sources of literature not located using more traditional sources, in particular grey literature. The importance of conferences and 'invisible colleges' should not be underestimated.

**Study reference:**

Vickers, A. J. Whose data set is it anyway? Sharing raw data from randomized trials. *Trials*. 2006;7:15. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1489946/>

**Study objectives:**

To examine scenarios and examples in which investigators are approached to share raw data from studies and to explore barriers to sharing and reasons to share.

**Study methods:**

The author reports on six cases where he tried to obtain raw study data by direct approach to researchers. Two of the studies were funded through US federal funds. None of the studies were unpublished, although the data being sought was.

**Study results:**

Five of the six case reports were unsuccessful. The author was never given an explicit reason for the rejection of his requests. He notes that offers of co-authorship do not necessarily seem to be persuasive to investigators and their funders and colleagues. A sense of obligation to patients who were involved in the trials also does not seem to motivate sharing. Nor do the prospects of increasing human knowledge or advancing science or healthcare seem persuasive. The author perceives a strong sense of personal ownership of data and suggests ethical and moral arguments for routine data sharing.

**Study limitations as noted by study authors:**

This is not a formal study with methods and results.

**Study limitations noted by abstractor:**

These are case studies to illustrate the author's arguments that data created through trials and other studies involving patients should be shared according to a series of guidelines to govern future collaborative responsible use.

**Key messages:**

The data produced as a result of research should be made publicly available and not concealed. Data and results do not belong to the researchers and should be made available along with the manuscript when it is published. Researchers who reuse such data also have responsibilities when using the data.

**Study reference:**

Vickers A J, Smith C. Incorporating data from dissertations in systematic reviews. *International Journal of Technology Assessment in Health Care*, 2000;16(2):711–713.

**Study objectives:**

To explore the practicalities of identifying and including data from unpublished dissertations in a systematic review.

**Study methods:**

The authors compiled a Cochrane review of massage for premature infants. Masters and doctoral theses were identified from PsycINFO, Dissertation Abstracts International and by checking the citation lists of retrieved articles. Dissertation authors were contacted for more information about their research.

The authors also looked at issue 4 of the 1998 Cochrane Library to see whether any of the 878 reviews incorporated data from dissertations.

**Study results:**

Of 17 dissertations identified, 13 were excluded. Of these 11 were excluded because the studies had no or improper randomization. Contacting authors can be problematic because authors move institutions and may change their names. The theses did not contribute to the main analyses of the review and exclusion of thesis material did not affect the review findings or conclusions.

Of the 878 reviews in the Cochrane Library, 24 reviews searched for dissertations. 5/24 identified at least one dissertation. Three reviews used dissertations as an included study and two reviews reported an excluded dissertation. One review included a single study, published both as a thesis and in a journal. One review included a dissertation in three of four meta-analyses, contributing up to 7% weight. In the third review a trial available only as a dissertation featured in a number of analyses.

**Study limitations as noted by study authors:**

This is one review which hampers generalizability.

**Study limitations noted by abstractor:**

No other limitations noted.



**Key messages:**

Few Cochrane reviews in 1998 reported searching for dissertations. Dissertations do not contribute significant volumes of studies to those reviews which searched for them. However, searching for dissertations and assessing them rigorously contributes to the overall assessment of knowledge, and contributes to reducing bias in systematic reviews. Systematic reviews should be resourced to identify and review dissertations in the awareness that those dissertations may not change the findings or conclusions of the review.

**Study reference:**

Viereck C, Boudes P. An analysis of current pharmaceutical industry practices for making clinical trial results publicly accessible. *Contemporary Clinical Trials*, 2009;30(4):293–299.

**Study objectives:**

To compare the clinical trial transparency practices of US/European pharmaceutical companies by analyzing the publicly-accessible clinical trial results databases for eight major global prescription drugs, and to evaluate database accessibility and utility from the perspective of the lay public.

**Study methods:**

The drugs selected were doripenem, varenicline, lapatinib, zoledronic acid, adalimumab, insulin glargine, raltegravir and gefitinib. For each drug, the accessibility of the clinical trial results on company and specific independent websites, and through Google, was evaluated. In addition, the format, content and presentation of the trial reports were assessed.

The authors explored several approaches that consumers might adopt to look for clinical trial results: through internal and external links on pharmaceutical company websites; using the search engines provided on pharmaceutical company websites; and a general internet search using the Google search engine. In addition, each company's homepage was briefly scanned for links to two websites well-publicized within the professional and patient medical community: <http://www.clinicalstudyresults.org> (a website maintained by the Pharmaceutical Manufacturers of America) (CSR.org) and <http://clinicaltrials.ifpma.org> (a clinical trials portal, including [ClinicalTrials.gov](http://ClinicalTrials.gov)) maintained by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA).

**Study results:**

Only two of the eight company homepages provided a direct link to the clinical trial results, although the results could be accessed by less obvious links for a further four companies. None of the company websites provided direct links to CSR.org or [ClinicalTrials.gov](http://ClinicalTrials.gov) from their homepages.

Using the search engines available on the company websites was even less successful: the first page of 'hits' for searches on generic or trade drug names failed to retrieve or link to the clinical trial database or results in any instance, yielding instead more general information. Searches for 'clinical trials' or 'clinical trial results' did, however, result in links to the drug database on six company websites.

Searches conducted using Google with 'clinical trial results' or 'clinical trial' were also not very fruitful. Within the first two pages of search hits there was only one relevant link, a direct link to [ClinicalTrials.gov](http://ClinicalTrials.gov), and no links to a clinical trial results database. Only one database was found when searching on a specific drug name.

The clinical trial results were posted on either the company website or CSR.org, or on both. The IFPMA portal yielded many hits that did not contain links to a results database. There was wide variation in the number of studies available with results, and the amount, content and accuracy of the information provided. Two databases provided trial results from all development phases. In some reports the results were only available through citations which the lay public may not be able to access, while others focused on the study design and methodology and provided little in the way of results. None of the clinical trial reports was written in lay language.

None of the databases offered all the search features examined. All databases were searched by generic drug name, but only two were searchable by trade name. Where provided, user-friendly support was of limited benefit. Glossaries, where included, focused on clinical research methodology and did not cover statistics, medical or other areas. Searching for the most recent updated reports was only possible in one database.

Study limitations as noted by study authors

The authors did not note any limitations of their study.

**Study limitations noted by abstractor:**

The currency of the websites and internal/external links does not appear to have been addressed.

**Key messages:**

The public faces significant hurdles in finding and understanding clinical trial results databases. Issues such as trial accessibility, website navigation and report presentation need to be addressed.

**Study reference:**

Viergever R F, Ghersi D. The quality of registration of clinical trials. PLoS ONE [Electronic Resource], 2011;6(2):e14701.

**Study objectives:**

To determine whether registered records in clinical trials contained complete and meaningful data for key items in the World Health Organization (WHO) Trial Registration Data Set, in particular, contact information, interventions and outcomes.

**Study methods:**

The authors took a random 5% sample of all clinical trial records of trials registered as interventional between 17 June 2008 and 17 June 2009 from the International Clinical Trials Registry Platform (ICTRP) database. At the time the sample was taken, the ICTRP Portal contained details (the WHO Trial Registration Data Set) of trials from nine different registries; further trial details may be available in the record on the source registry, access to which is provided through a hyperlink.

Relevant trial records were assessed for the presence of contact details, interventions in drug trials, and the quality of outcome reporting.

**Study results:**

The 5% sample contained 754 records, of which 731 were included. The number of included records sourced from the nine registries ranged from one to 628, with ClinicalTrials.gov yielding the most. All included records contained entries in the fields for recruitment status, date of first enrolment and public title. The majority of records (>95%) reported the primary sponsor, study design and methodology, sample size, participant age and gender. Nearly all records supplied a drug name or company serial number, but other specific intervention details were often missing.

The name of a contact person was provided in 81% (n=592) of records overall, and in 94.4% of records from non-industry funded trials and in 53.7% of records from industry funded trials. Contact by e-mail was possible in 59.4% (n=434) of records and by telephone in 64.2%% (n=469). Overall, 68.7% of records provided either an e-mail address or telephone number for contact purposes, corresponding to 76.5% of non-industry funded trial records and 56.5% of industry funded trial records.

**Study limitations as noted by study authors:**

The authors did not note any limitations of their study. They expressed their intention to repeat the study following the introduction of the International Standards for Clinical Trial Registries, and to continue to monitor the quality of registered data.

**Study limitations noted by abstractor:**

This study focused on the quality of registered trial data retrieved through the ICTRP Portal. It was not an evaluation of the individual trials registries covered by the ICTRP, or the methods used to identify trials.

**Key messages:**

Deficiencies in the key information provided in registered records undermine the potential of clinical trials registration to improve clinical trial transparency and reduce publication bias and selective reporting. It is essential that trial registration details are comprehensive, complete, up-to-date and accurate.

**Study reference:**

Von Elm E, Rollin A, Blumle A, Huwiler K, Witschi M, Egger M. Publication and non-publication of clinical trials: longitudinal study of applications submitted to a research ethics committee. *Swiss Medical Weekly*, 2008;138(13-14):197-203.

**Study objectives:**

To investigate the publication or nonpublication of clinical trials based on a cohort of protocols submitted to a research ethics committee of a university hospital in Switzerland.

**Study methods:**

The authors analysed all study protocols submitted from 1988 to 1998 to the research ethics committee of the University Hospital Bern for randomized clinical trials of drug interventions. The Cochrane CENTRAL database (the Cochrane Library 2006 Issue 2) was then searched for full publications relating to the included protocols. Between April and July 2006, the trial investigators were sent a survey and a list of any publications potentially related to the protocol. The questionnaire requested details of current project status, sought confirmation that any publications listed corresponded to the protocol in question, and asked for the references of any further publications. In the absence of a response, attempts were made to find recent addresses through electronic searches and to contact non-responders by letter, e-mail or telephone. For protocols submitted in 1997 and 1998 with no publications and no response from investigators, online trial registries and the internet were searched to determine study status; no ongoing studies were found.

A full publication was defined as an article published in a medical journal providing detailed information on methods and results.

**Study results:**

A total of 531 protocols submitted by 225 investigators were eligible for inclusion. Excluding those documented as 'stopped prematurely', the applicants of the remaining 487 protocols were contacted and responses received for 348 (response rate 71%). Overall, 80 studies were not completed: 57 were stopped prematurely, 16 never started, five were rejected and two were ongoing. This resulted in a final sample for analysis comprising 451 study protocols and 375 corresponding published articles, of which 49 were identified through the survey and 326 from the electronic searches. The publications related to 233 protocols, giving a publication rate of 52% (233/451).

Large multi-centre trials with non-commercial funding were more likely to be published than other trials, but most trials (81%) were funded by industry.

The authors commented that their results were applicable to research settings at home and abroad since most of the trials were international.

**Study limitations as noted by study authors:**

An assessment of publication bias was not feasible given the difficulty and time needed to obtain the results of unpublished studies from years ago. Not all publications may have been found. The restriction to drug trials means that some research fields may have been underrepresented. The study findings may be of limited relevance to clinical practice given recent initiatives for the registration of clinical trials.

**Study limitations noted by abstractor:**

The study focused on the publication of clinical trials and did not seek unpublished material or grey literature.

**Key messages:**

About half of the clinical drug trials approved by an ethics committee in Switzerland remain unpublished, the majority of these having a commercial sponsor. Compulsory trial registration and public funding of industry-independent clinical trials research are needed to address these issues.

**Study reference:**

Wagena E J, Knipschild P. The need for clinical trials registers: a case study in the field of addiction. *Addiction*, 2005;100(10):1392–1393.

**Study objectives:**

This abstract is based on an editorial highlighting the need for a comprehensive, system of registering clinical trials. It presents an example from a major pharmaceutical company's trials register to illustrate deficiencies in current systems.

**Study methods:**

The authors assessed whether the clinical trials register of GlaxoSmithKline (GSK) was comprehensive and complete for trials relating to bupropion. The results of an extensive literature search on the efficacy of bupropion for smoking cessation were compared with the bupropion trials found in the GSK register. The authors also met with the director of medical affairs and the medical affairs manager of GSK in the UK to discuss their findings.

**Study results:**

The literature search identified 6 trials that were not sponsored by GSK, 16 trials that were completely financially supported by GSK, 3 trials that were sponsored in part by GSK, and 2 trials where the sponsor could not be identified. The GSK register contained information on 11 of the 16 trials completely sponsored, but no information on trials that were only partially sponsored. The meeting with the medical affairs personnel resulted in reports and abstracts being obtained for the five fully sponsored trials that were not included in the register, in addition to another five unpublished trials, one of which was a randomized controlled trial (RCT).

Six out of 17 RCTs on bupropion were not registered, even though the GSK trials register is supposed to provide a comprehensive record of all phase II-IV studies conducted on GSK's registered medicines. It was noted that the register did not contain trial protocols or results, the trials were not registered before they started, and not all trials had been completed.

The authors commented that the medical affairs personnel they met were very helpful, but this will not always be the case.

**Study limitations as noted by study authors:**

This was an editorial and, as such, the authors did not note any limitations.



**Study limitations noted by abstractor:**

The case study was presented by way of example, and was not a formal evaluation of the GSK clinical trials register. However, the authors did not comment on whether any information was forthcoming on those studies partially funded by GSK.

**Key messages:**

Researchers have to make considerable efforts to discover what trials have been conducted since clinical trials registers developed by pharmaceutical companies do not provide comprehensive records. All trials which are of interest to (public) health should be registered.

**Study reference:**

Wallace, S., Daly, C., Campbell, M., Cody, J., Grant, A., Vale, L., Donaldson, C., et al. (1997). After MEDLINE? Dividend from other potential sources of randomised controlled trials [abstract]. Second International Conference Scientific Basis of Health Services & Fifth Annual Cochrane Colloquium; 1997 Oct 8-12; Amsterdam, The Netherlands.

Retrieved from <http://www.mrw.interscience.wiley.com/cochrane/clcmr/articles/CMR-657/frame.html>

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To assess the extra dividend, in terms of randomized controlled trials (RCTs), of augmenting a MEDLINE search with alternative search strategies in the context of six systematic reviews related to end stage renal disease.

**Study methods:**

Following a search of MEDLINE, the authors employed various strategies to identify additional RCTs. Searches were conducted in four electronic databases (EMBASE, CINAHL, BIOSIS and the Cochrane Library) and more specific sources (SIGLE, ChemAbs and CRIB). One key journal was hand-searched, and the reference lists of all relevant RCTs and possible RCTs found in MEDLINE were checked. Authors were also contacted for further trials.

**Study results:**

Sixty-five trials met the inclusion criteria, of which 45 were found in MEDLINE, 9 in the electronic databases, and 11 in other ways. Forty-nine of the 128 sets of authors responded, providing 72 references. Two more RCTs had been identified at the time of the abstract and were to be included in the final reviews.

**Study limitations as noted by study authors:**

The abstract did not note any limitations.

**Study limitations noted by abstractor:**

The results in the abstract were incomplete; a hierarchy of RCT yields by source was to be presented at the meeting.

**Key messages:**

Searching MEDLINE alone is not sufficient to ensure retrieval of all relevant studies. Contacting authors for additional studies shows promise.

**Study reference:**

Whittington C J, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet*, 2004;363:1341-5.

**Study objectives:**

To investigate the risk-benefit profile of individual selective serotonin reuptake inhibitors (SSRIs) in childhood depression using published data, unpublished data, and the combined dataset.

**Study methods:**

Four electronic bibliographic databases (EMBASE, MEDLINE, PsycINFO, CINAHL) and the Cochrane Library were searched (from inception to April 2003) for relevant randomized controlled trials published in English or with English language abstracts. The authors also searched the reference lists of retrieved articles, tables of contents of relevant journals, and previous systematic reviews and meta-analyses. Additional studies were also located through written requests to experts and using the knowledge of the Guideline Development Group. Unpublished data were extracted from a review of the efficacy and safety of SSRIs in paediatric major depressive disorder that was produced by the Expert Working Group of the Committee on Safety of Medicines (CSM).

**Study results:**

Five published trials met the inclusion criteria and were included in the meta-analysis. There were two published trials of fluoxetine, one of paroxetine, two of sertraline (published in one paper and reported as a combined analysis), none on citalopram, and one of venlafaxine. The CSM review found two unpublished trials each for paroxetine, citalopram and venlafaxine, but no unpublished trials of fluoxetine or sertraline. However, it did provide additional data that was not included in the published trials of fluoxetine and sertraline. The published data suggested a favourable risk-benefit for some SSRIs, but the addition of unpublished data to the analyses indicated that the risks could outweigh the benefits.

The authors commented that when developing the guideline for the treatment of depression in children and young people, as commissioned by the National Institute for Clinical Excellence (NICE), they contacted all the pharmaceutical companies who manufacture antidepressants with a request for unpublished data and none were forthcoming. They consider that withholding trial data, or not making the full trial reports available, undermines the NICE clinical guideline programme.

**Study limitations as noted by study authors:**

The authors did not note any limitations of their study.

**Study limitations noted by abstractor:**

The strategies used to obtain unpublished trials and data for the CSM review were not reported, and there was no indication of how extensive or successful these searches had been. The authors relied on the CSM review to provide the unpublished material, but it was unclear whether all of the studies included in this review were included in the CSM review.

**Key messages:**

The inclusion of unpublished data may alter drug recommendations founded on a very restricted published evidence base. All trial data should be made fully accessible and publicly available to avoid the potential for erroneous recommendations for treatment.

**Study reference:**

Wootton J C. U.S. patent documents on the Internet: an information resource for research in alternative and complementary medicine. *Journal of Alternative and Complementary Medicine*, 1996;2(2):261-269.

**Study objectives:**

This abstract is based on an account of a recent experiment to make the full text of US patent documents openly and freely available on the Internet.

**Study methods:**

Access to patent documentation typically requires visiting the public Search Room at Crystal City, Arlington (VA), travelling to one of the patent depository libraries in major US cities that hold microfiche records, or using commercial information services. As a trial project by New York University and the nonprofit Internet Multicasting Service, the full text of recent years of patent documents from the U.S. Patent and Trademark Office (PTO) was available for searching and downloading via the Internet Town Hall home page (<http://www.town.hall.org/patent/patent.html>) for a period of 18 months.

**Study results:**

During the period 1 January 1994 to 31 July 1995, a total of 1,588,132 files were accessed.

Open public access, next day, to the full text of patent documents was found to be technically feasible, widely used, economically viable, and fully justified under the provisions of the Freedom of Information Act.

Specific examples – the AIDS Patents database and the Patents Abstracts database – were discussed in terms of online search and display options, and the information provided in the retrieved records. A sample of arbitrarily chosen abstracts relevant to alternative and complementary medicine was presented.

The author commented that despite the success of the project, it was discontinued at the end of its contract and full text provision was withdrawn. This was apparently due to successful lobbying from companies offering patent information services.

**Study limitations as noted by study authors:**

The author did not note any limitations as this was an account of a recent experiment to make patent documentation freely available, and not a formal evaluation with methods and results.

**Study limitations noted by abstractor:**

It was unclear whether a formal evaluation of this project had been undertaken, or whether more comprehensive details of any methodology and results had been published.

**Key messages:**

Making the full text of patent documents freely and publicly available online was found to be technically feasible, widely used and economically viable. This service should be reinstated.

**Study reference:**

Xuemei, L., Li, Y., & Shangqi, S. Transparency of Chinese trials: the results are fully published after registered in WHO primary registries? Oral presentation at the Joint Cochrane and Campbell Colloquium; 2010 Oct 18-22; Keystone, Colorado, USA [abstract].

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To investigate the publication rate of Chinese trials registered in World Health Organization (WHO) primary registries.

**Study methods:**

The authors searched 11 WHO primary registries for the records of Chinese trials, and analysed their progress. Published results for the trials were sought, either by checking the publication citations in the trial registration record or through electronic searches of PubMed, EMBASE, Chinese Biomedical Literature Database (Chinese), China Knowledge Resource Integrated Database, and Chinese Science and Technology Periodicals Database. Authors of completed trials were contacted for details of unpublished trials.

**Study results:**

Records for 1294 Chinese trials were identified. Of the 1171 analysed, 428 were registered in ChiCTR and 743 in ClinicalTrials.gov. Publication rates were similar for Chinese trials in ClinicalTrials.gov and ChiCTR: 36.6% (53/145) and 36.3% (89/245), respectively. Industry-sponsored trials were less likely to be published than trials sponsored by non-industry (24.1% vs. 42.1%). Publication rates were higher for non-randomized trials (23.7%) and interventional studies (38.5%) compared with randomized trials (19.6%) and observational studies (32.1%), respectively.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor**

There is insufficient detail in the abstract (limited methodology and results) to comment on any likely limitations of the study.

**Key messages:**

Only about a third of registered Chinese trials have had results published. Trial investigators and sponsors should be encouraged to publish.



**Study reference:**

Young T, Hopewell S. Methods for obtaining unpublished data. *Cochrane Database of Systematic Reviews* 2011, Issue 11. Art. No.: MR000027. DOI: 10.1002/14651858.MR000027.pub2.

**Study objectives:**

To assess the effects of different methods for obtaining unpublished studies (data) and missing data from studies to be included in systematic reviews.

**Study methods:**

The Cochrane Methodology Register (Issue 1, 2009), MEDLINE, MEDLINE In-Process and EMBASE (to February 2009) were searched for primary studies comparing different methods of obtaining unpublished or missing data; update searches were conducted in April 2010. The reference lists in relevant reports were checked and researchers who were known or thought to have carried out relevant studies were contacted. In addition, the Science Citation Index and PubMed 'related articles' feature were used to identify any additional studies identified by other sources (19 June 2009).

**Study results:**

Of 15 studies of potential relevance, six met the criteria for inclusion. Five were published as abstracts and one as a full paper.

Two randomized studies and three observational comparative studies assessed methods for obtaining data that were missing from the published report. The three observational studies contacted authors by e-mail versus letter (n=3), versus both e-mail and letter (1 study) or fax (1 study). One study contacted 112 authors via 73 letters and 39 e-mails, and received 21 replies (19%). Eleven provided no useful information. In another study, of the 241 studies with missing data, 95 authors could not be contacted and only 46 (32%) of the 146 authors contacted replied. The response rate was highest for contact by both e-mail and letter (73%), followed by e-mail (47%) and letter (24%). The third study reported a response rate of 60% (15 authors), with contact by e-mail needing fewer attempts and resulting in a greater response than either letter or fax. Requests for clarification of methods resulted in a greater response than requests for missing data (50% versus 32%). Two studies found that e-mail had a shorter response time than post, e-mail and post, and fax

One randomized study found no significant difference between a single request for missing information (by e-mail or surface mail) versus a multistage approach (pre-notification, request for missing information and active follow-up). There was also no significant difference in the data supplied in terms of how they addressed the request for information.

The second randomized study compared the response of trial investigators to information requests with a covering letter signed by either the editor of the BMJ or an unknown

researcher, and found no significant difference in response rates: 34% versus 27% after 3 weeks, and 74% versus 67% after 5 weeks.

One observational comparative study evaluated methods to obtain data for studies that have never been published. Identifying unpublished studies ahead of time and then asking the drug industry to provide further specific detail yielded relevant unpublished information for four of the five systematic reviews, whereas a non-specific request failed to yield any unpublished information.

**Study limitations as noted by study authors:**

Despite extensive searches only six studies were eligible for inclusion in this review. The results should be interpreted with caution given the lack of high-quality studies. The strength of the evidence is limited by the completeness of the available data; five of the included six studies were published as abstracts and lacked information about the study methodology and their results. This systematic review was subject to the same problems of obtaining missing data which the review was trying to address.

**Study limitations noted by abstractor:**

No other limitations noted.

**Key messages:**

Contacting authors for missing or unpublished data may not be very successful, particularly for older studies. The most effective approach seems to be communication by e-mail, which results in the greatest response rate with the fewest number of attempts and the shortest response times.

Structured abstract template for clinical trials research records

**Study reference:**

Zani, B., Oliver, J., & Siegfried, N. Sorting the wheat from the chaff: How does the Cochrane HIV/AIDS Specialized Trials Register compare to searching standard electronic databases? Poster presentation at the 19th Cochrane Colloquium; 2011 Oct 19-22; Madrid, Spain [abstract].

**Study objectives:**

This abstract is based on an abstract of a conference presentation.

To determine the precision and sensitivity of the Cochrane HIV/AIDS Specialized Register compared with electronic searches for identifying randomized controlled trials (RCTs) for Cochrane reviews; and to identify limitations of the Register.

**Study methods:**

'Archie' (the Cochrane Collaboration's central server for managing documents and contacts details) was searched for Cochrane HIV/AIDS reviews published in 2010. Relevant keywords extracted from the retrieved reviews were then used to search the Register for relevant RCTs.

**Study results:**

Only three of the 18 reviews identified have been analysed. The number of records identified from standard electronic database searches ranged from 103 to 2317. Of the retrieved records, four, 13 and 36 RCTs were included in the three reviews.

Fewer records were retrieved from searches of the Register (10 to 132). The Register identified all four RCTs on massage therapy, eight of the 13 RCTs on home-based care, and 32 of the 36 RCTs on oropharyngeal candidiasis. Precision was higher than electronic searches (9.5 to 40% versus 0.6 to 5.6%) but sensitivity was lower (61.5 to 100% versus 94.4 to 100%). Three of the missed records were not identified by the Register, one did not contain the keywords in the title or abstract, and three were coded as awaiting assessment.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor**

The conclusions are based on an analysis of only three of the 18 reviews identified.

**Key messages:**

Reviewers should search additional databases to the Cochrane HIV/AIDS Specialized Register to maintain review quality.

Structured abstract template for clinical trials research records

**Study reference:**

Zimpel T, Windeler J. [Publications of dissertations on unconventional medical therapy and diagnosis procedures - a contribution to "publication bias"]. *Forsch Komplementarmed Klass Naturheilkd*, 2000;7:71-84.

**Study objectives:**

The paper is not in English and this abstract is based on the paper's abstract

To investigate whether or not a publication bias can be proven for results of medical theses on all kinds of complementary medical subjects, and which modifying factors can be identified.

**Study methods:**

The authors included all 140 medical theses on aspects of complementary medicine over the years 1982 to 1992. Publications associated with these theses were sought in MEDLINE and through contact with the authors and supervisors.

**Study results:**

Publications were found for 53 (37.9%) of the 140 medical theses included. Factors affecting the likelihood of publication were positive results, high-level statistical analysis, supervisors with a high publication output, and candidates of younger age.

**Study limitations as noted by study authors:**

The abstract does not note any limitations.

**Study limitations noted by abstractor**

There was no indication of how many authors and supervisors were contacted, or the response obtained.

**Key messages:**

More than half of the results reported within medical theses on complementary medicine remain unpublished. Positive results have a greater chance of publication.

## **APPENDIX A**

### **Search Strategies**

**Database:** MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE

Interface: OvidSP

Database coverage dates: 1946 to present

Search date: 5 Sept 2012

Retrieved records: 5320

Search strategy:

- 1 ((request\$ or obtain\$ or identify\$ or locat\$ or find\$ or detect\$ or search\$ or ask\$ or access\$) adj3 (unpublished or "un published" or "not published") adj3 (data or information or evidence or study or studies or trial\$1 or paper\$1 or article\$1 or report\$1 or literature or work)).ti,ab. 576
- 2 (Randomized Controlled Trials as Topic/ or Clinical Trials as Topic/) and Registries/ 1576
- 3 ((search or identify\$ or retriev\$ or locat\$ or find\$ or detect\$ or access) adj6 (trial\$1 register or trial\$1 registers or trial\$1 registry or trial\$1 registries)).ti,ab. 613
- 4 clinicaltrial\$.ti,ab. not (clinicaltrial\$ or ISRCTN).si. 1530
- 5 current controlled trials.ti,ab. 1042
- 6 (ictrp or mrct).ti,ab. 306
- 7 WHO portal.ti,ab. 0
- 8 or/1-7 5320

**Database:** Embase

Interface: OvidSP

Database coverage dates: 1974 to 2012 Week 35

Search date: 5 Sept 2012

Retrieved records: 5148

Search strategy:

- 1 ((request\$ or obtain\$ or identify\$ or locat\$ or find\$ or detect\$ or search or ask\$ or access\$) adj3 (unpublished or "un published" or "not published") adj3 (data or information or evidence or study or studies or trial\$1 or paper\$1 or article\$1 or report\$1 or literature or work)).ti,ab. 580
- 2 (controlled study/ or exp clinical trial/) and \*register/ 772
- 3 ((search or identify\$ or retriev\$ or locat\$ or find\$ or detect\$ or access) adj6 (trial\$1 register or trial\$1 registers or trial\$1 registry or trial\$1 registries)).ti,ab. 703
- 4 clinicaltrial\$.ti,ab. not (clinicaltrial\$ or ISRCTN).cn. 1888
- 5 current controlled trials.ti,ab. 1136
- 6 (ictrp or mrct).ti,ab. 320
- 7 WHO portal.ti,ab. 0
- 8 or/1-7 5148

## Database: Cochrane Methodology Register

Interface: Cochrane Library issue 8 of 12, August 2012 – Wiley online

<http://www.thecochranelibrary.com/view/0/index.html>

Date of search: 5 Sept 2012

Results imported into EndNote: 2898

#1	("study identification"):kw	1969
#2	("information retrieval"):kw	801
#3	("missing data"):kw	142
#4	("data collection" AND "unpublished data"):kw	77
#5	(request* NEAR/3 (unpublished OR "un published" OR "not published")):ti,ab,kw	12
#6	(obtain* NEAR/3 (unpublished OR "un published" OR "not published")):ti,ab,kw	24
#7	(identify* NEAR/3 (unpublished OR "un published" OR "not published")):ti,ab,kw	114
#8	(locat* NEAR/3 (unpublished OR "un published" OR "not published")):ti,ab,kw	17
#9	(find* NEAR/3 (unpublished OR "un published" OR "not published")):ti,ab,kw	20
#10	(detect* NEAR/3 (unpublished OR "un published" OR "not published")):ti,ab,kw	0
#11	(search* NEAR/3 (unpublished OR "un published" OR "not published")):ti,ab,kw	39
#12	(ask* NEAR/3 (unpublished OR "un published" OR "not published")):ti,ab,kw	9
#13	(access* NEAR/3 (unpublished OR "un published" OR "not published")):ti,ab,kw	3
#14	(trial NEAR/2 (register or registers or registry or registries)):ti,ab,kw	4005
#15	(trials NEAR/2 (register or registers or registry or registries)):ti,ab,kw	4005
#16	clinicaltrial*:ti,ab,kw	4620
#17	("current controlled trials"):ti,ab,kw	658
#18	ictrp:ti,ab,kw	123
#19	mrct:ti,ab,kw	143
#20	("who portal"):ti,ab,kw	1
#21	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)	2898



## **APPENDIX B**

**Papers which we have not been able to obtain and / or assess  
for relevance**

1. [All there is to know about clinical drug trials: [www.ifpma.org/clinicaltrials/](http://www.ifpma.org/clinicaltrials/)] Tout savoir sur les essais cliniques des médicaments: [www.ifpma.org/clinicaltrials](http://www.ifpma.org/clinicaltrials). *Actualites Pharmaceutiques*, 2005;(445):9.
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