

***Methods Guide for
Comparative Effectiveness Reviews***

**Finding Evidence for Comparing Medical
Interventions**



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Comparative Effectiveness Reviews are systematic reviews of existing research on the effectiveness, comparative effectiveness, and harms of different health care interventions. They provide syntheses of relevant evidence to inform real-world health care decisions for patients, providers, and policymakers. Strong methodologic approaches to systematic review improve the transparency, consistency, and scientific rigor of these reports. Through a collaborative effort of the Effective Health Care (EHC) Program, the Agency for Healthcare Research and Quality (AHRQ), the EHC Program Scientific Resource Center, and the AHRQ Evidence-based Practice Centers have developed a *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. This Guide presents issues key to the development of Comparative Effectiveness Reviews and describes recommended approaches for addressing difficult, frequently encountered methodological issues.

The *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* is a living document, and will be updated as further empiric evidence develops and our understanding of better methods improves. Comments and suggestions on the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* and the Effective Health Care Program can be made at www.effectivehealthcare.ahrq.gov.

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Finding Evidence for Comparing Medical Interventions

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Finding Evidence for Comparing Medical Interventions

Key Points

- A librarian or other expert searcher should be involved in the development of the search
- Sources of grey literature including regulatory data, clinical trial registries and conference abstracts should be searched in addition to bibliographic databases.
- Requests should be made to industry to request additional sources of unpublished data.
- For the main published literature search, more than one bibliographic database needs to be searched.
- Searches should be carefully documented and fully reported.

Introduction

While, this article both describes and advises on the process of literature searching in support of comparative effectiveness reviews (CERs) for the Effective Health Care Program, it does not address searching for previously published systematic reviews, which is discussed in other articles in this series.^{1,2}

Searches to support systematic reviews often require judgment calls about where to search, how to balance recall and precision, and when the point of diminishing returns has been reached. Searchers with more experience with complex search strategies are better equipped to make these decisions.³ A number of reviews of the quality of systematic reviews suggest that those reviews that employed a librarian or other professional searcher had better reporting of and more complex search strategies.⁴⁻⁶

Table 1 describes the various search activities discussed in this paper and identifies who is responsible for performing each of these tasks. As is evident from the table, the EPC conducting the review is responsible for most of these activities. Because the EPC is involved in the development of the Key Questions, is familiar with the literature, and consults with experts regarding studies relevant to the topic, the EPC is in the best position to develop the required search strategies. Because grey literature can provide primary documents to verify published results, EPCs should routinely search regulatory data, clinical trial registries, and conference papers and abstracts for all CERs. This has been a centralized activity conducted by the Scientific Resource Center (SRC), but is now an activity conducted by the EPCs. However, one aspect of the search strategy benefits from centralization. Centralizing the request to drug and device manufacturers for data on their products—what we call the Scientific Information Packet (SIP)—ensures that all requests to industry are conducted in the same manner; this also minimizes or eliminates contact between manufacturers and the EPC involved in writing the report.

Table 1. Centralized and disseminated tasks in the AHRQ Effective Health Care Program

Activity	Sources	Who does it
Key Questions and analytic framework	n/a	Evidence-Based Practice Center
Grey literature search	Clinical trial registries Regulatory information Conference proceedings	Evidence-Based Practice Center
Scientific Information Packets	Manufacturers of products under review	Scientific Resource Center
Main literature search	MEDLINE (plus in-process and other un-indexed citations) Cochrane Central Register of Controlled Trials	Evidence-Based Practice Center
Specialized database search	Variable (see Appendix B)	Evidence-Based Practice Center
Forward citation search	Scopus Web of Science Google Scholar	Evidence-Based Practice Center
Backwards citations (reading references)	Results of main literature search	Evidence-Based Practice Center
Hand search	Targeted journals	Evidence-Based Practice Center
Corresponding with researchers	Publication authors	Evidence-Based Practice Center

Regulatory and Clinical Trials Searching

In addition to searching for studies that have been formally published (as described below), a comprehensive search will include a search of the grey literature.^{7,8} Grey literature is defined as, “that which is produced on all levels of government, academics, business and industry in print and electronic formats, but which is not controlled by commercial publishers.”⁹ Grey literature can include abstracts presented at conferences, unpublished trial data, government documents, or manufacturer information. Grey literature is, by definition, not systematically identified, stored, or indexed and therefore it can be difficult to locate.

The primary goal of the grey literature search is to identify and overcome publication and reporting bias.^{10,11} Published literature does not always accurately represent trial results. Often, only articles with positive results are published, while those with “null” or negative results are not. And, even when studies are published, reporting can be biased in many other ways. Systematic reviews and meta-analysis based solely on published literature that report positive results will exaggerate any estimate of effectiveness. McAuley et al.¹² has shown an exaggerated estimate of 12 percent when grey literature is excluded, and Hopewell et al.¹³ found a 9 percent exaggeration.

The usefulness of the grey literature naturally varies by topic, but it is particularly helpful in areas where there is little published evidence, where the field or intervention is new or changing,¹⁴ when the topic is interdisciplinary,¹⁵ and with alternative medicine.^{16,17}

Despite these reasons to include grey literature, there are also potential problems. From a practical standpoint, grey literature is the least efficient body to search¹⁸ and may not turn up more evidence to evaluate. Even if grey literature is located it may be of low quality or may not contain usable data.¹⁹ Often unpublished studies are (or at least are perceived to be) of lower quality,^{17,20} although there is limited evidence to support this.¹³

Because we have found them to be the most useful for identifying primary documents to compare with published results, EPCs routinely search the following three types of grey literature for all CERs: regulatory data, clinical trial registries, and conference papers and abstracts.

Regulatory Data

The approval process for new drugs and devices involves submission to the Food and Drug Administration (FDA) of data that may not be published elsewhere. These approval documents—which can be found at [Drugs@FDA.gov](https://www.accessdata.fda.gov/drugsatfda)—may help identify publication bias even when complete methodological details of unpublished trials are not available.^{21,22} This information is not available prior to a drug's approval and may be redacted. When they are available, reviewers can compare results of published and unpublished trials, identify inconsistencies, and often find additional data. In one meta-analysis, investigators found that published trials reported larger estimates for the efficacy of quinine than did FDA documents.²³ Similar discrepancies have been found by Turner²⁴ for the efficacy of antidepressants.

The SRC identifies for potential inclusion, all available medical and statistical reviews for all drugs under consideration, regardless of indication. This is partly because it is difficult to distinguish specific indications in the database, but also because the actual clinical data within the reviews may cover more than one indication and harms data are of importance regardless of indication. In addition to searching for regulatory documents from the FDA, the SRC also searches the Health Canada Drug Products Database²⁵ and the European Medicines Agency's European Public Assessment Reports.²⁶

Trial Registries

Online trial registries such as [ClinicalTrials.gov](https://www.clinicaltrials.gov) may include results of completed but unpublished clinical trials. In a prospective study of two systematic reviews, Savoie²⁷ found trial registries to be useful in identifying studies eligible for inclusion in systematic reviews; registries were more sensitive sources than were scanning references, hand searching, and personal communication. Trial registries can be helpful in identifying otherwise unreachable trials and in providing additional details of trials that have been published. Mathieu has found that elective outcome reporting is prevalent when trial registry information is compared with published results.²⁸ Even without results, knowledge that the trial exists can be helpful for reviewers because the principle investigator can be contacted for more information.¹³ The FDA Amendments Act of 2007 mandates the expansion of [ClinicalTrials.gov](https://www.clinicaltrials.gov) to include results of completed trials of approved drugs and devices. The results database now contains 2,279 entries, 1,958 of them from industry.²⁹ Although [ClinicalTrials.gov](https://www.clinicaltrials.gov) contains trials completed and ongoing, we search only for completed trials, as those are the only trials that would potentially have data for inclusion in a systematic review. In addition to [ClinicalTrials.gov](https://www.clinicaltrials.gov), we routinely search the following trial registries, Current Controlled Trials,³⁰ Clinical Study Results,³¹ and WHO International Clinical Trials Registry Platform.³²

Abstracts and Conference Proceedings

Finally, abstracts and conference proceedings should be searched because those results often never end up as full publications,^{33,34} or more formally published results often differ from the preliminary data presented in abstracts.^{19,34} The SRC searches general databases of conference proceedings routinely and may search specific meetings as suggested by EPCs and key informants.

Scientific Information Packets: Requests to Industry

When interventions identified in key questions involve drugs or devices (or other products for which a manufacturer can be identified), it is important to supplement the literature search with a request to the manufacturer for a SIP. The SIP includes information about products available from the product label as well as information about published and unpublished trials or studies about the product. Requests for SIPs should not be confused with specific request to authors of publications about clarifications of data or to request additional information. These are ad hoc scientist-to-scientist communications and represent a different activity than the systematic request for SIPs from industry.

SIPs are important for two reasons. One is to overcome publication bias by identifying trials that remain unpublished. Manufacturers are not required to report results of studies of products marketed before 2008 to ClinicalTrials.gov, and so information on these studies may not be found when searching this data source. SIPs may also inform researchers about soon-to-be-published studies so that they can be included in the review without waiting for formal publication. A second reason for requesting SIPs is that they provide an explicit and transparent opportunity for drug and device manufactures to be actively involved in the CER and to provide data the manufacturer believes is important to the review of the topic. As noted above, to ensure consistency in the way SIPs are requested and to ensure transparency by eliminating contact between the EPC conducting the review and the manufacturers of products being reviewed, the SRC requests SIPs from manufacturers on behalf of the EPCs for all CERs and technical briefs.

Developing the Published Literature Search

The published literature search for a CER must begin with the concepts identified in the analytic framework and key questions that define the scale and scope of a project. The development of the key questions, the scope of the review, and the analytic framework is a formalized process undertaken by the systematic review team at an EPC.² Librarian involvement in the initial stages of the process, including reading the background materials that are prepared as the topic is developed, is an essential first step to understanding the key questions and crafting a pilot search. The searcher responsible for the main literature search is a member of the research team at the EPC performing the search. The analytic framework developed in the scoping explicitly describes both the relevant clinical concepts, as well as the logic underlying the mechanisms by which an intervention may improve health outcomes. Searchers should utilize the analytic framework to build queries for specific elements of the framework.

One thing to keep in mind while developing the search for a CER is that the retrieved results will be reviewed by hand with explicit inclusion and exclusion criteria dictated by the key questions and scope of the report. We recommend that the search be developed in tandem with these criteria.¹⁰ Many aspects of the key question may not be adequately addressed in the search because index terms for the relevant concepts are poor or nonexistent.³⁵ While developing the search, if there are concepts that are difficult to articulate using search criteria alone, be sure to specify that these aspects need to be addressed in the inclusion and exclusion criteria.

The results of the pilot search can be used to help resolve questions about the boundaries of the key questions. Checking the indexing of known relevant articles provided by experts or found via reference lists can suggest additional terms and concepts that can be added to the strategy to improve its effectiveness.^{35,36}

In the development of the main bibliographic search, we recommend the use of any validated hedges (filters) that exist for any of the concepts.³⁷⁻³⁹ Hedges are predefined search strategies designed to retrieve citations based on criteria other than the subject of the article, such as study methodology or to identify papers dealing with harms.³⁹ Using hedges will save the work of developing the search from scratch and add a level of consistency to the Effective Health Care Program's CERs. One set of hedges are the clinical queries that were developed by Haynes et al. for MEDLINE.⁴⁰ Additional filters are available from the Cochrane Collaboration,⁴¹ the Scottish Intercollegiate Guidelines Network,⁴² and the InterTASC Information Specialists' Sub-Group.⁴³ The Canadian Agency for Drugs & Technology in Health (CADTH) has developed a pragmatic critical appraisal tool for search filters to assist expert searchers working on systematic review teams to judge the methodological quality of a search filter.⁴⁴ For a comparison of filters designed to retrieve randomized controlled trials, see McKibbin et al.³⁹

Additionally be sure to use advanced searching techniques as described in Sampson et al.'s 2008 Peer Review of Electronic Search Strategies.⁴⁵ This is a tool developed for peer review of expert searches that can also be useful as a check of the search strategy. Items to consider are:

- Spelling errors
- Line errors—when searches are combined using line numbers, be sure the numbers refer to the searches intended
- Boolean operators used appropriately
- Search strategy adapted as needed for multiple databases
- All appropriate subject headings are used, appropriate use of explosion
- Appropriate use of subheadings and floating subheadings
- Use of natural language terms in addition to controlled vocabulary terms
- Truncation and spelling variation as appropriate
- Appropriate use of limits such as language, years, etc.
- Field searching, publication type, author, etc.

Although many of the items on the list are self-explanatory, some need further clarification. Use of both natural language and indexing terms is essential for a comprehensive search.^{37,46} Indexing is an important tool, but it often fails for any of the following reasons: lag time of indexing, inappropriate indexing, and lack of appropriate indexing terms or changes in indexing terms over time. Using only controlled vocabulary will miss any in-process citations in MEDLINE. As these represent the most recently published articles it is important to include natural language searching to retrieve them. When using natural language terms be sure to check for spelling errors, use truncation, and be aware of spelling variants, such as: anaemia, oesophagus, paralyse, etc.

Although the use of limits such as date ranges or age ranges may help improve the efficiency of the search, we don't recommend the use of the English language limit. Although the resources available to read or translate non-English language full text articles will vary, English language abstracts are usually available for reviewers to make an initial assessment of the study. Routinely limiting searches to English risks producing biased results.⁴⁷

We recommend the use of a bibliographic management software package such as EndNote or RefWorks to keep track of the results.¹⁰ We have no recommendation on specific software, however, Hernandez et al.⁴⁸ describe many currently available products. While many of these products have features that allow searches to be performed in databases such as

MEDLINE from within the software itself, we do not recommend the use of these features as they do not allow the complex searches needed for CERs.⁴⁹

Strategies for Finding Observational Studies

CERs emphasize the use of randomized controlled trials when they are available, as this study design is least susceptible to bias and can produce high quality evidence. However, CERs include a broad range of types of evidence to confirm pertinent findings of trials and to assess gaps in the trial evidence.⁵⁰ A common use of observational studies is to compare results of trials with results in broader populations or in everyday practice.⁵¹

Searches for observational studies should always be included in reviews when harms and adverse effects are studied, or if the topic itself is unlikely to have been studied with randomized controlled trials.⁵² For the most part, the decision on how to include observational studies will be made as the topic is being developed and is driven by the formulation of key questions and inclusion and exclusion criteria.⁵³ Unfortunately there is little empirical evidence on how best to approach a systematic search for observational studies.⁵⁴⁻⁵⁶ In the absence of evidence the following is advice based on the consensus of the Cochrane Adverse Effect Methods Group⁵⁷ and other experts.^{58,59}

Adverse Effects/Harms

A search for adverse effects should be more inclusive than a search for effectiveness.⁵³ While a search for studies about effectiveness would include only studies of the indication of interest, harms data should not be limited in this way; data about harms is of interest regardless of indication. The targeted search for adverse effects is best accomplished by combining the intervention search with terms to identify harms without limiting to any particular study type.^{51,54}

Golder et al.⁶⁰ describe a number of approaches to search strategies for harms in both EMBASE and MEDLINE. In general, remember to use textwords, MeSH headings, as well as floating subheadings to identify adverse effects.⁵¹ Because most hedges for adverse effects were designed within the context of a specific report, they may need to be adapted for new topics. For example a term such as “adverse drug reaction” would not be appropriate for nondrug interventions. Appendix A contains specific examples of these techniques and hedges.

Observational Studies in Other Situations

It can be challenging to search for observational studies because there are many designs and vocabulary is not used consistently.⁵⁶ Furlan et al.,⁶¹ Fraser et al.,⁵⁸ and the SIGN group⁶² have all explored hedges for retrieving observational studies. While they have not been validated outside of the reviews they were designed for, they offer a starting point for developing a strategy suited to the topic of the review and are described in detail in Appendix A.

While it is currently difficult to construct searches for observational studies, in the future, improved reporting and improved indexing may make it possible to develop standardized generic hedges that would be appropriate for systematic reviews. The STROBE statement^{59,63} gives specific advice for the reporting of observational studies, which is a necessary first step to more accurate indexing and retrieval of observational studies.

Specialized Database Searching

While the Cochrane Central Register of Controlled Trials and MEDLINE are necessary for a thorough search of the literature, they are hardly sufficient.⁶⁴ Many topics of interest to the Effective Health Care Program are interdisciplinary in nature and are concerned with more than strictly biomedical sciences. It is common, for example, to search databases such as CINAHL or PsycINFO for topics related to nursing or mental health, respectively. Failure to search multiple databases risks biasing the CER to the perspective of a single discipline and, because there is often little overlap between different databases,^{46,65,66} has a high risk of missing studies that would affect the outcome of a systematic review. Sampson et al.⁶⁷ investigated the effect of such failure on meta-analyses and found that the intervention effect was increased by an average of 6 percent when only those studies found using MEDLINE were used.

When performing additional database searches, adapt search terms for each database. While keeping the conceptual structure of the original search, review the controlled vocabulary headings for each database to identify appropriate terms. Often headings that have similar scopes or definitions may vary slightly in the terminology used or differ in granularity from one database to another. Finally, keep in mind that search syntax will be different with every database, so be sure to review each database's unique syntax before performing the search.⁶⁸ Many of the more specialized databases do not have the advanced search interfaces needed to conduct complex searches, thus the searches need to be simplified. The loss in precision from the simplified search is often made up for by the fact that the databases contain a smaller number of citations, so the absolute number of citations needed to be screened—even with a simplified search—is often small.

Finally, it is always helpful to ask key informants if they know of any databases specific to the topic of interest. Consult Appendix B for a listing of possible databases of interest.

Using Key Articles

Consultation with experts will identify key articles, and these can be an important resource. If these key articles were not identified in the initial search, investigate why. By looking at the indexing terms applied to key articles, additional search terms can be identified.^{35,36} Additionally, citation tracking—looking at both forward and backward citations of these key articles—can be invaluable for identifying studies.

Citation Tracking—Forward Citations

Citation tracking is an important way to identify articles because it relies on the author's choice to cite an article rather than keywords or indexing.⁶⁹ Therefore, citation tracking often identifies unique and highly relevant items. It can also be an efficient way of locating subsequent and tertiary articles stemming from a landmark trial, as these studies will all cite the original trial.

The Web of Science (which includes the Science Citation Index) is the original citation tracking service. In recent years, a number of other citation tracking databases have become available, including Google Scholar,⁷⁰ Scopus,⁷¹ PubFocus,⁷² and PubReMiner.⁷³ In addition, many publishers offer citation tracking within the pools of journals they publish.

While all citation tracking databases reveal who cited what, there is considerable variability in their coverage and search interfaces. Databases differ both in the number of

journals included as well as the number of years that are tracked, with Web of Science covering more years than the others.⁷⁴

Recent comparisons of Scopus, Web of Science, and Google Scholar found that there were unique items located with each source^{75,76} and that the amount of overlap varied considerably depending on the topic of interest.^{74,77} Because the variation between databases is sensitive to the topic being researched, it is difficult to determine beforehand which database would be most fruitful based on content coverage alone. The decision of what database to use for citation tracking will likely be driven by more pragmatic differences between databases such as cost, availability, and search interfaces.

Web of Science and Scopus are both subscription-based services. If access is available to either of these databases, we recommend their use as they have the most developed search and export interfaces. Free citation tracking databases include: PubReMiner, PubFocus, and Google Scholar. Of these, we recommend Google Scholar for its broader coverage and superior interface. Google Scholar offers the ability to download citations into bibliographic management software as well as to link through to full-text with Google Scholar's Scholar Preferences settings.

Although many publishers offer citation tracking within the set of journals that they publish, we do not recommend their use because the citations are limited to results from that single publisher. Similarly, we do not recommend the "find citing articles" feature of OVID Medline, as that is restricted to journals available from Journals@OVID and does not represent all forward citations.

Reading References—Backward Citations

In addition to finding what articles have cited key studies, articles the key study has cited are a valuable resource. Sources of grey literature such as conference proceedings or poorly indexed journals relevant to the key questions are often discovered in this manner.

Reading the references of key articles is standard practice for systematic reviews^{78,79} although this practice has not been systematically evaluated for effectiveness.⁸⁰ This step is often performed by the researchers tasked with reading the full text of studies and abstracting data. Since these people are often not the same people doing the literature searching, it is important to make sure that they communicate with each other during this process so that insights are not lost. We recommend that any articles that are identified through the reading of references be reviewed by the librarian conducting the search to examine why the original search strategy did not identify the article in question.

Often key articles are previous systematic reviews. The decision on when and how to use an existing review's search strategy and references is part of a larger question on how to utilize existing systematic reviews;¹ searchers should work closely with the review team to determine how to approach the use of previously published systematic reviews.

Related Articles Algorithms

Another way to use key articles is as a starting point for "related article" algorithms. Many databases offer a link to "related articles."³⁷ These links can be helpful in the preliminary, exploratory, and scoping stages of a search. However, we do not recommend them for the formal part of the search for a CER; it is difficult to be systematic about and report on these types of searches, and generally, they are impossible to reproduce.

Hand Searching Journals

Not all journals of interest will be indexed by the databases searched; often, abstracts, supplements, and conference proceedings are not indexed, even if the rest of the content of a journal is. Because many studies first appear (or only appear) in these nonindexed portions of a journal, hand searching journals can be an effective method for identifying trials.

We recommend that journals be hand searched if they are highly relevant to the topic of the report, but are not fully indexed^{35,81,82} or not indexed at all by MEDLINE.⁸³ It is often the case that articles were missed by the initial search strategy because the journal the article is published in is poorly indexed. Asking key informants about specific journals or conferences related to the topic is another way to identify candidates for hand searching.^{84,85}

Hand searching doesn't necessarily mean hand searching of the print journal (although that may be appropriate in some cases). Now that tables of contents and abstracts are often available electronically, hand searching can be done online by systematically reviewing the journal's content on an issue-by-issue basis. A more focused hand search may limit the number of years searched, or focus only on supplements or conference abstracts.

Corresponding With Researchers

During the course of preparing a CER it may be necessary to contact investigators and authors. Savoie²⁷ found that personal communication was a major source of identifying studies, especially when there are uncertainties surrounding a study's publication status. Direct contact with authors can often match these sources to full publications, confirm that there was no subsequent publication, identify unique published or soon-to-be-published sources, and clear up uncertainty surrounding duplicate publication.⁸⁶⁻⁹¹

E-mail makes author correspondence quite easy. Gibson et al.⁹² found that the response rate to e-mail was higher than for postal mail. Aside from the usual Google search, e-mail addresses can be identified by searching the author's institution's Web site. PubMed is also a good source of e-mail addresses, as they are included in the author institution field shown in the abstract display.

Updating and Reporting the Search Strategy

While conducting the search be sure to take detailed notes. These will be useful for reporting as well as rerunning the search in the future. EPC Program policy requires saving the main bibliographic searches to be rerun at the time the draft is sent for peer review. In addition, detailed notes about the full search strategy should be kept in order to accurately report the search strategy in the review. Transparency and reproducibility of the systematic review requires clear reporting;⁹³ critical appraisal is impossible if the search strategy is not thoroughly reported.⁹⁴

Unfortunately, there is no consensus on how to report search strategies in systematic reviews. Sampson et al.⁹⁴ identified 11 instruments, either specific to search strategy reporting or more global reporting instruments that include elements for the search strategy. From these 11 instruments, they extracted the following elements:

- Database used
- Dates covered by the search
- Date search was conducted
- Statement of the search terms used

- Statement of any language restrictions
- Statement of nondatabase methods used
- Additional inclusion/exclusion criteria
- Presentation of the full electronic search strategy
- Statement of any publication status restrictions
- Platform or vendor for electronic database
- End date of the search
- List of excluded references
- Qualifications of the searcher
- Is the reported strategy repeatable?
- Number of references identified
- PRISMA-style flow diagram or other accounting for all references
- Evidence of effectiveness of the search strategy
- Statement of any methodological filters used
- Description of the sampling strategy

The PRISMA-style flow diagram refers to a chart that accounts for all citations identified from all sources as well as accounting for all citations that were later excluded and why.^{95,96} See Appendix C for an annotated example.

Another element that falls outside of the basic mechanics of the search is evidence of the effectiveness of the search strategy.⁹⁴ The evidence of the effectiveness of the search strategy may be difficult to ascertain conclusively. However, reporting what techniques were used to check a strategy—such as expert review, use of previously published strategies or hedges, or testing against a group of known relevant articles (for example, from a previous review)—may be helpful.

With the lack of consensus on reporting, it is hardly surprising that current reporting of search strategies for systematic reviews is variable. In a recent review, Yoshii et al.⁹³ provided a good overview of studies of reporting of search strategies in systematic reviews; they also examined the reporting in Cochrane reviews. Reporting of search strategies is an area of systematic review methodology that can be improved, and the problems with poor reporting go beyond not being able to reproduce the search or build on it for updates. There is very little evidence on the effectiveness of various search strategies for CERs, and there is a need for primary research to identify the characteristics of valid searches.⁹⁴ Currently, it is difficult to do any research on this issue because reporting is so poor. Completely reported search strategies will build an evidence base from which research can be done on effective search strategies.

In the absence of reporting standards, we recommend working with the team writing the report to determine what to report in the review. Page limitations of journal publications may necessitate abbreviating the reporting in journal publications, but there is always room for complete reporting in the online appendices of the CER that are posted to the Effective Health Care Web site or included with the e-published version of the journal article.

Concluding Remarks

One of the most difficult aspects of conducting a comprehensive search is confidently knowing when to stop searching. Unfortunately, there is little guidance on how to determine that point. While Spoor et al.⁹⁷ suggests capture-mark-recapture statistical modeling to

retrospectively estimate the closeness to capturing the total body of literature, there is currently no tool that can easily be applied to searches for CERs. In the end, we rely on experienced searchers' judgments as to when the labor expended to search additional sources is likely to result in new and unique items or whether the search has reached the point of saturation. Like other decisions, such as the sensitivity of the search, the desire for comprehensiveness must be balanced with available resources.

Much of the methodology described here is not yet evidence based, but rather based on principles of expert searching and searcher experience. In order to develop more evidence-based methods we must first have an evidence base to work with. Poor reporting of search strategies in comparative effectiveness and other systematic reviews has hindered evaluations of the effectiveness of various techniques. Clear reporting of search strategies, therefore, is the first step needed to support further research on the effectiveness of various search techniques.

Within the AHRQ Effective Health Care Program, searching lacks the type of quality control that is found in many other steps in the process of conducting CERs, such as dual abstraction and internal peer review. The SRC, therefore, has initiated projects such as peer review of search strategies and improved structures for communication and dissemination of techniques intended to identify best practices that will help librarians share expertise across EPCs.

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Appendix A. Techniques for Observational Studies and/or Harms

Fraser 2006 Observational Studies—Surgery			
MEDLINE (OVID)		EMBASE (OVID)	
Precision	Specificity	Precision	Specificity
Comparative studies/ Follow-up studies/ (preoperat\$ or pre operat\$).mp chang\$.tw evaluat\$.tw reviewed.tw prospective\$.tw baseline.tw cohort.tw consecutive\$.tw (compare\$ or compara\$).tw	Comparative studies/ Follow-up studies/ Time factors/ (preoperat\$ or pre operat\$).mp chang\$.tw evaluat\$.tw reviewed.tw prospective\$.tw retrospective\$.tw baseline.tw cohort.tw case series.tw	Controlled Study/ Treatment outcome/ Major clinical study/ (preoperat\$ or pre operat\$).mp chang\$.tw evaluat\$.tw reviewed.tw (compare\$ or compara\$).tw	Controlled Study/ Treatment outcome/ Major clinical study/ Clinical trial/ chang\$.tw evaluat\$.tw reviewed.tw baseline.tw (compare\$ or compara\$).tw

Furlan 2006 Observational Studies	
MEDLINE	EMBASE
Cohort studies/ comparative study/ follow-up studies/ prospective studies/ risk factors/ cohort.mp. compared.mp. groups.mp. multivariate.mp.	clinical article/ controlled study/ major clinical study/ prospective study/ cohort.mp. compared.mp. groups.mp. multivariate.mp.

Golder 2006 Adverse Effects		
search approach	MEDLINE	EMBASE
specified adverse effects	<i>Drug terms</i> AND Exp LIVER DISEASES/ci	<i>Drug terms</i> AND Exp LIVER DISEASE/si
subheadings linked to drug name	Exp <i>DRUG NAME</i> adverse events, po, to	Exp DRUG NAMEadverse events, to
floating subheadings	<i>Drug terms</i> AND (ae OR po OR to OR co OR de).fs.	<i>Drug terms</i> AND (ae OR to OR co).fs.
text word synonyms of “adverse effects” and related terms	<i>Drug terms</i> AND (safe OR safety OR side-effect\$ OR undesirable effect\$ OR treatment emergent OR tolerability OR toxicity OR adrs OR [adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomse)])	<i>Drug terms</i> AND (safe OR safety OR side-effect\$ OR undesirable effect\$ OR treatment emergent OR tolerability OR toxicity OR adrs OR [adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomse)])
indexing terms for “adverse effects”	<i>Drug terms</i> AND exp DRUG TOXICITY/	<i>Drug terms</i> AND (exp ADVERSE DRUG REACTION/ OR Exp Side-Effect/)

Loke 2007—Indexing Terms (subheadings)	
MEDLINE	EMBASE
/adverse effects /poisoning /toxicity /chemically induced /contraindications /complications	/side effect /adverse drug reaction /drug toxicity /complication

Scottish Intercollegiate Guidelines Network (SIGN) Observational Studies		
MEDLINE	EMBASE	CINAHL
1 Epidemiologic studies/ 2 Exp case control studies/ 3 Exp cohort studies/ 4 Case control.tw. 5 (cohort adj (study or studies)).tw. 6 Cohort analy\$.tw. 7 (Follow up adj (study or studies)).tw. 8 (observational adj (study or studies)).tw. 9 Longitudinal.tw. 10 Retrospective.tw. 11 Cross sectional.tw. 12 Cross-sectional studies/ 13 Or/1-12	1 Clinical study/ 2 Case control study 3 Family study/ 4 Longitudinal study/ 5 Retrospective study/ 6 Prospective study/ 7 Randomized controlled trials/ 8 6 not 7 9 Cohort analysis/ 10 (Cohort adj (study or studies)).mp. 11 (Case control adj (study or studies)).tw. 12 (follow up adj (study or studies)).tw. 13 (observational adj (study or studies)).tw. 14 (epidemiologic\$ adj (study or studies)).tw. 15 (cross sectional adj (study or studies)).tw. 16 Or/1-5,8-15	1 Prospective studies/ 2 Exp case control studies/ 3 Correlational studies/ 4 Nonconcurrent prospective studies/ 5 Cross sectional studies/ 6 (cohort adj (study or studies)).tw. 7 (observational adj (study or studies)).tw. 8 or/1-7

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Appendix B. Specialized Databases

Please note that the topics listed are not the only topics indexed by that database, rather they are a subset of covered topics that are likely to be of interest to the Effective Health Care Program. References are to articles which discuss specific search strategies, present a general overview of the database, or discuss the use of these databases in systematic reviews. The URL's listed are for the database itself if it's a free resource, or a page describing the product if it's a subscription database. Please note that many of these databases are available from many vendors, and the choice of URL does not indicate a preference or endorsement of any particular vendor. If you are unsure about subscription databases, remember that free trials can often be arranged in order for you to evaluate its usefulness to your program.

Free Resources			
Database	URL	Topic Coverage	References
C2-SPECTR (Campbell Collaboration's Social, Psychological, Educational and Criminology Trials Register)	http://geb9101.gse.upenn.edu/	Trial Register for Social Sciences (similar to DARE)	Petrosio, 2000
ERIC (Education Resources Information Center)	http://www.eric.ed.gov/	Education, including the education of health care professionals as well as educational interventions for patients	Anon, 2006
IBIDS (International Bibliographic Information on Dietary Supplements)	http://ods.od.nih.gov/Health_Information/IBIDS.aspx	Dietary supplements	Tomasulo, 2000
ICL (Index to Chiropractic Literature)	http://www.chiroindex.org/	Chiropractic	Aker, 1996
NAPS (New Abstracts and Papers in Sleep)	http://www.websciences.org/bibliosleep/naps/default.html	Sleep	
OTseeker (Occupational Therapy Systematic Evaluation of Evidence)	http://www.otseeker.com/	Occupational therapy	Bennett, 2003 Bennett, 2006
PEDro (Physiotherapy Evidence Database)	http://www.pedro.org.au/	Physical therapy	Sherrington, 2000 Moseley, 2002 Giglia, 2008 Fitzpatrick, 2008
PILOTS	http://www.ptsd.va.gov/ptsd_adv_search.asp	PTSD and traumatic stress	Banks, 1995 Kubany, 1995 Lerner, 2007
PopLine	http://www.popline.org	Population, family planning & reproductive health	Adebonojo, 1994
PubMed	http://www.ncbi.nlm.nih.gov/pubmed/	Biology and health sciences	
RDRB (Research and Development Resource Base)	http://www.rdrb.utoronto.ca/about.php	Medical education	Anne, 1995
RehabData	http://www.naric.com/research/rehab/	Rehabilitation	Fitzpatrick, 2007
Social Care Online	http://www.scie-socialcareonline.org.uk/	Social care including: healthcare, social work and mental health	Gwynne-Smith, 2007
TOXNET	http://toxnet.nlm.nih.gov/	Toxicology Environmental Health Adverse Effects	Hochstein, 2007
TRIS (Transportation Research Information Service)	http://ntlsearch.bts.gov/tris/index.do	Transportation research	Wang, 2001
WHO Global Health Library	http://www.who.int/ghl/medicus/en/	International biomedical topics. Global Index Medicus.	

Subscription Resources			
Database	URL	Topic Coverage	References
AgeLine	http://www.csa.com/factsheets/ageline-set-c.php	Aging, health topics of interest to people over 50	Tomasulo, 2005
AMED (Allied and Complimentary Medicine Database)	http://www.ovid.com/site/catalog/DataBase/12.jsp	Complementary medicine and allied health	Hoffecker, 2006 Pilkington, 2007
ASSIA (Applied Social Science Index and Abstracts)	http://www.csa.com/factsheets/assia-set-c.php	Applied social sciences including: anxiety disorders, geriatrics, health, nursing, social work and substance abuse	LaGuardia, 2002
BNI (British Nursing Index)	http://www.bniplus.co.uk/about_bni.html	Nursing and midwifery	Flemming 2007
ChildData	http://www.childdata.org.uk/	Child related topics including child health	
CINAHL (Cumulative Index to Nursing and Allied Health)	http://www.ebscohost.com/cinahl/	Nursing and allied health	Avenell, 2001 Betran, 2005 Brettle, 2001 Stevinson, 2004 Subirana, 2005 Walker-Dilks, 2008 Wong, 2006
CommunityWISE	http://www.oxmill.com/communitywise/	Community issues including community health	
EMBASE	http://www.embase.com/	Biomedical with and emphases on drugs an pharmaceuticals, more non-U.S. coverage than MEDLINE	Avenell, 2001 Minozzi, 2000 Sampson, 2003 Suarez-Almozar, 2000
EMCare	http://www.elsevier.com/wps/find/bibliographicdatabasedescription.cws_home/708272/description#description	Nursing and allied health	Ulincy, 2006
Global Health	http://www.cabi.org/datapage.asp?iDocID=169	International health	Fitzpatrick, 2006
HaPI (Health and Psychosocial Instruments)	http://www.ovid.com/site/catalog/DataBase/866.jsp	Health and psychosocial testing instruments	Arnold, 2006
IPA (International Pharmaceutical Abstracts)	http://www.csa.com/factsheets/ipa-set-c.php	Drugs and pharmaceuticals	Fishman, 1996 Wolfe, 2002
MANTIS (Manual Alternative and Natural Therapy Index System)	http://www.healthindex.com/MANTIS.aspx	Osteopathy, chiropractic and alternative medicine	Hoffecker, 2006 Murphy, 2003 Tomasulo, 2001
PsycINFO	http://www.apa.org/pubs/databases/psycinfo/index.aspx	Psychological literature	Eady, 2008 Pilkington, 2007 Stevinson, 2004

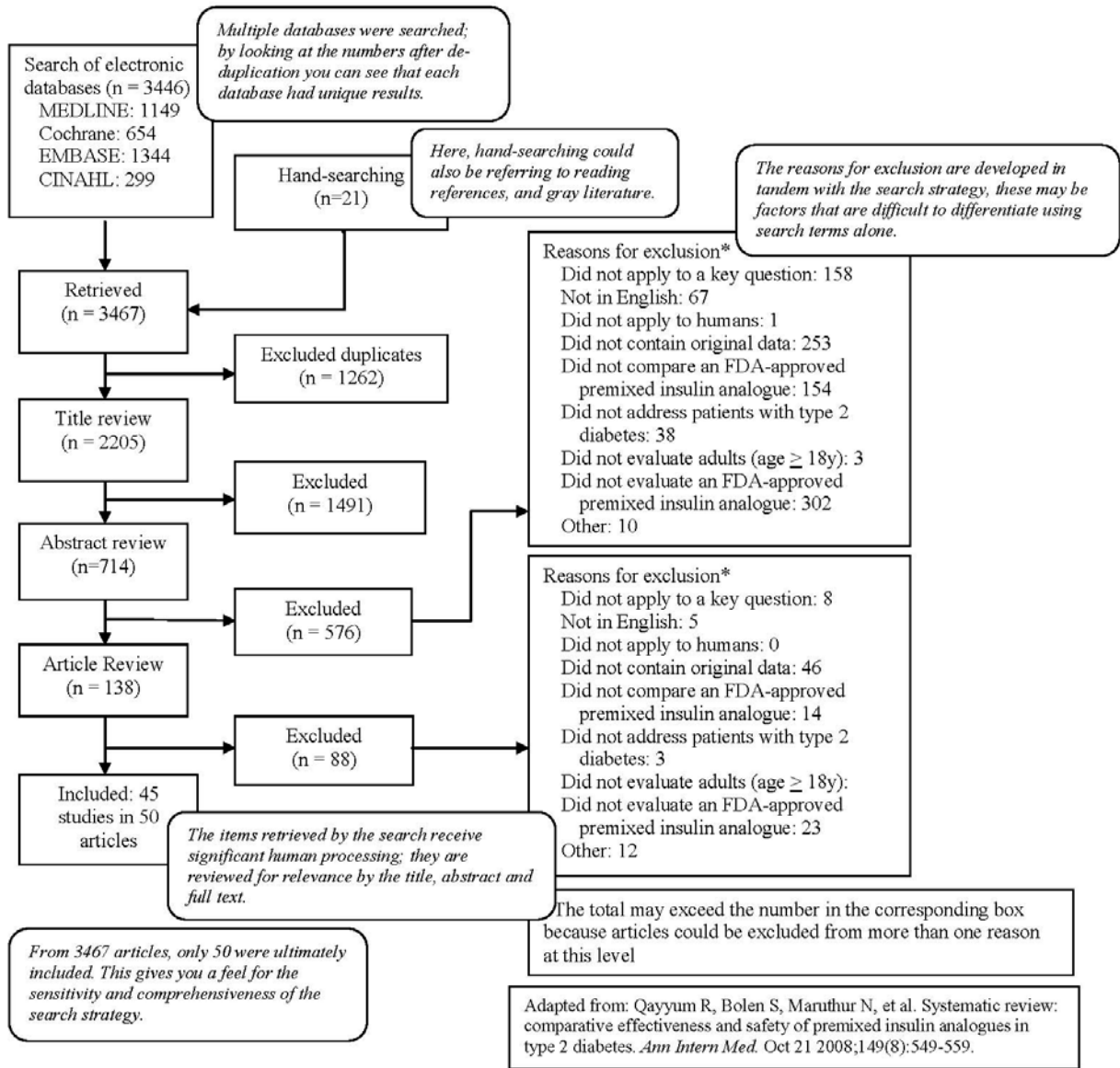
Sociological Abstracts	http://www.csa.com/factsheets/socioabs-set-c.php	Sociology including: health and medicine and the law, social psychology and substance abuse and addiction	DeLuca, 2008
Social Services Abstracts	http://www.csa.com/factsheets/ssa-set-c.php	Social services including: mental health services, gerontology and health policy	Taylor, 2007
Citation Tracking Databases			
Database	URL	Subscription Status	References
Google Scholar	http://scholar.google.com/	Free	Falagas, 2008 Jasco, 2005 Bakkalbasi, 2006
PubFocus	http://pubfocus.com/	Free	Plikus, 2006
PubReMiner	http://bioinfo.amc.uva.nl/human-genetics/pubreminer/	Free	
Scopus	http://info.scopus.com/	Subscription required	Falagas, 2008 Salsbury, 2009 Jasco, 2005 Bakkalbasi, 2006
Web of Science	http://thomsonreuters.com/products_services/science/science_products/a-z/web_of_science	Subscription required	Falagas, 2008 Salsbury, 2009 Jasco, 2005 Bakkalbasi, 2006

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Appendix C. PRISMA-Style Flow Diagram of Literature Search, Annotated



For more on the PRISMA flow diagram, see www.prisma-statement.org/statement.htm.