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# Evaluation of the usefulness of Internet searches to identify unpublished clinical trials for systematic reviews

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**Abstract.** *Primary objective*: To avoid selection and publication bias, systematic reviewers should employ a broad range of search techniques and make efforts to locate unpublished studies. We tried to establish whether searches on the World Wide Web (WWW) are useful to identify additional unpublished and ongoing clinical trials.
*Research design*: Search strategies of seven Cochrane systematic reviews were retrospectively adapted for the WWW in an attempt to find additional randomized controlled trials.
*Methods and procedures*: A search strategy with the general pattern 'study methodology NEAR intervention NEAR condition' for the Internet search engine AltaVista was evaluated by measuring search time, recall of Internet searches for published studies; precision (proportion of webpages containing hints to relevant published and unpublished randomized clinical trials); number of additional unpublished or ongoing studies found on the Internet.
*Main outcomes and results*: We reviewed 429 webpages in 21 hours and found hints to 14 unpublished, ongoing or recently finished trials, at least 9 were considered relevant for 4 systematic reviews. The recall of Internet searches to find references to published studies ranged between 0% and 43.6%, the precision for hints to published or unpublished studies range between 0% and 20.2%.
*Conclusions*: Information on unpublished and particularly ongoing trials can be found on the Internet. A potential problem is the appraisal of non-peer reviewed electronic publications with questionable quality. More powerful search tools are needed. An 'Open Trial Initiative' is proposed to define a syntax for publishing trials on the web and to ensure interoperability of trial registers, so that special search engines can harvest information on ongoing and complete clinical trials.

*Keywords: Information storage and retrieval; Internet; Data collection; Meta-analysis; Clinical trials; Evaluation studies; Publication bias; Recall; Precision; Evidence-based medicine.*

## 1. Introduction

Systematic reviews and meta-analyses are important methods for synthesizing research and evidence-based medicine. An international organization that prepares and maintains systematic reviews in the healthcare field is the Cochrane Collaboration [1].

Systematic reviews differ from traditional opinion-based, narrative reviews, as they do not represent the views of a selected expert, but aim to be a genuine, objective summary of all of the best evidence of effectiveness of a given

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intervention, including published and unpublished trial information, in English or in any other language. Systematic reviews have a strict methodology that is stipulated in a published scientific protocol, which sets out the parameters of the research to be undertaken, for example the aims of the review, the search strategy and the types of trials to be looked for.

A major threat to the validity of systematic reviews and meta-analysis is publication bias, i.e. the systematic overestimation of intervention effects resulting from the fact that trials with positive results tend to be published more frequently [2–5] and earlier than those with inconclusive or negative outcomes [6]. To avoid publication bias, an important aspect of a systematic review is to use multiple sources and strategies to identify trials and also to take the results of unpublished trials into account. Although how unpublished data should be evaluated and incorporated into a systematic review is still a somewhat controversial issue, there is consensus that unpublished data should not be systematically excluded and that efforts should be undertaken to identify information beyond searches in bibliographic databases and the published research literature [7–9]. Traditional methods to identify unpublished studies which are recommended in the Cochrane Collaboration Handbook include searches in trial registers, checking reference lists, hand searching [10], and personal communication [11]. These methods, as well as the standard search strategy for bibliographic databases [12], are all well evaluated and have been proven to be useful.

The role of the Internet for information identification is less clear. Although there are anecdotal reports of reviewers indicating that searches on the Internet may be useful to identify studies [13, 14] to date there has been no systematic investigation to evaluate the usefulness of the Internet for locating additional evidence nor have any search strategies been developed or evaluated. The Cochrane Collaboration Handbook and most Cochrane Collaborative Review Groups currently give no recommendation on whether and how the Internet should be used in the process of a systematic review. Also, little or no information is available on the suitability of different Internet search tools and search strategies for Systematic Reviews. In issue 2/1998 of the Cochrane Library [15] only in two out of 377 complete systematic reviews authors mentioned that they conducted a search of the Internet. Consequently, it is also not clear how 'incomplete' (and thus potentially biased) systematic reviews, which did not include Internet searches, are compared to those who did.

The hypothesis tested in this study was that searching the Internet with a generic search engine can lead to identification of additional studies which have not been mentioned by authors of systematic reviews who did not perform Internet searches. We also intended to answer some more practical questions useful for reviewers, such as what kind of websites would contain hints to unpublished studies, which search tools and strategies would be feasible and whether information can be retrieved and appraised in a reasonable amount of time. Experiences from searching the Internet to answer clinical questions [16] and considerations regarding quality of Internet information [17, 18] raise the question whether the signal-to-noise ratio of information on the World Wide Web (WWW) is good enough to use it as a serious research tool. Another aspect of this paper was to provide future directions of research to develop search tools for reviewers.

## 2. Methods

### 2.1. *Pilot study to identify suitable search tools and strategies*

This study focuses on the usefulness of general Internet searches with robot-based search engines. Search engines are software programs which continuously 'crawl' and index the WWW [19]. They do not index content in dynamic databases such as PubMed or trial databases [20].

For this study we first had to identify suitable search engines which were powerful enough to handle complex queries (table 1). A complex (Boolean) query string is required for searching clinical studies on the web, because in contrast to bibliographic databases, web documents have not been indexed with keywords from a controlled vocabulary. Moreover, while bibliographic databases only contain the abstracts of scholarly documents, which increases the a priori likelihood to find a relevant article, the Internet contains millions of irrelevant documents such as product descriptions or patient information. Therefore, a carefully designed, specific search must be conducted, as otherwise thousands of irrelevant documents will be retrieved. Thus, the possibility to link synonyms with an OR operator, to truncate word stems and to do a proximity search with a NEAR operator (specifying that two words must appear in the same sentence or close to each other) are crucial for conducting specific Internet searches.

### 2.2. *Search strategy*

As in all information retrieval processes, searching the Internet requires a trade-off between recall and precision. Depending on the manpower available to check web pages and also depending on what retrieval precision can be achieved in the respective topic area, the development of a search strategy is to a much larger degree a subjective process than for example development of a search strategy for a bibliographic database.

Our proposed search strategy connects the three concepts 'intervention', 'condition' and 'trial' with NEAR operators, e.g. '(study or trial or random* or evaluat*) NEAR (intervention OR intervention-synonyms) NEAR (condition OR condition-synonyms)' (figure 1). NEAR operators allow to limit the search to documents where the connected concepts occur close to each other. The use of the AND operator instead mostly leads to a large number of 'false positive' hits. This search strategy puts emphasis on specificity rather than sensitivity. For some topics, where less documents can be found on the web, more sensitive searches with AND replacing NEAR operators, may be possible.

For the 'intervention' and the 'condition' concepts, different synonyms should be added, connected by OR. Word stems with truncation operators should be used, so that documents using words in different grammatical forms or spelling variants or other languages can be found. The maximum length and complexity of a query string is typically very limited by the search engine, thus very complex queries are not possible or must be replaced by subsequent independent searches (not done in this study).

*2.2.1. Narrowing search.* Our search protocol specified the following measures to be taken if the initial search leads to too many hits. Some resulting pages were viewed and it was established, which search terms appeared to lead to unspecific results. Stepwise, these unspecific search terms were removed,

Table 1. Search tool features and test searches in different robot-driven search engines. The comparison of search features is partly based on the 'Comparison of Search Engine User Interface Capabilities' by Gilian Westera (http://ww.curtin.edu.au/curtin/library/staffpages/gwpersonal/senginestudy/zcompare.htm) and the 'Web Search Expert' by Diane Johnson (http://hansel.mig.missouri.edu/engines/).

| | Search features | | | | | | Benchmark searches | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Simple Boolean | Proximity searching | Phrase searching | Wildcards/ truncation | Capitalisation recognition | Special features | *Simple Boolean* AND: atopic eczema[a] [=atopic and eczema] | *Phrase search*: 'atopic eczema' | *Simple Boolean* OR: atopic eczema OR atopic dermatitis [=(atopic AND eczema) OR (atopic AND dermatitis)] | *Truncation*: atop* ecz* | *Complex Boolean with truncation*: (atopic eczema OR atopic dermatitis) AND antihistamin* | *Proximity search*: (atopic eczema OR dermatitis NEAR antihistamin* | *Complex promixity search*: (atopic eczema OR atopic dermatitis) NEAR antihistamin* NEAR (study OR trial OR random* OR eval*) |
| Alta Vista www.altavista.com (Advanced search) | AND/OR/ AND NOT | NEAR | yes | *(eg colo*r*) | yes | Allows wildcards within a word; can influence relevancy ranking in adv. search mode; offers natural language searching; can limit by language and date. | 3780 | 1465 | 6594 | 4900 | 765 | 54 | |
| Excite www.excite.com | AND/OR/ AND NOT (in simple mode; must be in uppercase; overrides Excite's concept-based search mechanism) | no | yes | no | no | Offers similar terms to help narrow your search (in simple mode); provides automatic synonym searching (concept search); offers a 'more like this' option in results; can sort by site. Allows max. 1000 results to be displayed | 781 | 289 | >1000[b] | not possible | not possible | not possible | not possible |
| FAST search www.alltheweb.com | no | no | yes | no | no | Is very fast. | 5427 | 2127 | not possible | not possible | not possible | not possible | not possible |
| Google www.google.com | no | no (although uses implied NEAR automatically) | yes | no | no | Includes your search term in context (and in bold) in the results page; automatically ANDs words together, ranks websites according to number of hyperlinks pointing to the site. | 4260 | 1499 | not possible | not possible | not possible | not possible | not possible |
| HotBot www.hotbot.com | AND/OR/NOT (must select 'the Boolean expression') | no | yes | *only left truncation (eg *man) (can also use ? for one character only) | only for mixed upper- and lower-case words (eg NeXT) | Can limit by date and continent; can select page depth within a Web site; offers word stemming; can limit from within a results page. Returns only up to 1000 results | 611 | 264 | 941 | not possible | not possible | not possible | not possible |
| Infoseek http://infoseek.go.com/ | implied in advanced search mode | no | yes | automatic; also finds word variations automatically (eg mice/ mouse) | yes | Can use a pipe \| to refine search results (eg dogs \| dalmations); automatically searches previous results to narrow search result; can limit by country and top level domain (eg edu, com) | 1084 | 351 | 1757 | not possible | not possible | not possible | not possible |

continued

Table 1. continued

| | Search features | | | | | | Benchmark searches | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Simple Boolean | Proximity searching | Phrase searching | Wildcards/ truncation | Capitalisation recognition | Special features | *Simple Boolean* AND: atopic eczema[a] [=atopic and eczema] | *Phrase search*: 'atopic eczema' | *Simple Boolean* OR: atopic eczema OR atopic dermatitis [=(atopic AND eczema) OR (atopic AND dermatitis)] | *Truncation*: atop* ecz* | *Complex Boolean with truncation*: (atopic eczema OR atopic dermatitis) AND antihistamin* | *Proximity search*: (atopic eczema OR dermatitis NEAR antihistamin* | *Complex promixity search*: (atopic eczema OR atopic dermatitis) NEAR antihistamin* NEAR (study OR trial OR random* OR eval*) |
| Lycos http://www.lycos.com | AND/OR/ NOT | ADJ, NEAR, NEAR/X, FAR, BEFORE | yes | no | no | Lycos has moved to concentrate on its subject directory and no longer updates the search engine. Test searches revealed strange effects | 1095 | 1095[c] | 1046[d] | not possible | not possible | not possible | not possible |
| Northern Light http://www.northernlight.com/ | AND/OR/ NOT | no | yes | * (eg colo*r*) (can also use % for one character only) | no | Has,in addition to the Web, indexed 6200 trusted, full-text journals, books, magazines, newswires, and reference sources, including full text versions of medical journals such as *The Lancet*. Groups results into 'custom folders' which enables more efficient locating of relevant information; can limit by date, language and type of Web page (ie.edu,.org,.etc) in power search mode. | 4920 | 1774 | 10346 | 6076[e] | 1298 | not possible | not possible |
| WebCrawler http://www.webcrawler.com/ | AND/OR/ NOT | no | yes | no | no | Offers a shortcuts option which also lists relevant sites from its directory in your results listing; offers natural language searching. | 144 | 33 | 249 | not possible | not possible | not possible | not possible |
| Medical World Search http://www.mwsearch.com | AND/OR/ NOT | NEAR | no | no | no | Concept based search, terms are mapped to UMLS/MeSH and can broaden the search to these synonyms and exploded terms | 203[f] | not possible | 203 | not possible | 40[g] | 21[h] | 7 |
| MedHunt http://www.hon.ch/MedHunt/ | AND/OR | | ADJ | * | no | Allows mapping to the MeSH and translation into 8 European languages. | 107 | 28 | 200 | 158 | 42 | not possible | not possible |

[a]in most search engines an entry like 'atopic eczema' would be treated like a Boolean 'atopic AND eczema'. If this is not the case (some search engines would use an implied OR as default), we used the appropriate syntax instead to force an 'AND' (for example '+atopic+eczema').
[b]"We have found that nearly 100% of users never have a need to drill down beyond the 1000th result for a given query. For these reasons, we no longer provide more than 1000 results per query submitted."
[c]phrase search does not seem to work properly: Revealed exactly the same results as an 'AND' search.
[d]OR search does not work properly: '(atopic AND eczema) OR (atopic AND dermatitis)' revealed 1046 hits, while (atopic AND eczema) revealed 1095 hits. Also, the number of hits were not reliable.
[e]modified as 'atop* AND ecze*', because truncated words must have at least four characters
[f]automatically searches for synonyms such as 'Atopic Dermatitis, Atopic, Neurodermatitis', etc
[g]mwsearch does not support truncation, but can explode terms such as 'antihistamines', taking into account more specific terms such as methdilazine, Tripelennamine, Promethazine. This search was done by using the search concepts 'atopic eczema' [exploded] AND 'antihistamine' [exploded]
[h]This search was done by using the search concepts 'atopic eczema' [exploded] NEAR 'antihistamine' [exploded]

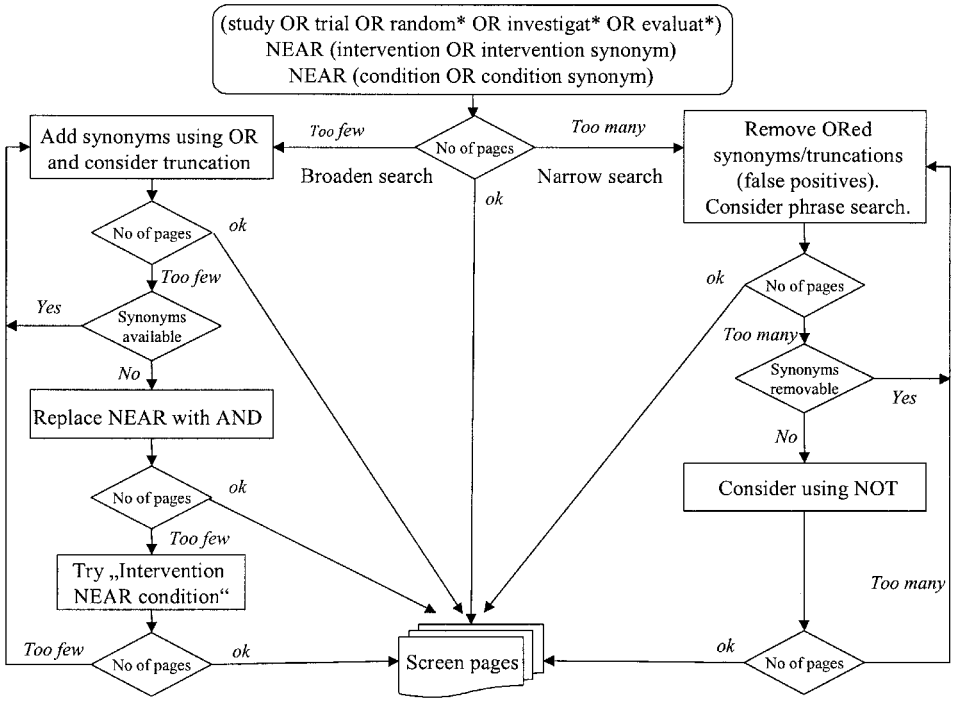


Figure 1. Search strategy to locate hints to randomized controlled trials on the Internet using AltaVista.

synonyms rephrased or truncations deleted if they led to false positive results.

Although not used in our searches, using capital letters could in certain cases also narrow the search and avoid undesired results (change for example 'aids' into 'AIDS'–AltaVista searches are case-sensitive if the search term is written in capital letters). Similarly, in certain cases also a phrase search, for example 'Graves disease', or the use of NEAR operators for combining words which belong together (for example, atopic NEAR eczem*) could be considered. As a last resort, irrelevant pages may be filtered out by using the NOT operator.

*2.2.2. Broadening search.* To broaden the search (find more documents), our search protocol prescribed the identification of further synonyms using the United Medical Language System (UMLS), and combination of them with OR. Spelling variants and terms in foreign languages could be added. However, search engines are extremely limited in their ability to digest long search strings, thus the number of synonyms that could be used was restricted.

Although not used in these searches, investigators may further broaden the search by stepwise replacing NEAR by AND, for example 'study AND (intervention NEAR condition)', or 'study NEAR (condition AND intervention)', finally using AND between all three concepts. For very specific searches it may also be worthwhile to remove the 'study' concept and to attempt to search only for the 'intervention NEAR condition' or even 'intervention AND condition' concepts, although this usually leads to a high number of false positive hits.

2.3. *Selection of systematic reviews and adaption of search strategies for the WWW*

We randomly selected a sample of seven Cochrane systematic reviews (CSRs) that were marked as 'updated' from the Cochrane Library Issue 2, 1998 (table 2). In none of these CSRs reviewers described that they have used the Internet. In order to adapt their search strategies for the web we analysed the bibliographic database search strategies described in the methods sections of these systematic reviews and adapted the search terms for the AltaVista search strategy. The search strategy was narrowed if the number of hits exceeded 200 according to our algorithm presented in figure 1. The resulting AltaVista search strategies for the CSRs are presented in table 2.

After the final search strategy had been determined, Internet searches were conducted in December 1998. web pages were screened for any references to published information or hints to ongoing or unpublished research in the question relevant for the systematic review ('relevant' here means that we felt that the studies should be assessed by the reviewers in detail whether they should be included or excluded for the review). Links were followed as appropriate. The time spent for searching and initial appraisal was recorded.

If references to published literature were found on the webpage, these were compared with the references to included or excluded studies or 'trials awaiting assessment' cited in the systematic review. Concordant findings were recorded and used for a recall estimate.

2.3. *Recall and precision estimates*

Accepted measurements to determine the utility of a information retrieval system or search strategy are recall and precision [21]. Similar to the measures sensitivity and specificity for diagnostic tests, these are defined as follows:

$$\text{Recall} = \frac{\text{Number of documents retrieved and relevant}}{\text{Number of relevant documents}}$$

$$\text{Precision} = \frac{\text{Number of documents retrieved and relevant}}{\text{Number of documents retrieved}}$$

As an estimate for the sensitivity of our searches we calculated the recall of published studies, defined as the number of published studies (references) retrieved on the web divided by total number of published studies mentioned as 'included' or 'excluded' in the systematic review (table 2, column 7). This should not be confused with the actual recall of trials (defined as hints to published and unpublished studies found on the web divided by the total number of relevant published or unpublished studies), as this figure could only be determined if the denominator would be known. As this is never the case (we don't know how many unpublished trials for a given question exist), we used the recall of published trials as an indirect estimation.

The precision of the search was calculated as the number of web pages with hints to published or unpublished (including planned or ongoing) studies possibly relevant for the systematic review divided by the total number of documents retrieved. Whether to choose to use the number of web pages containing hints or the number of hints to distinct studies as denominator for the precision estimate was not critical in this case, as each page pointed to a different study.

Table 2. Overview of the Cochrane Systematic Reviews for which we tried to find unpublished or ongoing trials on the Internet.

| | Cochrane Systematic Review (CSR) | Gold standard: Number of RCTs listed in the CSR | AltaVista advanced search strategy | Time needed for search (number of hits) | Hints to unpublished or ongoing studies found | Recall (=published studies found/ published studies in the CSR) | Precision (=pages with hints to published or unpublished RCTs/total hits) |
|---|---|---|---|---|---|---|---|
| PROM | Kenyon, S., Boulvain, M.<br>Antibiotics for preterm premature rupture of membranes. | Excluded: 22<br>Included: 12<br>Ongoing: 0<br>Total: 34 | (study or trial or investigat* or evaluat*) near ((antibiotic* or antimicrob* or ampic* or erythro* or metronid* or ceph*) near (PROM or pPROM or ((premature or preterm) near (rupture near membrane*)))) | 4 hours<br>(43 hits) | 1 | 4/34<br>(11,8%) | 5/43<br>(11,6%) |
| ACT | Marshall, M., Lockwood, A.<br>Assertive Community Treatment for people with severe mental disorders | Included: 20<br>Excluded: 50<br>Awaiting: 5<br>Ongoing: 2<br>Total references: 109 | ((study or trial or random*) near ((assertive near community near treatment) or (training near community near living) or (Madison near model))) | 4 h<br>(168 hits) | 3 | 31/109<br>(28,4%) | 34/168<br>(20,2%) |
| ASTH | Gibson, P. G.<br>The effects of self-management education and regular practitioner review in adults with asthma | Included: 25<br>Excluded: 27<br>Ongoing: 3<br>Total: 55 | (study or trial or random*) near asthma* near (education* or (self near management)) | 9 h<br>(159 hits) | 8 | 24[a]/55<br>(43,6%) | 32/159<br>(20,1%) |
| OSA | Wright, J., White, J.<br>The effectiveness of continuous positive airways pressure for the treatment of obstructive sleep apnoea | Included: 7<br>Excluded: 24<br>Ongoing: 0 (authors mention that they are aware of two ongoing trials) | (study or trial or random* or evaluation) near ((sleep or obstruct*) near (hypopn* or apn*)) near (CPAP or (positive near pressure) | 2.5 h<br>(46 hits) | 2 | 0/31<br>(0%) | 2/46<br>(4.3%) |
| CAF | Bara, A. I., Barley, E. A.<br>The bronchodilator effect of caffeine in asthma | Included: 6<br>Excluded: 3<br>Ongoing: 0 | (study or trial or random* or evaluation) near asthma* near (caffe* or coffee or tea or chocolate or cola) | <30 min<br>(8 hits) | 0 | 0/9<br>(0%) | 0/8<br>(0%) |
| DPA | Phelps, D. L., Lakatos, L., Watts, J. L.<br>D-Penicillamine to prevent retinopathy of prematurity | Included: 2<br>Excluded: 2<br>Ongoing: 0 | ((retrolent* near fibroplas*) or (retinopat* near prematur*)) near (penicillami*) | <30 min<br>(5 hits) | 0 | 0/4<br>(0%) | 0/5<br>(0%) |
| DIG | Soll, R. F.<br>Digoxin in the prevention or treatment of respiratory distress syndrome | Included: 2<br>Excluded: 0<br>Ongoing: 0 | (digoxin or digitalis) near ((respirat* near distress) or RDS) | <30 min<br>(0 hits) | 0 | 0/2<br>(0%) | 0/0<br>(0%) |
| Total | | | | 21 hours<br>429 hits<br>(av. 3 min/hit) | 14 | | |

[a]including one publication cited on http://www.cfah.org/website2/fol2-5.htm. Berg, J., Dunbar-Jacob, J., Sereika, S. M., 1997, An evaluation of a self-management program for adults with asthma. *Clin Nurs Res*, **6**, 225–238, which was not mentioned in the CLIB Iss 2/98, but appears in Iss 1/2000 as included study.

2.5. *Critical appraisal*

If hints to planned, ongoing or unpublished studies were found, we tried to gather as much information as possible about the study, for example by contacting the authors of the web page or the investigators of the trial, and by conducting MEDLINE searches to see whether the study was already published.

In order to determine whether the study was potentially relevant for the systematic review, we contacted the CSR authors and asked them to comment on the potential relevance of the studies found. We also asked whether these studies had been known to them.

As a further hint of the relevance of a study identified on the web, we checked MEDLINE and the latest version of the systematic reviews (Cochrane Library Iss. 1/2000) in March 2000, 15 months after the searches were conducted, to see whether the formerly unpublished study had in the meantime been published and/or mentioned in the systematic review as 'ongoing', 'excluded', 'included' or 'study awaiting assessment'.

## 3. Results

3.1. *Results of the pilot study to identify suitable search engines*

Table 1 shows the results of a pilot study, first performed end of 1998 and repeated and updated in March 2000. We evaluated nine major generic and two medical search engines for their ability to handle complex queries. Only one search engine, AltaVista, turned out to be sufficiently flexible and powerful to handle complex Boolean queries involving truncations and proximity operators. Google and NorthernLight are new search engines that were not available in 1998.

NorthernLight is noteworthy as it contains an additional database with indexed full tests of journal articles, e.g. from newspapers or medical journals. Two other search engines, Medical World Search [22] and MedHunt [23], work with an underlying medical thesaurus such as the MeSH (Medical Subject Headings) or UMLS (Unified Medical Language System) and allow concept based searches, i.e. they automatically also find pages which contain synonyms, allow translations into other languages and explosion of search concepts to include more specific terms. However, the total number of web pages indexed by these search engines is very low.

In summary, only AltaVista was found to be suitable for this study, but future systematic reviewers may also use and compare other search engines.

3.2. *Hints to published and unpublished studies*

For four out of the seven systematic reviews a total of 59 hints to published and 14 hints to unpublished studies were found (table 2). The remaining three systematic reviews, for which we found no hints or references, were all 'mini-reviews' with very few randomized controlled trials included in the review.

The 14 hints to unpublished (i.e. not published in peer-reviewed journals as full papers) studies were found on:

- five department or institution homepages describing ongoing research;
- two personal homepages of researchers stating their research interests or ongoing projects;

- two online published conference proceedings or meeting abstracts;
- two online published announcements of grants or funding awared;
- one online published press releases of departments or institutions containing information about ongoing or recently finished studies;
- one online published full paper (unrefereed); and
- one website designed for recruitment of study participants.

We did not encounter any web pages of institutional review boards (IRB's) or ethics committees, listing approved research projects or publishing protocols on the web.

References to published studies were found in reference lists of web articles, on virtual journal clubs or online published tables of content of printed journals.

Among the hints to published studies two first appeared to be hints to unpublished studies, but a closer investigation revealed that they were already published and mentioned in systematic reviews: one department homepage mentioning an 'ongoing trial' was outdated, the study was already finished and published [24].

Another web page contained a meeting abstract about an ongoing trial, which also has been published as a full paper [25]. The abstract was not cited in the systematic review, but the full paper was.

### 3.3. *Critical appriasal of hints to unpublished studies*

In total, we found 14 hints to unpublished studies. Where possible and necessary, we contacted the authors of the studies by fax or e-mail and asked whether it was a randomized controlled trial and whether it was published or unpublished.

- Nine of these studies were considered relevant for the systematic review and not mentioned in the systematic reviews in Cochrane Library 2/1998. All of these studies were ongoing randomized controlled trials as of 1998, except one asthma education trial, which was published already in 1997 [26]. Three of these studies were later (after the Internet searches) published: one Asthma RCT [27], one OSA trial [28] and one ACT trial [29] (the latter referring to a RCT already conducted in 1991).
- Two asthma studies were, after contacting the investigators and asking for details, found to be probably not relevant for the systematic review, as one was not a randomized trial, and the other referred to a software system for use by clinicians during consultation, which is probably outside of the scope of the systematic review, which focussed on self-management for patients with asthma.
- In three cases (all asthma trials), the relevance of the studies for the systematic review remained unclear.

### 3.4. *Quality issues*

We encountered an interesting quality problem, which may be characteristic for Internet searches. We found a online published paper with the title 'Buteyko Breathing in Asthma: A Controlled Trial', published on the apparently commercial website 'Buteyko New Zealand Ltd.', which promotes videos and courses on a special breathing technique, the Buteyko breathing technique (BBT). We were unable to find this study in Medline, but after contacting the

investigators we found out that the trial had just been published in the *Medical Journal of Australia* in the very same week that we conducted the search [27]. It is interesting to note that the online published study (now no longer online) was not exactly identical with the article published in the peer-reviewed literature. The version published in the peer-reviewed journal contained a description of the adverse events in both study arms and the discussion raised the possiblity of study contamination as 'some of the BBT subjects who were experiencing difficulties with the technique were contacted frequently by the Buteyko therapist ..., which leaves the study open to the criticism that the BBT group were influenced in ways the control groups were not'. This information was omitted in the online version.

## 4. Discussion

### 4.1. *Principal findings*

To our knowledge, this is the first study evaluating the usefulness of the Internet for conducting systematic reviews and shedding light on the future role of the Internet in synthesizing research. It may even be an example of what Jadad and colleagues call a 'needed synergy between the Internet and evidence-based decision making' [30].

The primary aim of this study was to find *unpublished* studies, as it is clear that bibliographic databases are far better suited to search for published trials. This study shows that the proposed search strategy for the Internet has the potential to identify unpublished and especially ongoing studies for systematic reviews. We found 14 web pages containing information about unpublished trials, including at least nine trials that appeared to be relevant but were not mentioned in the systematic reviews. The reason that these trials were not mentioned in systematic reviews however, was not necessarily failure of the reviewers to identify them, but it appeared that they were still ongoing or just recently finished studies. We found no evidence for a trial that remained unpublished because of negative results, but our insight into the results of the studies which have not yet been published remains limited as we had no access to the original data and we don't know which of them will eventually remain unpublished.

### 4.2. *Potential problems of Internet searches*

Today's search engines are subject to considerable limitations. Not only do they cover only a fraction of the web [20], they are also unable to index information contained in dynamic databases such as trial registers or on password-protected pages, and most are not able to handle the more complex queries necessary to search for trials. Not surprisingly, Internet searches do not perform very well in picking up *published* studies. The recall for references of published studies in three studies was 8.8%, 27.5% and 43.0%, respectively, and 0% for four systematic reviews (table 2). It is unclear to which degree these recall figures also reflect the potential of Internet searches to retrieve ongoing studies. Unpublished studies generate numerous digital traces on the Internet, such as scientists announcing ongoing research on their homepages or recruiting participants online, so that it could be argued that ongoing trials could be no

less difficult to find than published studies. The main reason why it is so difficult to find hints to published or unpublished studies on the web is that very few web authors use metadata and a controlled vocabulary (such as the Medical Subject Headings).

The development of a Internet search strategy is not trivial and should be conducted by an experienced Internet searcher. To alleviate this problem, we propose to develop specialized search engines for trial searches, especially to overcome the language bias and allowing concept-based searches. Such a specialized search engine could also contain expert knowledge on which sites ongoing studies are published and access dynamic databases and meta-trial registers.

Another concern is the quality of information retrieved. In two instances we encountered outdated web pages, which pointed to apparently ongoing trials, which in reality were already finished and published. More importantly, the appraisal of online published studies which have not been published in the peer-reviewed literature is difficult and time-consuming. Reviewers must be wary of promotional, non-peer-reviewed material on the web and – even if an article appear to be peer-reviewed – must expect that online published material can be different from the published peer-reviewed article, as the case described above illustrates.

### 4.3. *Limitations of this study*

The primary aim of this study was to develop and evaluate a search strategy for finding trials on the Internet. We did not attempt to show a bias of systematic reviews where no Internet searches were performed as compared to a systematic review where the Internet was searched. This would have required us to obtain the complete results from the studies which we found on the Internet and to do a systematic review in parallel with another group which develops a systematic review without Internet searches.

One limitation of this study is that the Internet searchers were no domain experts. If the Internet searches had been conducted by systematic reviewers themselves, it is possible that they may have found additional evidence. Also, the actual reviewers may have classified some of the studies we judged as relevant for their systematic review as not relevant. In several cases we were not sure whether hints to studies we located were actually within the scope of a given review (in particular in the asthma education review). We tried to minimize these limitations by requesting help from the reviewers in appraising the studies found.

We restricted our search to English and German sites – sites with other languages were not evaluated and the search strategy was optimized to find English documents. Comprehensive Internet searches may broaden the search by including synonyms in other languages and translating retrieval pages (AltaVista has an automastic translation tool for some languages). This could increase the number of retrieved studies.

### 4.4. *Conclusions for systematic reviewers*

We conclude that carefully designed Internet searches may, in addition to 'traditional' searches in bibliographic and trial databases, represent an additional source for identifying evidence for systematic reviews, particularly ongoing

trials. By conducting Internet searches and identifying and prospectively monitoring the progress of ongoing trials reviewers may reduce the risk of overlooking evidence. In addition, grey literature such as dissertations, and articles published in obscure journals, online journals and e-print servers may be found using Internet searches. These sources may contain hints to negative trials or trials that hve been finished early.

Internet searches with the proposed search strategy proved to be feasible and resulted in search results with reasonable precision, despite the vast amount of irrelevant information on the web. The search strategy also appears to be rather sensitive. For example, reviewers of the OSA review mentioned in their review that they were aware of two ongoing trials, and we also found two ongoing trials on the web.

However, these possibilities of general web searches have to be balanced against risk of invoking false leads and increasing the cost of reviewing. Current search engines are subject to significant limitations in search functionality and are unable to index information contained in dynamic web-databases. To decrease the time and costs required to search the Internet it has been proposed to develop a specialized search engine for locating ongoing and unpublished trials on the web (a specialized Cochrane search engine) that is linked with meta-trial registers [31].

While results of this study suggest that Internet searches can in some cases be useful for detecting unpublished and ongoing studies for conducting systematic reviews, and could avoid publication bias if reviewers follow-up the development of ongoing trials identified on the web, we found no real reasons to suggest that systematic reviews which are not performing Internet searches are necessarily invalid. Nevertheless, we recommend that Internet searches are conducted in addition to other efforts to locate unpublished evidence, such as personal communication with experts.

Future research should compare newer search engines such as NorthernLight and Google, as well as different search strategies. As various Internet-accessible trial registers are being launched, it will also be interesting to evaluate their use for locating studies and avoiding publication bias in the context of reviews. To facilitate future research, it also seems important that systematic reviewers carefully document their Internet search strategy in reports of systematic reviews (rather than just mentioning that 'Internet searches have been performed') so that factors influencing the effectiveness and necessity of Internet searches can be identified.

### 4.5. *Future role of the Internet in linking trials*

To prevent unknowing duplication of clinical research and to detect underreporting of research it has been long demanded to establish prospective registers of clinical trials [32–35]. It is however unlikely that there will ever be one complete central multinational database. Instead, multiple resources set up by numerous different organizations will exist [36]. Internet technology will play a central role in linking the evidence. As information contained in these trial databases will probably always be incomplete, especially on an international scale, general searches on the WWW will remain important. Even if a trial does not make it into a trial database, authors of randomized controlled trials will increasingly leave their 'digital footprints' on the Internet, in form of traces left

by grant proposals, funding agencies, and by the process of recruiting participants. These traces can be found by reviewers, even if the trial remains unpublished. We recommend that funding agencies, institutional ethic committees, researchers, patient organizations and other groups who all share a common interest (and the ethical responsibility) in ensuring that clinical research is published [37] should assist reviewers and researchers in this task by at least publishing trials they have funded, approved, supported or heard of on a robot accessible web page. This can be done for example by listing trials on a web page using the standard format 'randomized trial on (intervention) in (condition)', together with study details, trial identifier and the name and contact details of the principal investigator, all in English, so that they can be indexed by search engines and found by systematic reviewers.

A better way would be to agree on a common syntax and organizational structure for representing and exchanging information about ongoing and finished trials. XML (the eXtensible Markup Language), for example the syntax used by McCray and Ide [38], could not only be used to represent information internally in trial registers, but also to publish XML-tagged information on the web, for example on department homepages by investigators themselves or IRBs, thereby enabling harvesting of this information by specialized search engines. Similarly, trial databases, including databases designed to recruit patients such as Centralwatch, should ideally be interoperable [39]. Much as the Santa Fe Convention of the Open Archives initiative presents a technical and organizational framework designed to facilitate the discovery of content stored in distributed e-print archives, an 'Open Trial Registry' initiative is needed to facilitate knowledge discovery about ongoing and finished clinical trials, to ensure interoperability of trial registers and to enable discovery and harvesting of this kind of information from homepages of funding agencies, institutional review boards, individual researchers and department homepages.

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## References

1. Chalmers, I, 1993, The Cochrane collaboration: preparing, maintaining, and disseminating systematic reviews of the effect of health care. *Ann N Y Acad Sci*, **703,** 156–163.
2. Easterbrook, P. J., Berlin, J. A., Gopalan, R. and Matthews, D. R., 1991, Publication bias in clinical research [see comments]. *Lancet*, **337,** 867–872.
3. Easterbrook, P. J. and Matthews, D.R., 1992, Fate of research studies. *J R Soc Med*, **85,** 71–76.
4. Dickersin, K., Min, Y. I. and Meinert, C. L., 1992, Factors influencing publication of research results. Follow-up of applications submitted to two institutional review boards [see comments]. *JAMA*, **267,** 374–378.
5. Scherer, R. W., Dickersin, K. and Langenberg, P., 1994, Full publication of results initially presented in abstracts. A meta-analysis [published erratum appears in *JAMA* (1994) **272,** 1410]. *JAMA*, **272,** 158–162.

6. Egger, M. and Smith, G. D., 1998, Bias in location and selection of studies. *BMJ*, **316,** 61–66.
7. Clarke, M. and Oxman, A. D., editors, 1999, Cochrane Reviewers Handbook 4 [updated July 1999]. In: *The Cochrane Library, Issue 4*, (Oxford: Update Software), updated quarterly.
8. Sutton, A. J., Duval, S. J., Tweedie, R. L., Abrams, K. R. and Jones, D. R., 2000, Empirical assessment of effect of publication bias on meta-analyses. *BMJ*, **320,** 1574–1577.
9. Assendelft, W. J., van Tulder, M. W., Scholten, R. J. and Bouter, L. M., 1999, The practice of systematic reviews. II. Searching and selection of studies. *Ned Tijdschr Geneeskd*, **143,** 656–661.
10. Jefferson, T. and Jefferson, V., 1996, The quest for trials on the efficacy of human vaccines. Results of the handsearch of Vaccine. *Vaccine*, **14,** 461–464.
11. McManus, R. J., Wilson, S., Delaney, B. C., Fitzmaurice, D. A., Hyde, C. J., Tobias, R. S., Jowett, S. and Hobbs, F. D., 1998, Review of the usefulness of contacting other experts when conducting a literature search for systematic reviews. *BMJ*, **317,** 1562–1563.
12. Dickersin, K., Scherer, R. and Lefebvre, C., 1994, Identifying relevant studies for systematic reviews (see comments). *BMJ*, **309,** 1286–1291.
13. Roberts, L., Ahmed, I. and Hall, S., 1998, Intercessory prayer for the alleviation of ill health (Cochrane Review). In: *The Cochrane Library 2*, (Oxford: Update Software), database on disk and CDROM.
14. Surfing Systematically – Experience Of Searching The Internet. 1998, *Symposium on Systematic Reviews: Beyond the basics*. St John's College, Oxford, UK, 8th and 9th January 1998.
15. Mulrow, C. D. and Oxman, A. D., 1998, (Oxford: Update Software), database on disk and CDROM.
16. Hersh, W. R., Gorman, P. N. and Sacherek, L. S., 1998, Applicability and quality of information for answering clinical questions on the Web [letter]. *JAMA*, **280,** 1307–1308.
17. Allen, E. S., Burke, J. M., Welch, M. E. and Rieseberg, L. H., 1999, How reliable is science information on the Web? [letter; comment]. *Nature*, **402,** 722.
18. Eysenbach, G. and Diepgen, T. L., 1998, Towards quality management of medical information on the internet: evaluation, labelling, and filtering of information [see comments]. *BMJ*, **317,** 1496–1501.
19. Lawrence, S. and Giles, C. L., 1998, Searching the world wide Web. *Science*, **280,** 98–100.
20. Lawrence, S. and Giles, C. L., 1999, Accessibility of information on the web [see comments]. *Nature*, **400,** 107–109.
21. Hersh, W. R., Detmer, W. M. and Frisse, M. E., 2001, Information-Retrieval Systems. In *Medical Informatics*, edited by E. H. Shortliffe and L. E. Perreault (New York: Springer), pp. 539–572.
22. Suarez, H. H., Hao, X. and Chang, I. F., 1997, Searching for information on the Internet using the UMLS and Medical World Search. *Proc AMIA Annu Fall Symp*, 824–828.
23. Baujard, O., Baujard, V., Aurel, S., Boyer, C. and Appel, R. D., 1998, A multi-agent softbot to retrieve medical information on Internet. *Medinfo*, **9,** 150–154.
24. Mercer, B. M., Miodovnik, M., Thurnau, G. R., Goldenberg, R. L., Das, A. F., Ramsey, R. D., Rabello, Y. A., Meis, P. J., Moawad, A. H., Iams, J. D., *et al.*, 1997, Antibiotic therapy for reduction of infant morbidity after preterm premature rupture of the membranes. A randomized controlled trial. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network (see comments). *JAMA*, **278,** 989–995.
25. Herinckx, H. A., Kinney, R. F., Clarke, G. N. and Paulson, R. I., 1997, Assertive community treatment versus usual care in engaging and retaining clients with severe mental illness. *Psychiatry Serv*, **48,** 1297–1306.
26. Ford, M. E., Havstad, S. L., Tilley, B. C. and Bolton, M. B., 1997, Health outcomes among African American and Caucasian adults following a randomized trial of an asthma education program. *Ethn Health*, **2,** 329–339.
27. Bowler, S. D., Green, A. and Mitchell, C. A., 1998, Buteyko breathing techniques in asthma: a blinded randomised controlled trial [see comments]. *Med J Aust*, **169,** 575–578.
28. Jenkinson, C., Davies, R. J., Mullins, R. and Stradling, J. R., 1999, Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised prospective parallel trial [see comments]. *Lancet*, **353,** 2100–2105.
29. Salkever, D., Domino, M. E., Burns, B. J., Santos, A. B., Deci, P. A., Dias, J., Wagner, H. R., Faldowski, R. A. and Paolone, J., 1999, Assertive community treatment for people with severe mental illness: the effect on hospital use and costs. *Health Serv Res*, **34,** 577–601.
30. Jadad, A. R., Haynes, R. B., Hunt, D. L. and Browman, G. P., 2000, The Internet and evidence-based decision-making: a needed synergy for efficient knowledge management in health care. *CMAJ*, **162,** 362–365.
31. Eysenbach, G., 1999, Use of the World-Wide-Web to identify unpublished evidence for systematic reviews – the future role of the Internet to improve information identification. [Abstract] VII Cochrane Colloquium, Rome, Italy, October 5–9, 1999 (Abstracts Book), p. 18.
32. Simes, R. J., 1986, Publication bias: the case for an international registry of clinical trials. *J Clin Oncol*, **4,** 1529–1541.

33. Chalmers, I., Dickersin, K. and Chalmers, T. C., 1992, Getting to grips with Archie Cochrane's agenda [editorial] [see comments]. *BMJ*, **305,** 786–788.
34. Chalmers, I., Gray, M. and Sheldon, T., 1995, Handling scientific fraud. Prospective registration of health care research would help [letter; comment]. *BMJ*, **311,** 262.
35. Horton, R. and Smith, R., 1999, Time to register randomised trials. The case is now unanswerable [editorial]. *BMJ*, **319,** 865–866.
36. Tonks, A., 1999, Registering clinical trials. *BMJ*, **319,** 1565–1568.
37. Pearn, J., 1995, Publication: an ethical imperative [see comments]. *BMJ*, **310,** 1313–1315.
38. McCray, A. T. and Ide, N. C., 2000, Design and implementation of a national clinical trials registry. *J Am Med Inform Assoc*, **7,** 313–323.
39. Sim, I., 1997, *Trial banks: An informatics foundation for evidence-based medicine.* (Stanford, CA, USA: Stanford University).