eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

SECOND DRAFT GUIDELINE

Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness

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The primary objective of EUnetHTA JA2 WP 7 methodology guidelines is to focus on methodological challenges that are encountered by HTA assessors while performing relative effectiveness assessments of pharmaceuticals or non-pharmaceutical health technologies.

As such the guideline represents a consolidated view of non-binding recommendations of EUnetHTA network members and in no case an official opinion of the participating institutions or individuals.

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This methodological guideline on “Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness” has been developed by Institute for Quality and Efficiency in Health Care (IQWiG) / Germany

With assistance from draft group members from
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The guideline was also reviewed and validated by a group of dedicated reviewers from
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State Health Care Accreditation Agency (VASPVT) / Lithuania

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Acronyms - Abbreviations

AHRQ - Agency for Healthcare Research and Quality

AMSTAR - A Measurement Tool to Assess Systematic Reviews

CRD - Centre for Reviews and Dissemination

EMA - European Medicines Agency

EU-CTR - EU Clinical Trials Register

FDA - Food and Drug Administration

HTA – Health Technology Assessment

IFPMA - International Federation of Pharmaceutical Manufacturers & Associations

ICTRP - International Clinical Trials Registry Platform

IQWiG - Institute for Quality and Efficiency in Health Care

MeSH - Medical Subject Headings

NICE - National Institute for Health and Care Excellence

NLM - National Library of Medicine

PICOS – Patient or Population / Intervention / Comparison / Outcome / Study design

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PRESS Checklist - Peer Review of Electronic Search Strategies Checklist

RCT - Randomized Controlled Trials

SuRe Info - Summarized Research in Information Retrieval for HTA

1 Summary and table with main recommendations

2 Problem statement

3 Systematic reviews and Health Technology Assessments (HTAs) on clinical effectiveness
4 aim to support evidence-based decision-making in health care. Information retrieval for
5 systematic reviews needs to be performed in a systematic, transparent and reproducible
6 manner.

7 The aim of this methodological guideline is to provide an up-to-date and transparent
8 overview of the whole information retrieval process. The methods described refer to
9 searches for randomized controlled trials (RCTs), but can largely also be applied to
10 searches for other study designs.

11 In particular, the requirements presented in this methodological guideline aim to provide
12 orientation for systematic searches on clinical effectiveness conducted within the
13 framework of EUnetHTA.

14 Methods

15 The guideline authors screened methods manuals of various organizations to identify the
16 relevant literature. In addition, we used the internal IQWiG database, which contains the
17 literature identified by IQWiG's regular searches for articles on information retrieval. We
18 also performed various search techniques to identify further relevant publications.

19 The guideline was primarily based on empirical evidence. If this was not available, the
20 experiences of the guideline authors and other information specialists were considered.

21 The relevant sections of the literature used for the guideline were screened by one author
22 and extracted. A second author performed quality assurance by checking the extracted
23 text and its suitability for the guideline.

Recommendations	The recommendation is based on arguments presented in the following publications and / or parts of the guideline text
1st recommendation: Information specialists should form a regular part of the project team of a systematic review from the beginning of the project.	2.1.2
2nd recommendation: Searching MEDLINE alone is insufficient to identify all published relevant studies on the topic of interest and may produce biased results.	2.2.3
3rd recommendation: A systematic review should regularly include a search for unpublished literature to identify both unpublished studies, and unpublished data from published studies. Clinical study reports and registry entries should be	2.1.1, 3

preferred to conference abstracts.	
4th recommendation: Individual search strategies should be developed for selected databases. Both free-text terms and subject headings should be used, where possible.	2.2.4
5th recommendation: Reference lists of relevant primary studies and systematic reviews should be checked for further relevant studies.	2.2.5
6th recommendation: Search strategies should undergo peer reviewing to ensure high-quality search strategies	2.2.5, 2.3.5
7th recommendation: The search process should be documented in real time and reported in a transparent manner.	2.2.8, 2.3.8

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1. Introduction

1.1. Definitions of central terms and concepts

1.1.1. Search interface

Bibliographic databases can often be accessed via different search interfaces. For example, MEDLINE is freely accessible via PubMed, which is provided by the National Library of Medicine (NLM). However, MEDLINE is also searchable via the fee-based interface OvidSP or ProQuest. These two interfaces differ with regard to structure and functionalities, but contain nearly the same data pool.

Study registries are generally searched via the interface offered by the registry provider. The meta-registry ICTRP Search Portal publishes the data pool provided by different registries in a common database.

1.1.2. PubMed Segments

PubMed consists of various segments (subsets) and users can limit a search to a particular segment. Only the MEDLINE segment has been indexed with MeSH terms and has undergone a quality control procedure.

Extract from [1]:

Status Tag	Citation Status
PubMed - as supplied by publisher	Citations recently added to PubMed via electronic submission from a publisher, and are soon to proceed to the next stage, PubMed - in process (see below). This tag is also on citations received before late 2003 if they are from journals not indexed for MEDLINE, or from a journal that was accepted for MEDLINE after the citations' publication date. These citations bibliographic data have not been reviewed.
PubMed - in process	Citations bibliographic data will be reviewed and indexed, i.e., MeSH terms will be assigned (if the subject of the article is within the scope of MEDLINE).
PubMed - indexed for MEDLINE	Citations that have been indexed with MeSH terms, Publication Types, Substance Names, etc. and bibliographic data have been reviewed.
PubMed	Citations that have been reviewed for accurate bibliographic data but will not receive MEDLINE indexing, because they are for articles in non-MEDLINE journals, or they are for articles in MEDLINE journals but the articles are out of scope or they are from issues published prior to the date the journal was selected for indexing, or citations to articles from journals that deposit their full text articles in PMC but have not yet been recommended for indexing in MEDLINE.
PubMed - OLDMEDLINE	This tag identifies citations in the OLDMEDLINE subset.

1.1.3. Search terms

Search terms: All terms used in a search, i.e. subject headings and free-text terms (see below).

Free-text terms (so-called text words): Terms included in the title and abstract of a publication in a bibliographic database, or in the title and other fields of an entry in a study registry.

Subject headings: Controlled vocabulary used by bibliographic databases to describe the content of a publication. Most of the major databases have their own controlled vocabulary. Medical Subject Headings (MeSH) are the controlled vocabulary indexing system developed by the NLM for indexing publications in MEDLINE. MeSH is also used in other databases (e.g. CENTRAL). Emtree thesaurus is used in Embase.Subheadings: Qualifiers that can be used in conjunction with subject headings to limit them to a particular aspect or as a stand alone to extend a search strategy.

Search string: An individual search query.

Search strategy: The combination of the individual search terms and strings used in a search.

1.1.4. Search functions

It should be noted that search functions differ depending on the source and the search interface.

Boolean operators: Define the type of relation between two search terms. The most usual are:

- "AND": Both search terms must be included in the search result.
- "OR": At least one of the terms needs to be included in the search result.
- "NOT": Any search term placed after this operator should not be included in the result.

"Proximity operator": Two search terms have a specified distance between each other independent of the word order. For example "skin adj3 infection" in Ovid identifies phrases such as "skin infection" or "infection of the skin". Adj3 means there can be a maximum of only two words between the words "skin" and "infection".

Truncation: Can be used to search for variant forms of words (e.g. vaccin* identifies words such as vaccination, vaccine and vaccines). Different interfaces use different truncation marks. Some interfaces allow truncation at the beginning or in the middle of the word.

"Explode"-function: Automatically combines the subject heading via OR with all related subordinate subject headings.

Focus: Limits the search to those publications where a specific subject heading is classified as a "major topic".

Search fields: Fields of references in which the search is conducted. These usually need to be defined for the search strings (e.g. with the abbreviation [tiab] for a search in titles and abstracts via PubMed).

Search syntax: The rules about how search terms and search functions (such as operators or search fields) are spelled, combined and arranged (depends on the search functions of the database).

1.1.5. Surveillance search techniques

Snowballing: Search technique for identifying further relevant articles by means of a known relevant article. This can be achieved by screening the reference list of a known article (backward citations) or by checking which other articles have cited the relevant article (forward citations). The main citation tracking systems providing this “cited-by” service are Google Scholar, Web of Science, and Scopus.

Pearl growing: Search terms and subject headings of one relevant article are examined and form the search strategy. Further relevant articles will be identified with this search strategy. The articles are used to examine more search terms and subject headings to extend the search strategy. This approach can be repeated until no further relevant search terms and subject headings are identified.

“Related citations” function: Identifies similar articles to a selected article using an algorithm calculated by means of the frequencies of subject headings and free-text terms in titles and abstracts.

1.1.6. Limits

Search filters: A predefined combination of search terms developed to filter references with a specific content. They often consist of a combination of subject headings, free-text terms and publication types, and are used to limit searches to specific study designs (e.g. RCTs), populations (e.g. elderly patients) or topics (e.g. adverse events). Search filters should be validated using an independent set of relevant references. They are often developed with different characteristics, for example, maximum sensitivity (“broad”), maximum specificity (“narrow”), and optimized search filters (“minimizing difference”).

Other limits: Filters integrated in the search interface of a database that can be used to limit the search results to, for example, specific publication years and languages. Limits can vary depending on the interface or the database.

1.1.7. Statistical measures

In the field of information retrieval, the sensitivity (recall) for a given topic is defined as the proportion of relevant documents for the topic that were retrieved. Precision is the proportion of retrieved documents that were relevant.

Sensitivity and precision are inversely interrelated, meaning an increase in sensitivity normally goes along with a decrease in precision. In order to know about real sensitivity a gold standard must be defined, for example, by hand searching or relative recall of included studies from multiple systematic reviews.

1.1.8. Accession number

An accession number is a specific (mostly multi-digit) identification number for a reference in a bibliographic database or an entry in a study registry. In MEDLINE these numbers are referred to as “PubMed identifiers” (e.g. PMID: 19230612). A reference included in several databases has several accession numbers.

1.1.9. Auto alert

The search interfaces of bibliographic databases often provide the option to save search strategies. The auto-alert function allows the automatic repetition of the saved strategies at specified intervals (e.g. once monthly). If new references are identified, users receive an e-mail.

1.1.10. Bias

“A bias is a systematic error, or deviation from the truth, in results or inferences. Biases can operate in either direction: different biases can lead to underestimation or overestimation of the true intervention effect [2]”. Different types of bias exist in clinical research, for example, selection, performance, detection, attrition, and reporting bias (a detailed overview is provided in the Cochrane Handbook [2]).

1.2. Objective(s) and scope of the guideline (problem statement)

Systematic reviews and Health Technology Assessments (HTAs) on clinical effectiveness aim to support evidence-based decision-making in health care. (This guideline applies to both types of reports. However, for reasons of simplicity, “systematic reviews and HTAs” is abbreviated to “systematic reviews”.)

Information retrieval for systematic reviews needs to be performed in a systematic, transparent and reproducible manner. The aim is to identify all relevant studies and study results on the question of interest (within resource limits) [3]. This requires both searches in several information sources and the use of comprehensive search strategies [3-5]. This approach is a key factor in minimizing bias in the review process [5].

The aim of this methodological guideline is to provide an up-to-date and transparent overview of the whole information retrieval process. The methods described refer to searches for randomized controlled trials (RCTs), but can largely also be applied to searches for other study designs.

In particular, the requirements presented in this methodological guideline aim to provide orientation for systematic searches on clinical effectiveness conducted within the framework of EUnetHTA.

<u>Aspects of the guideline</u>

Bibliographic databases are the main sources for information retrieval in systematic reviews on clinical effectiveness. However, study registries and study results registries have become more important to identify ongoing and unpublished studies. (In the following text, the term “study registries” will be used for both types of registries.)

Since preliminary searches for systematic reviews are an important part of the information retrieval process, special focus will be placed on how to perform these searches. Different approaches will be described, including the use of special search techniques to identify primary studies [6,7].

Besides the conceptual approach for identifying search terms [3], the objectively derived approach will also be presented [7,8]. The latter is an increasingly important approach in information retrieval for systematic reviews [9]. The use of search filters for RCTs and other limits, peer review of search strategies [7,10-12], reference management (including

different software programs), as well as issues around the documentation and reporting of search strategies [13,14], will be described in detail.

The technical process of screening titles, abstracts and selected full texts (e.g. using a web-based trial selection database [15]) will be a further component of the guideline.

Further information sources

Further information sources, such as reference lists of publications (primarily systematic reviews) [16], conference abstracts [17], queries to authors [18], regulatory documents [19,20], and unpublished company documents [21] will also be described.

Excluded Aspects

The description of searches for studies on specific aspects such as safety, diagnostic accuracy, and economic evaluations (for HTAs) will not form part of this guideline. Summarized Research in Information Retrieval for HTA (SuRe Info) provides research-based evidence on methods to use when searching for these specific aspects [22]. The description of the technical screening process will not contain the process of study selection by means of inclusion and exclusion criteria.

1.3. Related EUnetHTA documents

No EUnetHTA document is exclusively dedicated to HTA information retrieval. Several internal guidance documents contain sections with ”recommendations“ on how to conduct information searches in the context of the given activity or product. These sections are on different levels of detail. They provide context-specific advice, which can be useful in addition to the recommendations given in this methodological guideline which is focusing on clinical effectiveness assessment. Some of these EUnetHTA documents are expected to be updated during JA 2. The identified documents are

- EUnetHTA WP5 Joint Action 2: HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals version 3.0 (01.03.2013), Appendix 3. “Systematic review of the literature, p. 63 – 68
- EUnetHTA WP5 Joint Action 2: Procedure Manual WP5 Strand B: RAPID ASSESSMENTS OF OTHER HEALTH TECHNOLOGIES SUCH AS MEDICAL DEVICES, SURGICAL INTERVENTIONS OR DIAGNOSTICS, V3 (29.04.2013), Chapter 2.3 “Sources of information for the assessment”, p. 15-17
- EUnetHTA Joint Action 2 WP4: Methodological Standards and Procedures (MSP) for core HTA content development (2013), V1.1, General issues: carrying out evidence searches, p. 48 – 50

2. Analysis and discussion of the methodological issue

2.1. Methods of information retrieval for guideline development

The following literature was used in the development of the guideline:

- Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Comparative Effectiveness Reviews [4]
- Centre for Reviews and Disseminations (CRD's) Guidance for Undertaking Reviews in Health Care [5]
- Cochrane Handbook for Systematic Reviews of Interventions [23]
- Methodological Standards for the Conduct of New Cochrane Intervention Reviews [24]
- Institute of Medicine's Standards for Systematic Reviews [25]
- AHRQ Methods for Effective Health Care [26] (for unpublished literature)
- PRESS: Peer Review of Electronic Search Strategies [10] (for bibliographic databases)

In addition, we used the internal IQWiG database, which contains the literature identified by IQWiG's regular searches for articles on information retrieval. This database contains, among other things, the results of an ongoing systematic literature search for topics related to information retrieval, which started in 2008 (see Annexe 2 for details). The list of citations can be provided on request.

In addition, the guideline authors performed various search techniques such as snowballing or PubMed's related citation search and simple searches (see Annexe 2) to identify further relevant publications.

The guideline was primarily based on empirical evidence published after the year 2000. If this was not available, the experiences of the guideline authors and other information specialists were considered.

The relevant sections of the literature used for the guideline were screened by one author and extracted into Excel. A second author performed quality assurance by checking the extracted text and its suitability for the guideline.

2.2. General issues

2.2.1. Addressing reporting bias (including publication bias)

Searches in bibliographic databases aim primarily to identify published studies (see Section 2.2). However, much research is never published or is published with delay [27-30], and published studies tend to overestimate the effectiveness of interventions and underestimate harms [29,30]. To reduce publication and outcome reporting bias, a systematic review should regularly include a search for unpublished literature to identify both unpublished studies and unpublished data from published studies (see Sections 2.3 and 2.4). The data retrieved can be used to verify or supplement published data [26].

2.2.2. Expertise in searching

Information specialists should form a regular part of the project team of a systematic review from the beginning of the project [5,25], as information retrieval has become increasingly professionalized over the last years. For instance, the assessment and further development of search methods [9] requires the regular screening of the relevant

literature, as well as a scientific exchange with peers. In addition, navigating through different information sources is a complex task [25], especially as the structure and functionalities of the databases and their interfaces are regularly modified.

The tasks of information specialists are manifold [3,31-33]. They are responsible for the development and peer review of search strategies, as well as the actual conduct of the search [11,25,34]. In addition, they commonly deal with methodological challenges (e.g. how to balance sensitivity and precision in the development of a search strategy [4]), draft or write the search methods section of the review [35,36], and are responsible for the implementation of software solutions in information management [36].

The call for the regular involvement of information specialists in systematic reviews is supported by research findings: search strategies developed and reported by information specialists were shown to be more easily reproducible than those that were not [37] and also contained fewer consequential errors [38].

2.3. Bibliographic databases

2.3.1. Process of searching bibliographic databases

The figure shows the process of searching bibliographic databases. The steps will be explained in the following sections in detail (Figure 1). In addition, a practical example can be found in the Annexe 4.

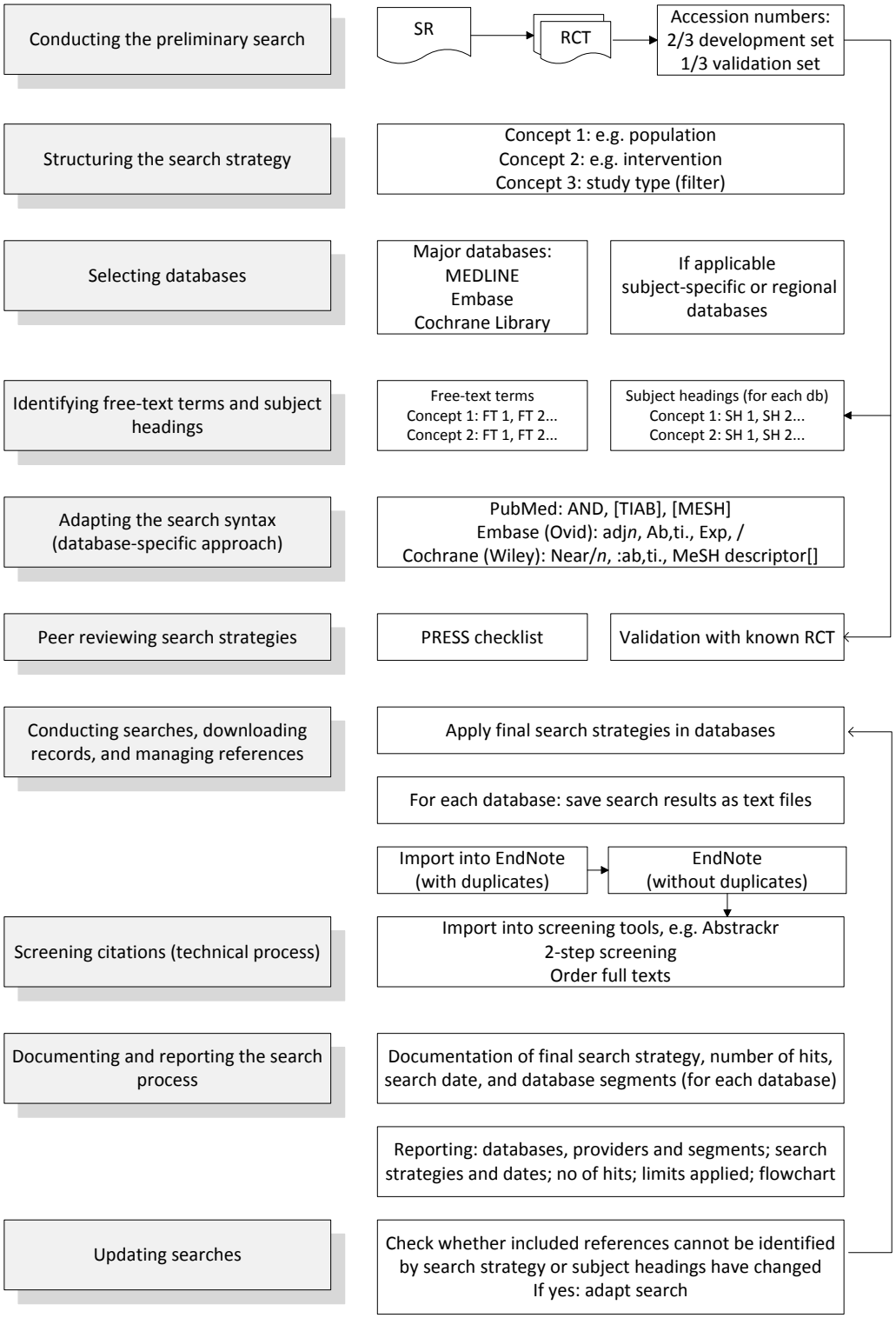

Figure 1: Search in bibliographic databases

2.3.2. Conducting preliminary searches

At the start of a project – before the development of the actual search strategy – a preliminary search (also known as a scoping search) should be conducted. This preliminary search has various goals.

Firstly, to help prepare the overall project [35], i.e. understanding the key questions [4], identifying existing systematic reviews [5,39,40], identifying a first set of potentially relevant primary studies [41], and estimating the resources necessary to perform the systematic review [39]. Secondly, a preliminary search helps prepare information retrieval itself. For example, a list of search terms is generated from the analysis of relevant articles [4,42-44] and subsequently used in the development of the search strategy.

Two main methods for conducting preliminary searches are described in the literature. With the first method, systematic reviews on the topic of interest are systematically searched for in preselected information sources [5,39,40,45] such as the Cochrane Library, CRD databases or the POP database [46]. The second method comprises an iterative process with different search techniques such as “snowballing” [4,44,47] and checking the “related citation” link in PubMed [6,48,49]. The starting point is a relevant article either already known or identified by a very precise search. Several cycles of reference identification with these techniques and screening for relevance are then performed [4,44].

The most effective way of conducting a preliminary search is first to search for systematic reviews. The techniques described above are used to search directly for primary studies if the first search produced no relevant or only poor-quality reviews [44].

See example: Conducting preliminary searches (bib. Databases)

2.3.3. Structuring the search strategy

Before the development of a search strategy, the structure of the search has to be defined. This requires a clearly formulated research question following the Patient or Population / Intervention / Comparison / Outcome / Study design (PICOS) approach [3]. The research question is commonly broken into concepts, and only the most specific ones are used to develop the search strategy [50]. The main challenge is not to introduce too many concepts [3,10], as many may not be adequately addressed in the title, abstract, and subject headings of the articles [4].

In general, a search strategy will include the population, intervention(s), and types of study design [3]. Outcome is usually not included in a systematic search. For more complex review questions, it may be necessary to use several combinations of search concepts to capture a review topic [9,51] or to use other search approaches to capture relevant studies (see section 2.2.1).

The search terms are divided into search blocks according to the structure of the search. Within each concept, the relevant subject headings and free-text terms are combined with the Boolean operator “OR” [3]. In this context it is recommended to separate free-text terms and subject headings on different lines of the search [10]. Validated study filters are used for the search block on study design (see Section 2.2.4.1). All search blocks are then combined with the “AND” operator [3]. If limits are a component of the structure of the search, they also need to be applied.

Search limits (e.g. for language or search period) resulting from the inclusion and exclusion criteria of the systematic review, must be justified by methodological or other content-related reasons and commented on in the methods chapter. These limits should be applied carefully as they may introduce bias [3,4,10], and should only be considered if they can be reliably applied in the individual databases.

See example: Structuring the search strategy (bib. Databases)

2.3.4. Choosing information sources

The production of a systematic review requires a systematic search in several bibliographic databases. For example, previous research has shown that searching MEDLINE alone is insufficient to identify all published relevant studies on the topic of interest and may produce biased results [52-55]. This is due to the fact that journal inclusion rates differ between databases [56,57]. Furthermore, the time and quality of indexing differs [53,57-59], meaning that a reference might be more difficult to find or be found with delay in some databases, but not in others.

However, insufficient empirical evidence is available so far on how many and which databases should be regularly searched. The Cochrane Handbook names MEDLINE, Embase and CENTRAL as the three most important bibliographic databases (for primary studies) [3]. Analyses of retrieval rates of relevant studies indicate that most of the published studies can be found in these sources [54,60,61].

Depending on the objective of the systematic review, regional or subject-specific databases may also be relevant [3-5,25,62]. However, the additional impact of searching in regional databases has been insufficiently investigated, and many of such databases seem to provide restricted functionalities [63,64]. In contrast, at least for some objectives the use of subject-specific databases may identify additional relevant studies (e.g. on complementary and alternative medicine) [65,66]. A list of regional and subject-specific databases is provided in the Cochrane Handbook [3].

See example: Choosing information sources (bib. Databases)

2.3.5. Developing search strategies

2.3.5.1. Identifying search terms

A combination of subject headings (including publication type) and free-text terms is required in the development of search strategies [67-69]. Different approaches to identify search terms are described in the literature [7,70]. The traditional or subjective approach [71,72] is recommended by the pertinent literature. Sources used in this approach include the MeSH database, medical dictionaries, scanning of relevant publications or consultations with experts to identify a wide range of subject headings and free-text terms [3,5,41]. In addition, a key article is commonly chosen as a starting point to identify further relevant terms using methods such as “pearl growing” [50]. This process is usually repeated until no further material is found [73].

A more objective approach to developing a search strategy is to use text-analytic procedures to identify free-text terms and subject headings through a frequency analysis

[7,8,73-76]. In this context relevant articles already known [7,8,74,77] or newly identified through broad searches [73,75] are systematically analysed. Different software packages are available that in part clearly differ with regard to costs and functionalities (e.g. PubReMiner [7], Wordstat [75,78], TerMine [79], EndNote [80], Text Mining Package of R [8], and Leximancer [73]).

In the next step the terms chosen are assigned to the individual blocks of the search strategy, independently of which approach was chosen to identify subject headings and free-text terms [10,50]. To avoid redundancies, free-text terms should be truncated at the word stem [81] and subject headings and related subordinate subject headings should be summarized with the “explode”-function [3,10], if meaningful. The inclusion of further search fields (e.g. substance name, original title), as well as the restriction of subject headings via subheadings or focus (for topic-specific results) must be checked separately for each research question.

Terms related to study design need not be identified if well-tested, high-quality filters for study design are available [4]. Such filters are provided by the InterTASC Information Specialists' Sub-Group [82] or the Cochrane Handbook [3] and can be evaluated before the search using critical appraisal checklists [83,84].

The search for references not yet indexed in PubMed is a major challenge. For this purpose, free-text terms and study filters may need to be adapted [85,86] as searches are usually optimized for a combined subject headings and free-text search.

See example: Identifying search terms (bib. Databases)

2.3.5.2. Adapting the search syntax

After the structure of the search, the search terms and the databases have been determined, the actual strategy can be developed. Instead of using cross-database search options, each database should be searched individually [36]. For this purpose, the free-text terms previously identified can usually be applied across databases [5].

Subject headings however must be specifically adapted for each database [3-5,10,87]. In this context it is advisable to adapt the search strategy developed first (commonly in MEDLINE [31]) to the requirements of the other databases [3,4,10,87]. It should also be noted that certain features are implemented differently by the interfaces of the various databases (e.g. truncation, proximity operators, and the “explode”-function). Uniform application of the search syntax is thus not possible and may produce inconsistent search results [81,88].

See example: Adapting the search syntax (bib. Databases)

2.3.6. Peer reviewing search strategies

A high-quality search strategy is required to ensure the accuracy and completeness of the evidence base used in a systematic review [10,11]. However, due to their complexity, search strategies in bibliographic databases are prone to error [34].

The “Peer Review of Electronic Search Strategies” (PRESS) checklist was developed to support the peer review process [10,11]. Analyses of peer reviews using the PRESS checklist show that this tool identifies errors and may increase the number and quality of relevant references retrieved [89,90]. The peer review process using the checklist should be completed before the search strategy is run [25,34,89].

A peer review using the PRESS checklist is primarily a formal review. In addition, the completeness of the search strategy should be assessed by testing the final search strategy against a validation set containing an independent pool of relevant references [4,7,87,91-93], i.e. it is tested whether relevant references identified beforehand (see Section 2.2.1) can be found by the specific search strategy.

See example: Peer reviewing search strategies (bib. Databases)

2.3.7. Conducting searches, downloading records, and managing references

After development, search strategies should be saved individually for each database and subsequently applied when the strategy is run. It should be ensured that each strategy fulfils the current quality assurance requirements. After conducting the search in the selected databases, the references retrieved are downloaded, combined, and prepared for the screening process. For this purpose, the use of reference management software such as EndNote [94], RefWorks [95] or Mendeley [95] is recommended [3-5,25,96]. These software programs enable the efficient management of references, including in-text citation [97].

Searching several databases produces duplicates. Qi et al. [98] showed that about 10% of references retrieved in a systematic search are duplicates. They recommend a 2-step procedure for deletion of duplicates using reference management software. About two-thirds of duplicates can be identified via automatic comparison (matching of author, title, and year). To identify the remaining duplicates, the remaining references are sorted by the first authors’ names and then screened manually.

Duplicates can also be directly deleted during the search by means of the accession number. For instance, search strings can be generated with the accession numbers of references already identified in MEDLINE and Embase; it is then possible to exclude these records from a search in CENTRAL [3].

Some interfaces also offer the option of directly deleting duplicates in the bibliographic database via a search command (e.g. in OVID MEDLINE with the command “..dedup x [search line]”, in Embase.com with “x NOT[medline]/lim”).

In Ovid it is also possible to conduct separate searches in each database with individual search strategies and then deduplicate [36]. The individual database searches can be run simultaneously by limiting the search sets to the respective databases using Ovid database codes [99]. Once this is done the duplicates can be removed by Ovid.

See example: Conducting searches, downloading records etc (bib. Databases)

2.3.8. Screening citations (technical process)

After the references have been saved in a reference management program, the selection process begins. The documentation of this process must be transparent and include the decision on the inclusion or exclusion of each reference retrieved [5,25].

The selection of references is usually administered by a reference management program or by manual handling of paper copies [5]. However, in practice this is often problematic, particularly if the search produces a large number of hits. Internet-based systems [100] such as Abstrackr [101], Covidence [102], and EPPI-Reviewer [15] have therefore been developed which, in addition to documenting the assessment of the references, offer the advantage of documenting the consensus process if assessments between reviewers differ.

In a 2-step procedure, the titles and abstracts of the references are first screened against the inclusion and exclusion criteria, followed by the screening of the full texts of potentially relevant publications identified in the first step [5,25,103]. The screening usually involves two reviewers to reduce the possibility of missing relevant publications [103]. The selection of studies to be included in the systematic review also should always be performed by at least two reviewers [103]. Current techniques aim to automatically support the screening at title and abstract level [104-110].

In the study selection process, information specialists are increasingly involved in data management between different software applications [9,31]. In addition, they play a key role in the ordering of full texts. Due to complex copyright and licensing conditions, full texts are obtained via various routes. Copyright and licensing conditions have to be checked separately for each full text. Most scientific institutions, such as HTA agencies, possess licences for the most important medical journals, are members of national consortia, use ordering services such as Subito or Infotrieve, or obtain articles via library or open access. The time and costs required for ordering full texts should also be considered when planning information retrieval [111].

See example: Screening citations (bib. Databases)

2.3.9. Documenting and reporting the search process

Internal documentation

The search process should be documented in real time, i.e. both at the time of the development of the search strategy and the conduct of the search, and not retrospectively [5,25]. The aim is to document the search process as exactly as possible so that all information required for reporting is available [3]. The strategy for each bibliographic database, including the hits per line, should be copied and pasted as run and saved in text format [3,36]. Many databases offer facilities to save search strategies [36].

When exporting search results from the databases, the references should first be saved as text or RIS-files and not imported directly into the reference management program. This ensures the safe storage of search results [36]. In addition, information on the databases and interfaces searched should be documented, including the search dates and the search periods covered [3,5,36]. The complete documentation process is described in detail by Rader et al. [36].

Reporting

Clear and transparent reporting of all aspects of the search enables the assessment of quality and completeness [14,112], as well as search replication for future updates [4,5,13,36]. Several guidelines on reporting search methods are available [14,113]. Mullins et al. [113] analysed ten of them and identified eight common reporting elements (see Annexe 3). In addition, the study selection process should be displayed in a flowchart in the results section of the systematic review [4,5,25] (see PRISMA for a template [112,114]). Furthermore, the references of the studies included and excluded should be presented in separate reference lists [103,115]. In contrast to journal publications, HTA reports do not have space restrictions and should therefore document the search process as precisely as necessary [25].

See example: Documenting and reporting (bib. Databases)

2.3.10. Updating searches

The literature search is usually conducted at the initial stage of the production of a systematic review. In consequence, the results of a literature search may be outdated before the review is published [116-118]. The last search in a review should be conducted less than 12 months before publication [24,117]. Search updates are therefore often conducted before the planned publication date.

Auto alerts [5] and other surveillance search techniques [48] can help identify new relevant articles immediately after publication. However, they usually cannot replace a search update but may provide early signals for the necessity of such a search.

Before conducting a search update, the performance of the search strategies in each database should be checked. For this purpose, the references included in the review are used to determine whether they can be identified by the search strategy. If this is not the case, the search strategy should be adapted [3,12] and it should be assessed whether further databases need to be searched [119].

To limit the number of hits retrieved, the search update should only identify references that are added to databases after the last search was conducted. In general, to limit the search period, the date the record entered the database, not the “publication date”, should be used [120]. A further technique excludes all references identified in a database in the initial search via a “NOT” link. These “old” references can be reliably identified via their accession number.

See example: Updating searches (bib. Databases)

2.4. Study registries

2.4.1. General aspects

The importance of study registries has increased markedly over the last years. For example, in 2005 the International Committee of Medical Journal Editors specified that the prospective registration of clinical studies was a precondition for publication [121].

Furthermore, in 2007 the United States introduced mandatory registration of studies and summary results in Clinical.Trials.gov for most FDA-regulated drugs and devices [122]. In 2011 the European Medicines Agency (EMA) established the EU Clinical Trials Register (EU-CTR) [123] for most studies submitted during the drug approval process; the posting of summary results became mandatory in July 2014 [124].

Study registries do not generally contain full clinical study reports and, as with journal publications, the information posted is often insufficient for the assessment of a study. However, registries and publications may supplement each other [21].

Structure of study registries

Study registries are publicly available and commonly web-based databases or platforms; they contain key information from the study protocol, including outcomes, and/or summary results [26].

Different types of individual registries have been established (see Table 1). In addition, meta-registries such as the ICTRP Search Portal [125] contain regularly updated data from individual registries or access individual registries directly at the time of the search query.

Types of study registries	**Examples**
National registry	Deutsches Register Klinischer Studien [126] Nederlands Trial Register [127]
Regulatory registry	ClinicalTrials.gov [128] EU Clinical Trials Register (Europe) [123] PharmNet.Bund – Arzneimittel-Informationssystem (Germany) [129]
Industry registry	GlaxoSmithKline Clinical Study Register [130] Forest Clinical Trial Registry [131]
Disease-specific registry	ALOIS: A Comprehensive Register of Dementia Studies [132]
Meta-registry	ICTRP Search Portal of the WHO [125]

Table 1: Types of study registries

The information contained in study registries is generally entered and updated by those responsible for the conduct of the study. However, entries may be incomplete or contain errors [133-135] and the study status may be outdated [136]. It should also be noted that registries have previously been closed down at short notice (e.g. clinicalstudyresults.org [137] or the web crawler of the IFPMA Clinical Trials Portal [138]).

2.4.2. Structuring the search strategy

Searches in study registries should be simple, highly sensitive, and ideally structured to search for one concept (e.g. intervention or indication) [139]. It is advisable to first conduct the search using the terms of the concept that can be most clearly specified and will thus probably generate the lowest number of hits. The scope of the search should only be limited further by adding the second concept if too many hits are retrieved in the first

search. Due to the varying quality of the individual registry entries, it is not advisable to apply additional limitations (e.g. with regard to study status or phase).

See example: Structuring the search strategy (Study registries)

2.4.3. Choosing information sources

Several registries should be searched, as no registry contains all studies [136,139,140]. The search should include at least the ICTRP Search Portal as well as ClinicalTrials.gov [24,26,139]. The ICTRP Search Portal is a meta-registry currently containing 16 worldwide national study registries (including ClinicalTrials.gov) and covers a high percentage of clinical studies [136,141]. However, it only offers limited search functions [139] and often produces error messages [142]. In addition, the posting of study results is not mandatory, therefore major registries such as ClinicalTrials.gov should always be searched directly [139].

For systematic reviews of drugs, the relevant company registry [143], as well as the EMA registry (EU-CTR), should also be searched. In addition, national legislation should be considered: for instance, summary results are provided for drugs approved in Germany via the drug information system of PharmNet.Bund [129]. This database may include otherwise unavailable results from studies conducted outside Europe and the United States.

Only a few suitable disease-specific study registries are available and they are often difficult to find. These registries are frequently established for temporary research programmes and are commonly no longer updated when funding ceases. They are thus not very useful and should only be searched for in exceptional cases [144].

See example: Choosing information sources (Study registries)

2.4.4. Developing search strategies

2.4.4.1. Identifying search terms

The syntax for the search in bibliographic databases provides the basis for the selection of search terms for the search in registries. Known terms of a search concept should be considered in a sensitive search [139]. It should be noted that registries such as ClinicalTrials.gov (see [133] for an example) and the ICTRP Search Portal offer a search for synonyms [144]. Both provide a list of synonyms for search terms (in ICTRP this is only available via the “advanced search” function), which enables a reduction in the number of search terms. This is necessary because study registries only provide limited search functions and only a few search terms can thus be used.

See example: Identifying search terms (Study registries)

2.4.4.2. Adapting the search syntax

The search syntax has to be adapted for each registry. The functionalities provided vary considerably and these differences need to be observed (e.g. concerning truncation, use of brackets, and implementation of Boolean operators). For example, no brackets to structure the search can be used in ICTRP Search Portal. In addition, complex search

queries may generate error messages or errors which may not always be visible to the user. Furthermore, in contrast to bibliographic databases, search lines in registries generally cannot be linked by means of operators. Glanville et al. provide an example of the adaption of the search syntax in ClinicalTrials.gov and the ICTRP Search Portal [139].

The York Health Economics Consortium provides a comprehensive overview of the search functions of different registries [145].

A sensitive search should be conducted in as many fields as possible, which is usually feasible with the “basic search” function [139,144].

See example: Adapting the search syntax (Study registries)

2.4.5. Peer reviewing search strategies

The peer review of search strategies developed for study registries should follow the procedure applied for bibliographic databases. The PRESS checklist [10,11] can be used as a guideline but should be adapted (e.g. if the list of synonyms for search terms for each study registry has been checked).

A check for completeness of the search should also be performed. For example, Glanville et al. describe an approach for identifying registry entries on known relevant studies [139]. To the relevant studies already identified in bibliographic databases in the preliminary search (see Section 2.2.1) a set of relevant registry entries can thus be determined. It is then tested whether the final search strategy actually identifies these entries.

See example: Peer reviewing search strategies (Study registries)

2.4.6. Conducting searches, downloading records and managing references

The search in study registries should follow the procedure applied for bibliographic databases.

Major registries such as ClinicalTrials.gov offer the direct export of search results as xml or text files [145], which can then be imported into a reference management program using an import filter. For ClinicalTrials.gov this type of filter is provided by the Cochrane Information Retrieval Methods Group [146]. The search results can then be processed for screening.

If no export function is available, the search results can be copied and pasted into Excel and processed [144].

As different registries may provide different information on the same study, the deletion of duplicates is not advisable (except for entries with identical registration numbers).

See example: Conducting searches, downloading records etc. (Study registries)

2.4.7. Screening citations (technical process)

The screening of search results is similar to the procedure applied for bibliographic databases. Using a screening tool (see Section 2.2.7), the registry entries should be screened by two reviewers. The information on the relevant studies contained in the registry entries (study protocol, and, if applicable, study results and/or other documents) should be saved.

See example: Screening citations (Study registries)

2.4.8. Documenting and reporting the search process

The documentation of the search in study registries follows the procedure applied for bibliographic searches: real-time documentation of the name of the registry searched, the search date, the number of hits retrieved, as well as storage of the search strategy and the raw search results. If the database has more than one interface (basic and advanced search) this should also be noted. If it is not possible to store raw results, it is advisable to document the search results with screenshots to enable later comparison with the results of a search update [144].

It is not clearly regulated which type of registry information should be reported. Balshem et al. recommend the following: “Construct a table that provides information on trials found in the registry, their publication status, and whether they are completed or currently active trials, and provide a count of the number of unique trials found along with their status at the time of the search […] Match trials with publications found from the standard search, noting 1) trials with an entry in ClinicalTrials.gov, and 2) trials for which no publication was found” [26].

The search strategy itself should also be reported to enable the reproduction of search results [139,147,148].

See example: Documenting and reporting (Study registries)

2.4.9. Updating searches

If applicable, a search update in registries should be performed close to the time of the search update in bibliographic databases. It is advisable to dispense with time limits (e.g. by means of the entry date) during the direct search in each study registry and instead perform a manual comparison using registration numbers. This duplicate check can be carried out in a reference management program or in Excel.

If ongoing studies were identified in the initial search, their status should be checked at the time of the search update.

See example: Updating searches (Study registries)

2.5. Further information sources

2.5.1. Unpublished company documents

Full information on clinical studies and their results is required to provide adequate assessments of drugs and non-drug interventions. This can best be achieved with clinical study reports, which are submitted to regulatory authorities during the approval procedure for a drug but are rarely made publicly available.

These documents are generally prepared following the International Conference on Harmonisation's Guideline for Industry: Structure and Content of Clinical Study Reports (ICH E3) [149] and provide detailed information on the methods and results of a study [150]. They contain far more relevant information than journal publications or registry reports [21,149,150]. Although clinical study reports are considerably longer than journals publications [151] and require specific expertise with regard to data extraction and assessment, they are indispensable for gaining an unbiased picture of the available research evidence [21,29,149-152].

In 2014 the EU Parliament passed a law specifying the publication of complete clinical study reports for all studies used in the drug approval process from 2016 onwards [153]. In addition, EMA has introduced a new policy on data transparency, which includes the publication of clinical study reports [154], but it is still unclear how this will be implemented [155,156]. No plans currently exist for the publication of reports on clinical studies of medical devices.

Search process

As clinical study reports are not currently published by regulatory authorities or pharmaceutical companies, the latter should be asked to provide unpublished information [26]. For example, IQWiG currently applies the following approach for this purpose [157]: Before requesting data, an agreement is reached between the authors of the systematic review and the relevant company concerning the transmission of information on the drug of interest. [1] In this context, to avoid bias by selective provision of data it is important for the company to agree a priori to the publication of all relevant data (not the publication of all full documents). A 2-step procedure then follows: Firstly, the company is asked to provide a complete list of studies on the drug or medical device to be assessed. Secondly, the authors identify potentially relevant studies from this list and request detailed information from the company on unpublished studies or additional information on published studies.

2.5.2. Regulatory documents

Regulatory authorities publish sections of reports prepared during the approval process [26]. These documents can offer important insights into clinical studies [158] and may also include a list of studies that are potentially relevant for a systematic review. Research evidence shows that the search for regulatory documents can identify unpublished studies

[1] Agreement upon manufacturer data between IQWiG and the German Association of Research-based Pharmaceutical Companies https://www.iqwig.de/en/press/press_releases/press_releases/agreement_upon_manufacturer_data.2246.html

or unpublished data from published studies [19,20,25,26,30,159]. However, similar to other sources such as reports from study registries, regulatory documents do not usually contain all relevant information on a study [152].

Websites of regulatory agencies are rarely included as information sources in systematic searches [159,160]. In Europe, information on centrally authorized drugs (e.g. European public assessment reports) can be found on the EMA website [161]. In the United States, the Medical and Statistical Reviews of drugs approved by the FDA can be found via Drugs@FDA [162].

In contrast to the United States, there is no centralized authorization procedure for medical devices in Europe. If clinical studies are conducted for European market access, the EU member states are obliged to post the corresponding information in the European Databank on Medical Devices (EUDAMED) [163]. However, this source is not publicly accessible. Information on medical devices is sometimes made available by individual countries, for example, in the NICE list of interventional procedures in the UK [164]. In the United States, information on FDA-approved devices, including data used for approval, is available via Devices@FDA [165].

Search process

A search for regulatory documents should at least include the FDA and EMA websites. Regulatory authorities in other countries such as Canada [166] or Japan [167] also publish potentially relevant documents and should be considered in individual cases.

A **search** for the drug name and active ingredient (or for the name of the medical device) is conducted on the websites of the relevant regulatory authorities. If no relevant documents are found, it is advisable to also conduct a search in Google (e.g. for “FDA advisory committee” AND “active ingredient”). Turner [168] has provided a detailed overview on how to access and process FDA documents [168]. However, navigating on the FDA website and searching in documents can be challenging [134].

The **internal documentation** for regulatory sources used in a systematic review includes information on the website, the search date, and the search terms used. The regulatory documents are saved and the text is screened to identify information on clinical studies and any other potentially relevant information.

In addition to the search details (website, search date, search terms), the number and titles of the regulatory documents identified should be **reported in the review**. It should also be described whether further studies or data were found in addition to the literature identified in other sources.

2.5.3. Queries to authors

The reviewers should contact the study authors if the published reports of potentially relevant studies lack the necessary details required to ascertain a study’s eligibility or to determine its methodological quality [4,25,169].

It may also be necessary to contact the study authors to clear any uncertainties about a study’s publication status. The study author can often help link the identified information to full publications, confirm that there was no subsequent publication, inform about soon-to-be-published publications, and clear uncertainties surrounding duplicate publication [4].

Overall, there is no clear evidence stating what the most effective method for obtaining missing data from the study authors is, but contacting authors by e-mail seems to be a useful method [170]. In addition, the evidence shows that multiple requests do not seem to lead to more comprehensive information or to a greater response rate than single requests [170]. Sending one email request to each study author may therefore be considered sufficient.

When reviewers contact authors, they should report to what extent and how it was done, i.e. the number of studies for which authors were contacted, the response rate, the information requested and the response from authors to the request [4,169].

Systematically contacting authors of all identified relevant studies, as well as topic experts and manufacturers, may also be considered to identify additional unpublished, ongoing or difficult to locate studies that may be useful for the review.

2.5.4. Conference abstracts

Only about half of all studies first presented as abstracts will subsequently reach full publication, and studies reported in abstracts are more often published in full text if their results show a positive treatment effect or have significant results [17]. Conference abstracts often provide limited details of study methodology, and may contain limited reporting of outcome data [171]. There can be differences between data presented in an abstract and that included in the full publication [5,172]. For these reasons, reviewers should always try to obtain the full report or further study details, before considering whether to include the results in the review [5,171].

Especially if systematic literature searches for published studies yield no or very few studies, searching conference abstracts and proceedings may be considered [171]. Conference abstracts and proceedings may be identified by searching bibliographic databases that index meeting reports [4], such as Embase, BIOSIS Previews and Scopus, and by hand searching of journal supplements, meeting abstract books, and conference websites [171].

If the project team decides to include conference abstracts, they should report the search approaches used to identify them. Handsearching or scanning the pdfs of conference proceedings should be reported by listing the names of conference proceedings, years searched and search terms used (when relevant). For reporting searches in bibliographic databases, please see section 2.2.8. The project team should also describe how they have assessed the identified abstracts for inclusion, how the data were used and their effects on the results of the review [171].

2.5.5. Reference lists of publications

Checking reference lists of relevant primary studies and systematic reviews is often recommended by search manuals and may be useful sources to identify further studies of interest to a specific topic [3,5,173]. This said, reference lists should be used with caution and as an adjunct to other search methods since reviewers may selectively cite studies with positive results [174]. Browsing reference lists may identify unique relevant studies or reviews, especially when identifying relevant research in databases is difficult, but evidence to support this recommendation is weak [173].

Relevant conference proceedings or other grey literature and poorly indexed journals, are often identified by scanning reference lists [4].

Furthermore verifying the studies identified solely through checking reference lists can validate the effectiveness of the search in bibliographic databases [45]. If the search in bibliographic databases has missed relevant articles, revising and rerunning the search strategy should be considered [173].

We recommend scanning the reference lists by one person and checking these assessments by another. Two persons should screen all citations chosen for further assessment in full-text independently. When reporting, all scanned references should be listed in the appendix, and the number of additionally identified studies should be stated.

2.5.6. Dissertation and reports

Searching for dissertations and reports seem helpful only in exceptional cases (e.g. religion and mental health [175]. Numerous databases for dissertations and research reports (e.g. BL EThOS, DART Europe, ProQuest Dissertations & Theses Database, c OpenGrey, NIH RePORTER) exist but are not recommended to search routinely.

3. Conclusion and main recommendations

The information sources listed in the present guideline show different strengths and weaknesses. For instance, a search in bibliographic databases is generally easy to implement [3]. However, many studies are never published and cannot be found in these databases. The production of a systematic review thus requires the regular search of additional information sources, even though this usually involves considerable additional effort.

Unpublished company documents (clinical study reports) provide the most comprehensive information on clinical studies and should therefore be considered as additional sources. They minimise the problem of reporting bias and are thus indispensable for gaining an unbiased picture of the available research evidence. As clinical study reports are often not publicly accessible, they should be routinely requested from the responsible companies.

Study registries are also an important information source. They offer the advantage that the registration of studies and the posting of study results are now mandatory in many countries. However, the corresponding laws largely apply to studies of drugs submitted to regulatory authorities during the drug approval process. This also applies to regulatory documents, which often have different structures and formats and are difficult to search.

Queries to authors of study publications are a further option to obtain relevant additional information on studies identified in a literature search. However, such queries often remain unanswered [18].

A search for conference abstracts may be of only limited use. This is primarily conducted to identify further studies; the results presented in abstracts are often based on interim analyses and therefore cannot be readily used in systematic reviews [30].

Reference lists of relevant study publications should be used as a standard information source. If searches conducted in bibliographic databases have failed to identify published studies included in the reference lists, search strategies should be reviewed and, if necessary, adjusted.

The types of information sources considered in a systematic review largely depend on the topic of interest, the review's objective, the risk of reporting bias, the time frame of the work, and the available resources. The requirements outlined in AMSTAR may be regarded as a minimum standard; i.e. a search in at least two bibliographic databases plus a further information source (in addition to the screening of reference lists of included publications) [115].

The choice of information sources for identifying unpublished studies should be based on the completeness and reliability of data: for instance, clinical study reports and registry entries should be preferred to conference abstracts.

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Annexe 2. Documentation of the literature search

The internal IQWiG database includes literature retrieved from

1) Literature monitoring via AutoAlert in MEDLINE

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	**Searches**
1	(search$ or identify$).ti. or (filter$ or hedge$ or search strat$).ti,ot,ab.
2	databases/ or exp databases, bibliographic/
3	information services/ or bibliography/ or bibliometrics/ or databases, bibliographic/
4	vocabulary, controlled/ or exp subject headings/
5	exp "Abstracting and Indexing"/mt, st, sn, ut [Methods, Standards, Statistics & Numerical Data, Utilization]
6	exp Periodicals as Topic/st, sn, ut [Standards, Statistics & Numerical Data, Utilization]
7	*"Information Storage and Retrieval"/ or "Information Storage and Retrieval"/mt, st, sn, ut [Methods, Standards, Statistics & Numerical Data, Utilization]
8	or/2-7
9	1 and 8

#	**Searches**
1	zarin da.au.
2	deangelis cd.au.
3	1 or 2
4	"ClinicalTrials.gov".ti.
5	3 or 4

#	**Searches**
1	(search strategies or search strategy or search engine* or search filter* or search method* or OVID search or search term* or search sensitivity or search result* or literature search or search method* or Mesh search or text word search or search string or search result* or hand search).ti.
2	Databases as Topic.sh.
3	Information Systems.sh.

4	Databases as Topic.sh.
5	Medical Subject Headings.sh.
6	Bibliometrics.sh.
7	Subject Headings.sh.
8	Medline.sh.
9	PubMed.sh.
10	"Information Storage and Retrieval".sh.
11	Databases, Bibliographic.sh.
12	"Abstracting and Indexing as Topic"/
13	6 or 11 or 3 or 7 or 9 or 12 or 2 or 8 or 4 or 10 or 5
14	Review Literature as Topic/ or Evidence-Based Medicine/ or Randomized Controlled Trials as Topic/ or Meta-Analysis as Topic/ or Technology Assessment, Biomedical/
15	13 and 14
16	1 or 15

2) Screening of abstracts and posters of relevant meetings

- Cochrane Colloquium
- HTAi Annual Meeting
- International Congress on Medical Librarianship
- Medical Library Association Annual Meeting
- American Medical Informatics Association Annual Symposium
- Annual Meeting of the German Network for Evidence-based Medicine

3) Screening of relevant journals

- J Clin Epidemiol
- BMJ
- J Med Libr Assoc
- BMC Med Res Methodology
- J Am Med Inform Assoc

4) Screening of the reference lists of relevant articles

5) Screening of literature identified elsewhere

Searches to identify additional references on "Queries to authors", "Conference abstracts", and "Reference lists of publications"

Cochrane Library (Wiley)
Search date: 21.08.14

#	Searches
1	reference next list*:ti or (conference next (proceeding* or abstract*)):ti or (author* near (quer* or contact*)):ti (Word variations have been searched)
2	systematic next review*:ti or (health next technology next assessment*) or HTA:ti or evidence next synthes*:ti (Word variations have been searched)
3	#1 and #2

PubMed (NLM)
Search date: 21.08.14

((((systematic review*[Title]) OR health technology assessment*[Title]) OR HTA[Title])) AND ((((reference list*[Title]) OR conference proceeding*[Title]) OR conference abstract*[Title]) OR author*[Title])

Annexe 3. Common reporting elements

Common reporting elements of the analysis of Mullins et al. [113]:

- Databases [5,23,25,114,115,176-180]
- Name of Interface (host/platform) [5,25,114,176,180]
- Years covered by search [5,23,25,114,115,176-180]
- Date last search was run [5,23,25,114,179]
- Complete search strategy [5,23,25,114,115,176,178-180]
- Language limits [23,114,115,176-180]
- Supplemental search [5,23,25,114,115,176,177,179,180]
- Qualification of searcher [25,176]

Annexe 4. Example: Ultrasound screening for abdominal aortic aneurysms

The present example refers to the assessment of the benefit of ultrasound screening for abdominal aortic aneurysms. For this purpose a systematic search for RCTs was conducted. The aim of the example is to give a quick impression how to perform a systematic search in bibliographic databases and study registries.

Implementation of the search in bibliographic databases

Conducting preliminary searches *(Back to top)*

At the start of the project – before the development of the actual search strategy – a preliminary search for high-quality systematic reviews on ultrasound screening for abdominal aortic aneurysms was conducted in the Cochrane Library (Wiley).

The search was kept as simple as possible, in the present example for “ultrasound screening” and “abdominal aortic aneurysms”. One Cochrane Review (CD002945 [181]) was identified that precisely covers the research question (Figure 2).

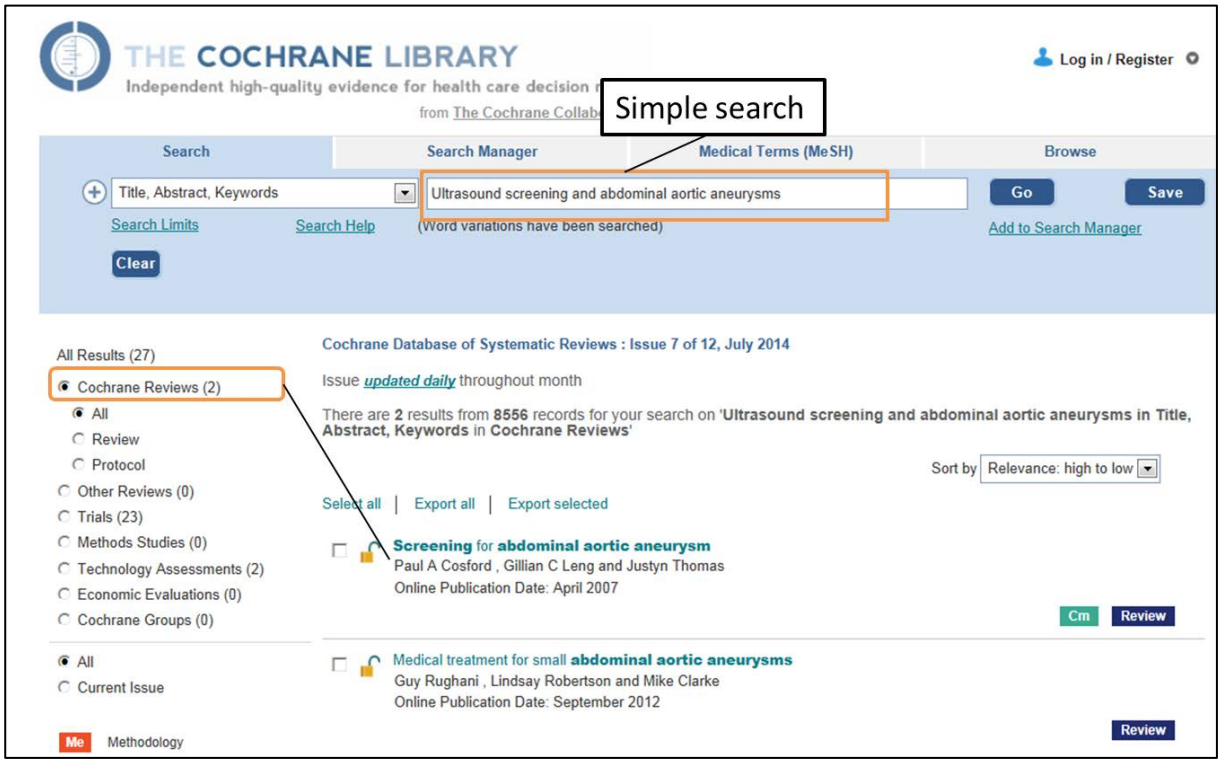


Figure 2: Preliminary search in Cochrane Library (Wiley)

The background section of the Cochrane Review was read to learn more about the topic; more importantly, the primary studies in the review could be used. A search in PubMed and on websites of HTA agencies identified two further systematic reviews [182,183].

The inclusion and exclusion criteria, as well as the information retrieval processes, were assessed to estimate the completeness of the evidence base considered in the systematic reviews identified. The evidence base was assessed to be comprehensive and thus suited to serve as a basis of our search strategy. A total of three systematic reviews and 38 relevant references were available and could be used for the development and validation of our own search strategy.

Structuring the search strategy *(Back to top)*

Organizing topics into concepts is relatively simple in the present example, as the individual concepts were clearly distinguishable from the inclusion and exclusion criteria of our systematic review.

The search was structured as follows

Concept 1 (indication): abdominal aortic aneurysm

Concept 2 (intervention): ultrasound screening

Concept 3 (study typ): RCTs

No further limits were specified.

Choosing information sources *(Back to top)*

The systematic search was to be conducted in MEDLINE, Embase (via the interface Ovid) and the Cochrane Library (via Wiley). In addition, non-indexed references were directly searched for via PubMed, as Ovid does not fully provide these references.

Other subject-specific or regional databases were not selected.

Name of database	Interface
MEDLINE	Ovid
Embase	Ovid
Cochrane Library	Wiley
Pubmed	NLM

Table 2: Databases and interfaces

Developing search strategies: Identifying search terms *(Back to top)*

Objectively-derived approach

In the objectively-derived approach, the relevant references identified in the preliminary search are searched for in bibliographic databases (MEDLINE and Embase) and imported into EndNote. A text analysis is then performed. In the present example, a total of 38 references could be identified in MEDLINE. Two-thirds of these 38 references were used for the development of the search strategy (development set) and one third for the subsequent validation (validation set).

Free-text terms

The Wordstat tool was used for the text analysis of free-text terms [7]. Not only the most common terms were identified, but also those overrepresented in the development set.

The results from Wordstat were exported into Excel and processed; the overrepresented terms were then assigned to the predefined concepts (indication and intervention).

Further, each of these terms was checked to determine whether a further restriction to phrases and word combinations was possible.

The following over-represented terms were identified for concept 1.

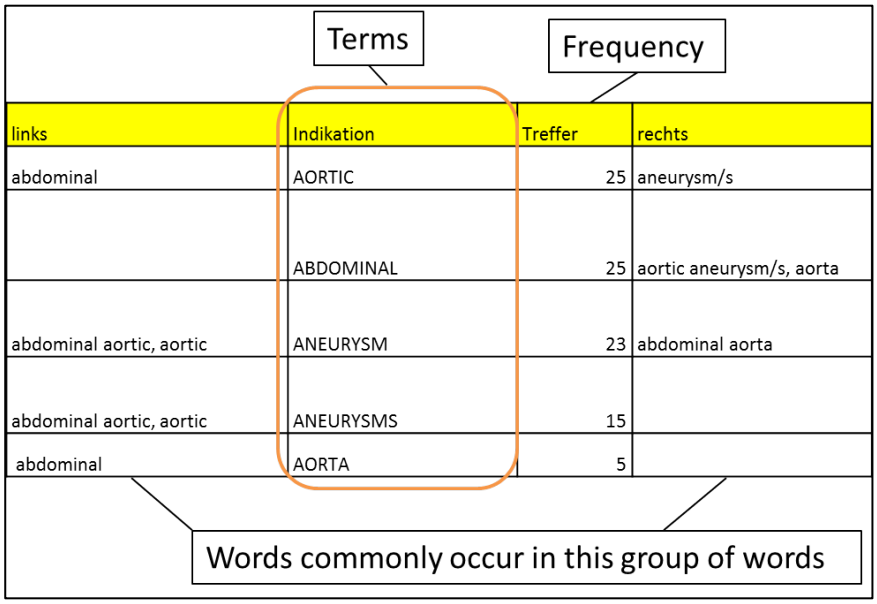


Figure 3: Common terms for concept 1

The following relevant phrases and word combinations were determined for these terms.

Phrases from Figure 3	**Consequences**	**Example of the search syntax in Ovid**
abdominal aortic aneurysm(s)	The words commonly occur in this group of word; the three terms are therefore linked with a proximity operator	abdominal adj1 aortic adj1 aneurysm (preliminary)
abdominal aortic / aorta	• "Aneurysm" is used both in the singular and plural form: this term is therefore truncated.	abdominal adj1 aort* adj1 aneurysm*

aneurysm(s)	• “Aorta” is also used in addition to “aortic”; the word stem “aort” is thus also truncated.	(preliminary)
aneurysm of the abdominal aorta	The terms may also be used in a different sequence or with a greater distance between words; the distance to “aneurysm*” is therefore increased	abdominal adj1 aort* **adj3** aneurysm* (final)

Table 3: Phrases and consequences for implementation using the example of MEDLINE via OvidSP

Subject headings

Subject headings are identified via EndNote. The subject headings of the references can be listed according to frequency by means of the “Subject Bibliography” function. This list was then exported into Excel and the individual subject headings were sorted according to the predefined concepts (see Figure 4).

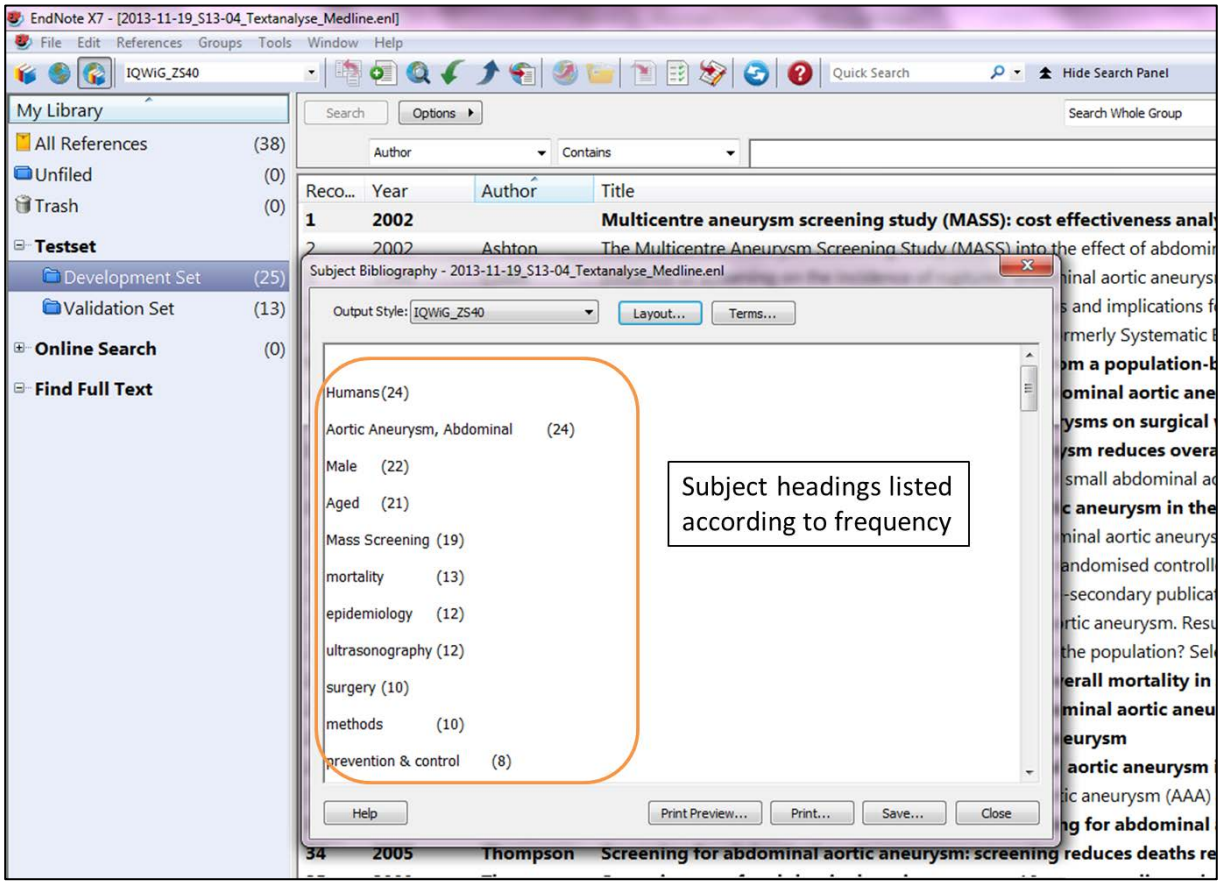


Figure 4: Analysis of subject headings in EndNote via the “Subject Bibliography” function

The following subject heading was identified in MEDLINE for concept 1:

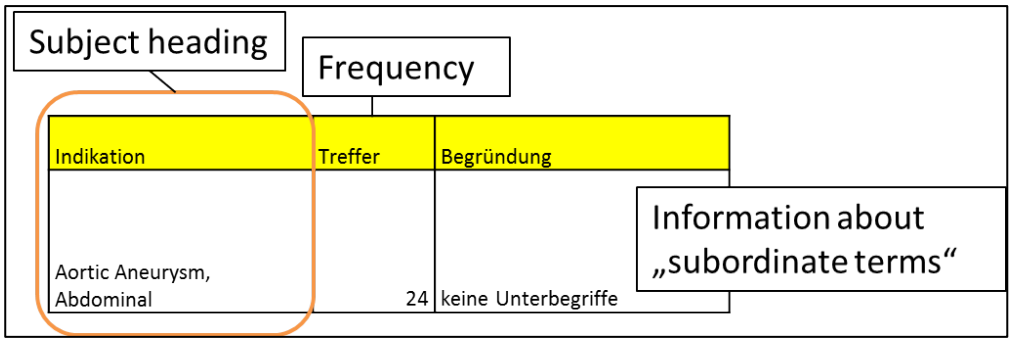


Figure 5: Common subject headings for concept 2 using the example of MEDLINE

A MeSH term was identified in Medline for concept 1 that was consistently assigned to all references from the test set. No further MesH terms were therefore required for concept 1. The “explode”-function was not used, as there are no subordinate terms for “Aortic Aneurysm, Abdominal”.

The procedure was used in Embase for a separate analysis of EMTREE terms (Embase subject headings). As the Cochrane Library uses MeSH terms, a separate analysis of subject headings was not required for this database, as the subject headings from the MEDLINE strategy were used.

Study filter

A validated study filter was used for the search for RCTs. In the present example, we decided to use the “Cochrane highly sensitive search strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version” (2008 revision) [3].

Developing search strategies: Adapting the search syntax (database-specific approach) *(Back to top)*

The search strategy was first developed for MEDLINE (Ovid) and then for other databases. The free-text terms identified could be used across all databases. However, they had to be adapted to the different databases/interfaces. The example in Table 4 shows the proximity operators differ depending on the interface. The subject headings were identified separately for each database (see Table 5).

Our example shows the implementation for concept 1:

Database (interface)	Free-text terms
MEDLINE und Embase (Ovid)	(abdominal adj1 aort* adj3 aneurysm*).ti,ab.
Cochrane (Wiley)	(abdominal NEAR/1 aort* NEAR/3 aneurysm*):ti,ab
PubMed (NLM)	abdominal*[tiab] AND aort*[tiab] AND aneurysm*[tiab]

Table 4: Database- and interface-specific tags for free-text terms

Database (interface)	Subject headings
MEDLINE (Ovid)	Aortic Aneurysm, Abdominal/
Embase (Ovid)	Abdominal Aorta Aneurysm/
Cochrane (Wiley)	MeSH descriptor: [Aortic Aneurysm, Abdominal] this term only
Pubmed (NLM)	No subject headings are used to search for new, non-indexed references (including Epub ahead of print references). Non-indexed references are identified in PubMed via the syntax "#x NOT medline[sb]".

Table 5: Database- and interface-specific tags for subject headings

The search strategy was organized according to blocks for search in individual databases. For each concept, first the subject headings and then the free-text terms were entered. For one concept, all search lines were combined with "OR"; the concepts were then joined together with "AND" (see Table 6).

Our example shows the implementation for MEDLINE:

#	Searches	Results
1	Aortic Aneurysm, Abdominal/	13646
2	(abdominal* adj1 aort* adj3 aneurysm*).ti,ab.	14046
3	or/1-2 **[Concept 1]**	18402
4	Mass Screening/	83663
5	ultrasonography.fs.	198380
6	screening*.ti,ab.	341139
7	(ultraso* adj3 scan*).ti,ab.	14122
8	or/4-7 **[Concept 2]**	567366
…		
15	Line 9-15 **[Study filter: RCT]**	391739
16	and/3,8,15 **[Concept 1 AND Concept 2 AND Study filter]**	520

Table 6: Structure of search strategy in MEDLINE (Ovid)

Before running any searches, a second person was asked to peer review the search strategies.

Peer reviewing search strategies *(Back to top)*

Peer reviewing of the draft search strategy was performed in 2 steps:

Application of the PRESS checklist: The search strategy was checked for errors by a second person using the PRESS checklist (see Table 7). For the process of text analysis, questions 3 and 4 were checked by means of the internal documentation on the text analysis.

Element	Question
1. Translation	Is the search question translated well into search concepts?
2. Operators	Are there any mistakes in the use of Boolean or proximity operators?
3. Subject headings	Are any important subject headings missing or have any irrelevant ones been included?
4. Natural language	Are any natural language terms or spelling variants missing, or have any irrelevant ones been included? Is truncation used optimally?
5. Spelling & syntax	Does the search strategy have any spelling mistakes, system syntax errors, or wrong line numbers?
6. Limits	Do any of the limits used seem unwarranted or are any potentially helpful limits missing?
7. Adapted for db	Has the search strategy been adapted for each database to be searched?

Table 7: PRESS Checklist [10]

Check for completeness: It was also assessed whether the draft of the search strategy identifies all references of the validation set (VS). For this purpose a search string was created using the accession numbers of the respective references. The search strategy was checked against the validation set in order to see if it was able to capture all the references included in this set (see Figure 6).

In the present example, one reference was not found with the selected study filter. As no other validated study filter would have found this reference either (Wong – High sensitivity strategy, Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)), the study filter was not changed.

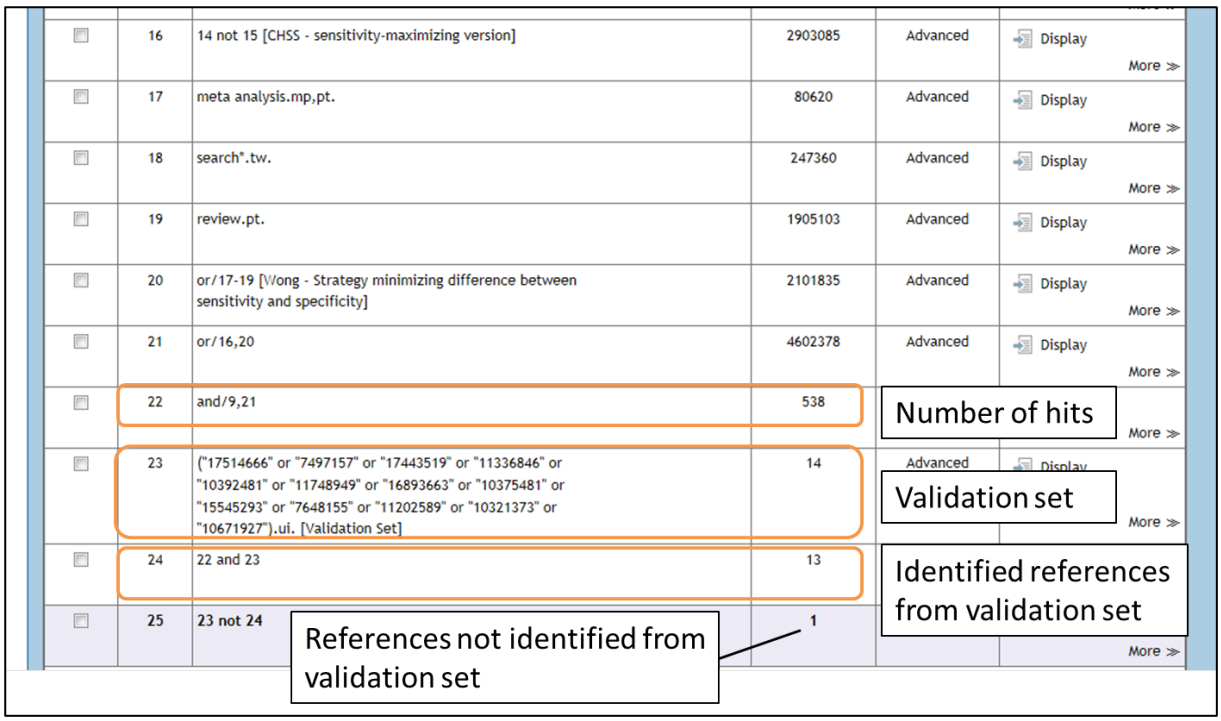


Figure 6: Validation set

Conducting searches, downloading records and managing references *(Back to top)*

After implementation of the comments on quality assurance, the preparations were completed. The final search strategies that had been saved could then be applied. PubMed was searched for non-indexed references followed by MEDLINE, Embase and the Cochrane Library.

The text files with the reference were annotated (date of search, database and interface searched, person who searched) and the references then imported in EndNote. The duplicates were then removed in a multi-step procedure.

For this purpose, first the automatic “find duplicates” function in EndNote was used. The references were sorted according to author and title, and the list was manually checked for duplicates. The references were then processed for screening.

Screening citations (technical process) *(Back to top)*

In a 2-step procedure the references were screened and assessed by two reviewers independently of one another. IQWiG’s own screening tool was used for this purpose (webTSDB; [184]). In the first screening step, 623 of the 702 references could be excluded on the abstract and title level, and 79 references were assessed for relevance in full texts. A total of 20 relevant publications based on 4 studies were identified.

Documenting and reporting the search process *(Back to top)*

Internal documentation

The whole conduct of the search was documented in real time. The search strategies and the number of hits were saved in Word (see Figure 7) and the references were saved as text files (see Figure 8). In addition, a table was created including the search dates, search interfaces, the database segments, as well as the results of the duplicate check (see Table 8).

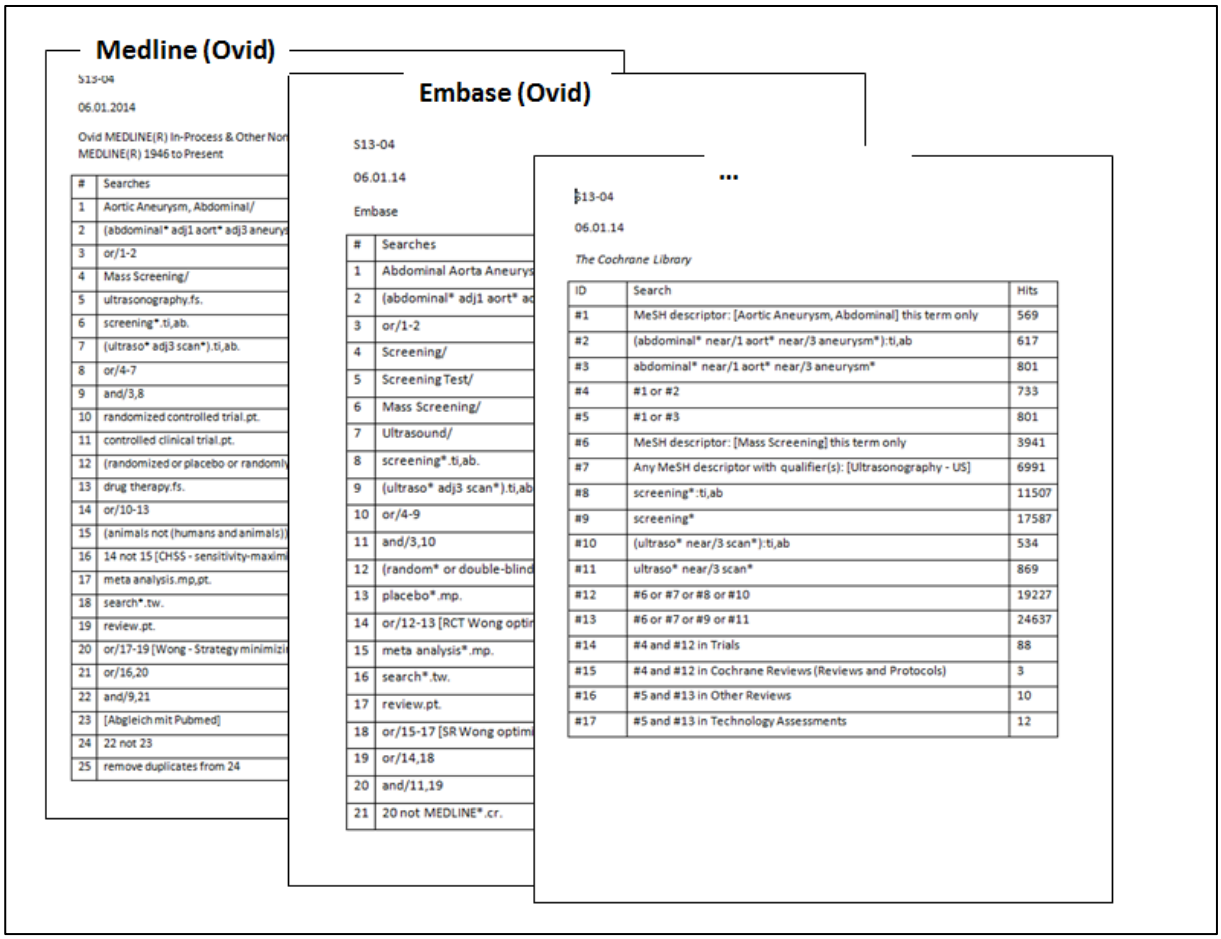


Figure 7: Documentation of the search strategies in the individual bibliographic databases

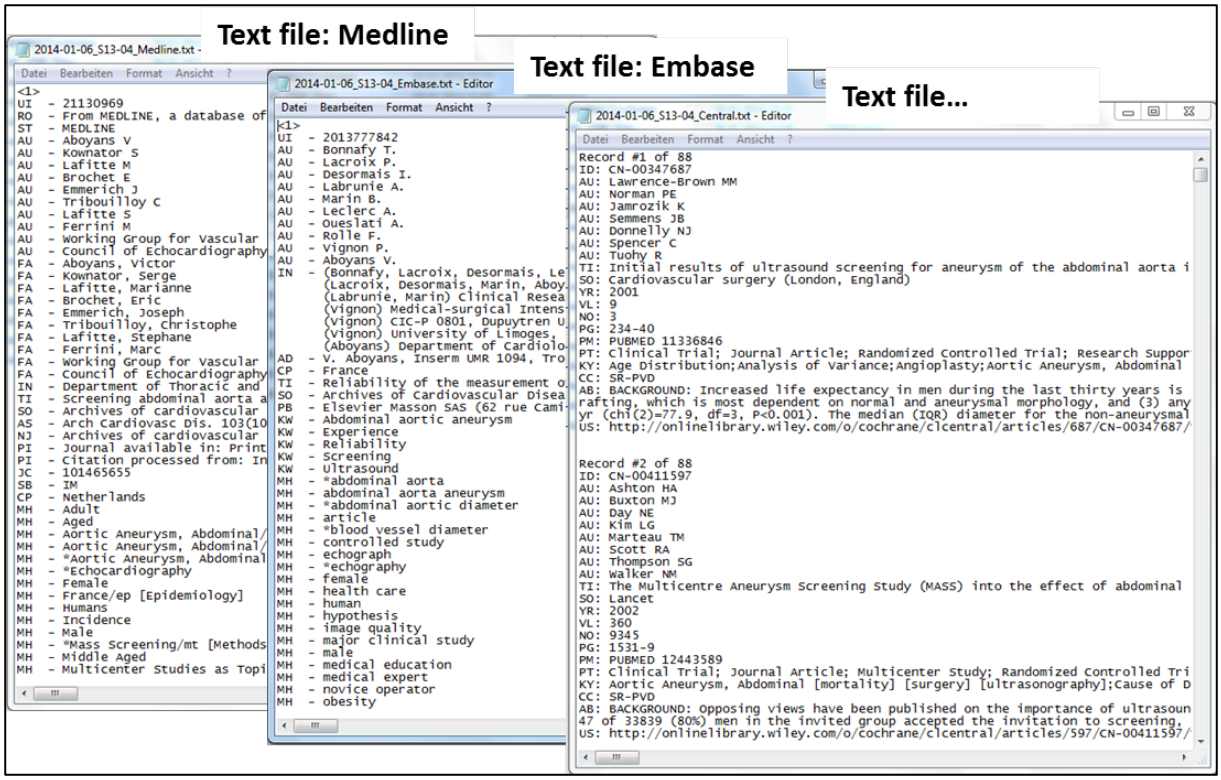


Figure 8: Documentation of the references in the individual bibliographic databases (as text files)

Database (Provider)	Database segment	Date	Hits
MEDLINE (Ovid)	Ovid MEDLINE (R)1946 to November Week 3 2013, Ovid MEDLINE (R) Daily Update November 20, 2013, Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations January 03, 2014	06.01.2014	491
Embase (Ovid)	Embase 1974 to 2014 January 03	06.01.2014	326
…	…	…	…
Total hits			**951**
Duplicates			249
Hits without duplicates			**702**

Table 8: Documentation of the search process in Excel

Reporting

All databases searched were listed in the methods section of the report, as well as the date of the last search. The search strategies for all databases, the database segments, and the interfaces used were presented in the appendix of the report (see Figure 9).

MEDLINE
Suchoberfläche: Ovid

Database and interface

- Ovid MEDLINE(R)1946 to January Week 1 2014
- Ovid MEDLINE(R) Daily Update January 14, 2014
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 14, 2014

Database segment

Es wurden folgende Filter übernommen:
Systematische Übersicht: Wong – Strategy minimizing difference between sensitivity and specificity;
RCT: Lefebvre – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)

Search filter

#	Searches
1	Aortic Aneurysm, Abdominal/
2	(abdominal* adj1 aort* adj3 aneurysm*).ti,ab.
3	or/1-2
4	Mass Screening/
5	ultrasonography.fs.
6	screening*.ti,ab.
7	(ultraso* adj3 scan*).ti,ab.
8	or/4-7
9	and/3,8
10	randomized controlled trial.pt.
11	controlled clinical trial.pt.
12	(randomized or placebo or randomly or trial or groups).ab.
13	drug therapy.fs.
14	or/10-13
15	(animals not (humans and animals)).sh.
16	14 not 15
17	meta analysis.mp,pt.
18	search*.tw.
19	review.pt.
20	or/17-19
21	or/16,20
22	and/9,21

Search strategy

Figure 9: Reporting of the search strategy of the report using the example of MEDLINE

The results of the search, the check for duplicates, and the selection of studies following PRISMA [112] were presented in the results section of the report (see Figure 10).

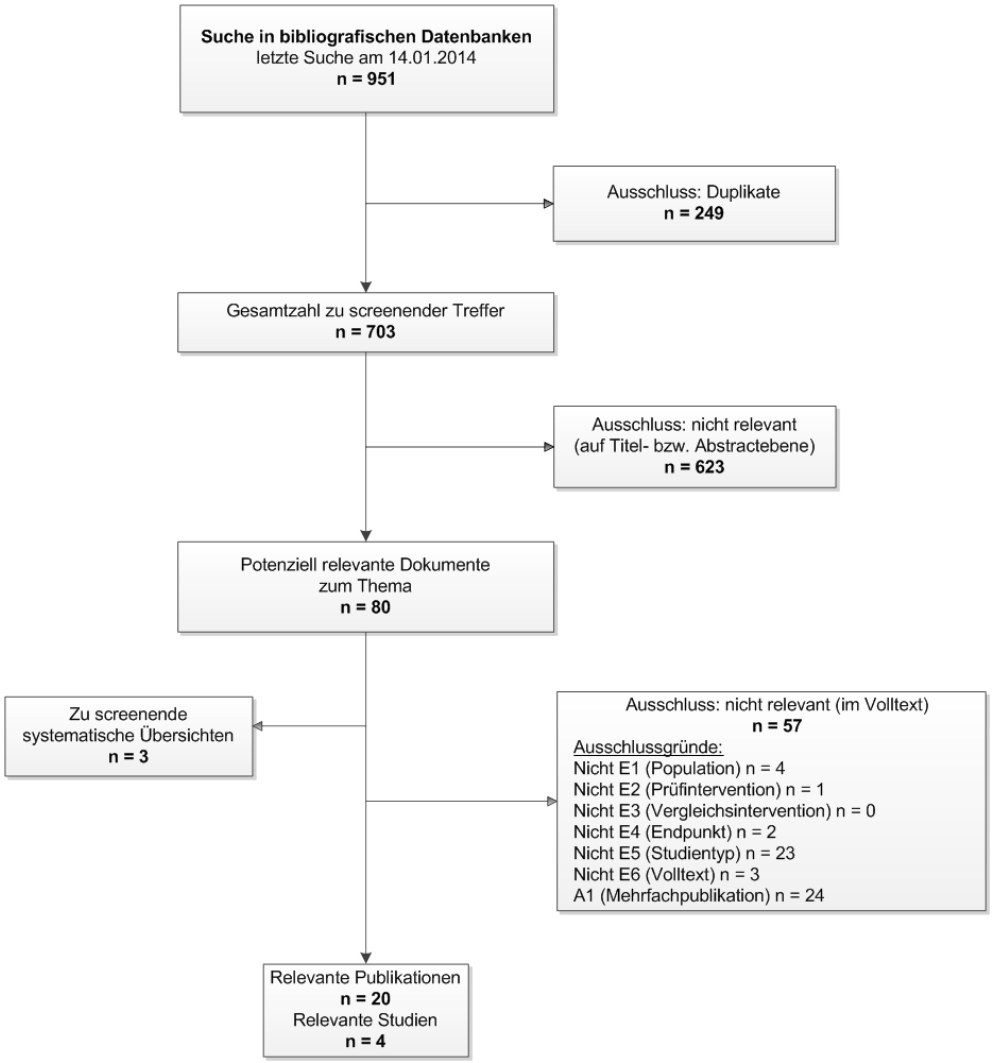


Figure 10: Flow chart in the results section of the report

In addition, the report contains the citations of all included studies and all excluded studies, together with the reasons for exclusion, (see Figure 11 and Figure 12).

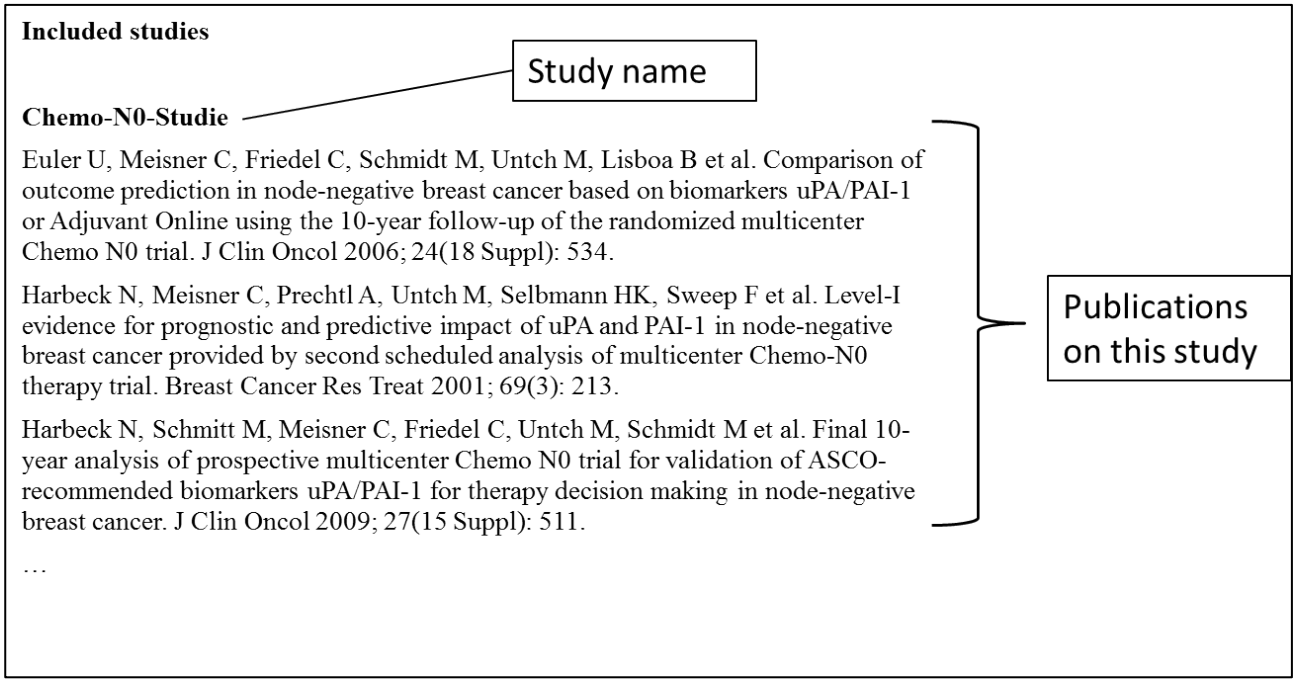


Figure 11: Reporting of included studies in the HTA report

Figure 12: Reporting of excluded studies in the HTA report

Updating searches *(Back to top)*

If the report is published after January 2015 (12 months after the initial search), an update search will be performed.

The procedure is as follows: It is first checked in which databases the 20 relevant publications were found and whether they could be identified with the search strategies. This means that it is checked whether, for instance, references contained in MEDLINE can be identified with the MEDLINE strategy. If this is not the case then the strategy is adjusted. Any changes in subject headings of the individual databases should also be considered.

To remove the duplicates of the initial search from the update search, a search string is created in the databases MEDLINE, Embase and PubMed using all accession numbers of the respective references from the initial search. This search string and the search strategy are linked with “NOT” to obtain the results of the update search (Figure 13). In the Cochrane Library, this approach is only possible for references from MEDLINE and Embase. The remaining duplicates are then removed in EndNote.

The further search process follows the standards in “Conducting searches, downloading records and managing references”.

The combined results of the initial and update search will be presented in the report.

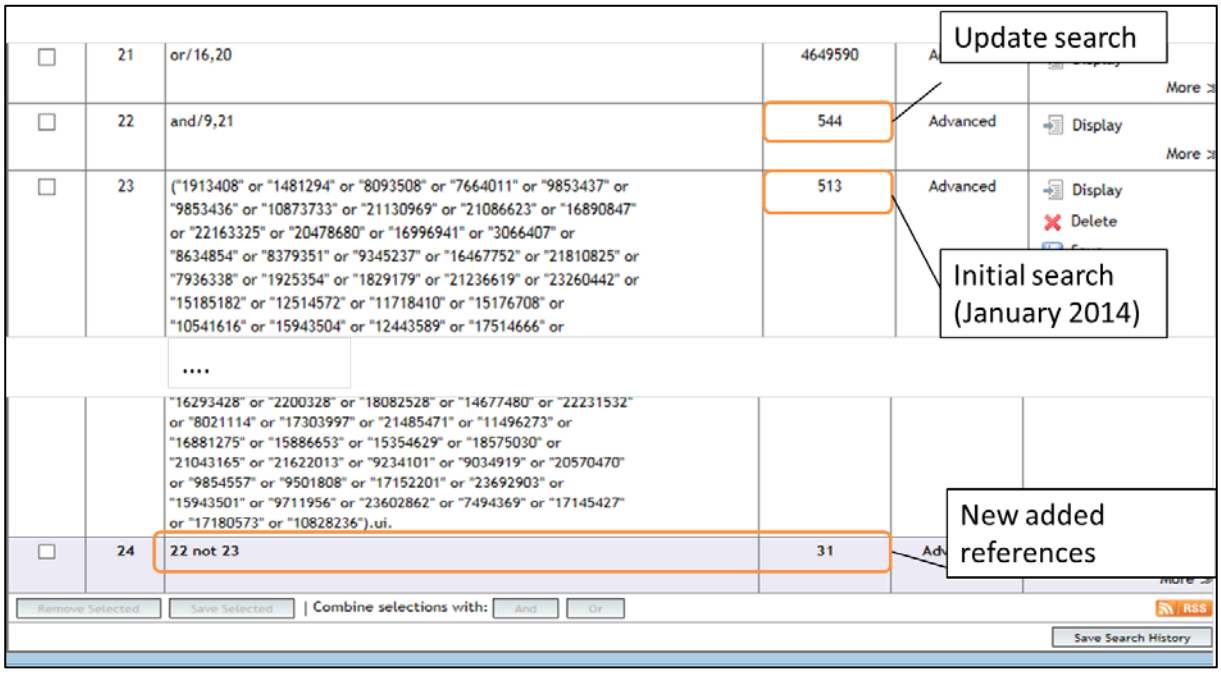


Figure 13: Result of the update search

Implementation of the search in study registries

A search in study registries was conducted to search for published or ongoing studies.

Structuring the search strategy *(Back to top)*

Since study registries have limited search functions, only the following 2 facets were searched.

Concept 1 (indication): abdominal aortic aneurysm

Concept 2 (intervention): screening, scan

The term “ultrasound” was not included in the search - in contrast to the search strategy in bibliographic databases. No limitation on the type of study was applied.

Choosing information sources *(Back to top)*

The systematic search in study registries was to be conducted in ClinicalTrials.gov, EU Clinical Trials Register and the ICTRP Search Portal. Other topic- or disease-specific study registries were not selected.

Study registries	
ClinicalTrials.gov	ClinicalTrials.gov
ICTRP Search Portal	International Clinical Trials Registry Platform Search Portal
EU Clinical Trials Register	EU Clinical Trials Register

Table 9: Study registries

Developing search strategies: Identifying search terms *(Back to top)*

The results of the text analysis in bibliographical databases were used for the development of the search strategies. For ClinicalTrials.gov and ICTRP Search Portal, the selection of search terms was matched with the registry-specific synonym search.

For concept 1 (“abdominal aortic aneurysm”) ClinicalTrials.gov synonyms corresponded with the identified terms in the text analysis (see Figure 14). No further adjustment was therefore necessary.

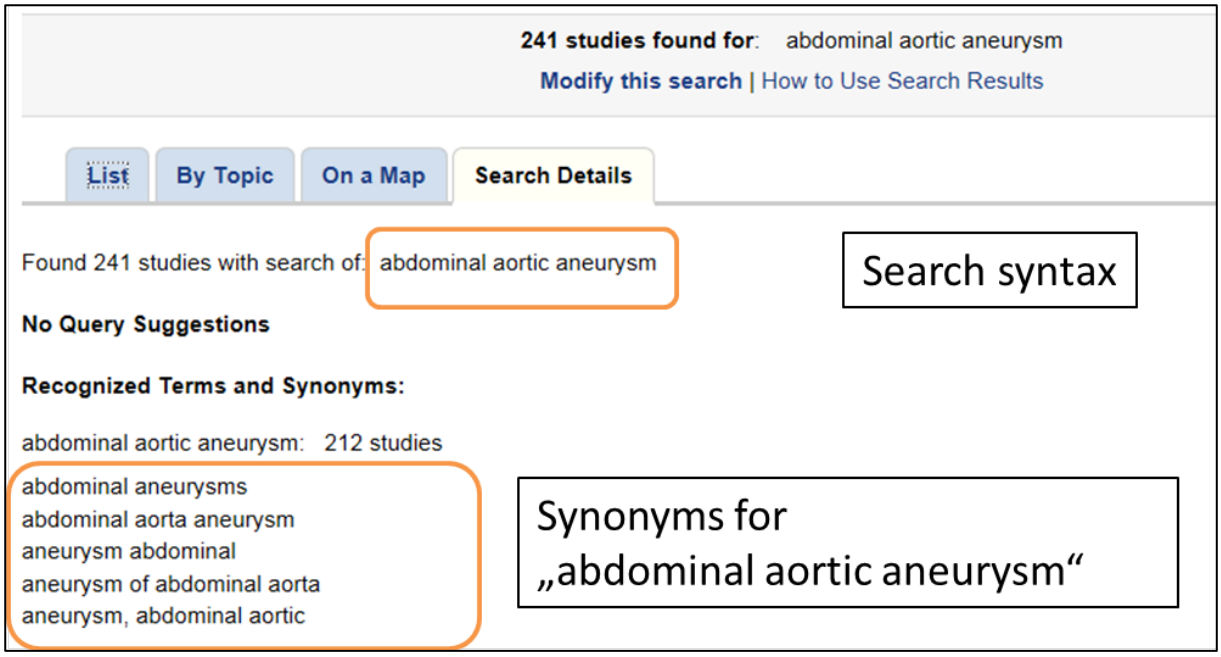


Figure 14: Synonyms for “abdominal aortic aneurysm” using the example of ClinicalTrials.gov

The synonym search of “screening” did not cover all terms from the text analysis. The term “scan” was therefore added to the search (see Figure 15).

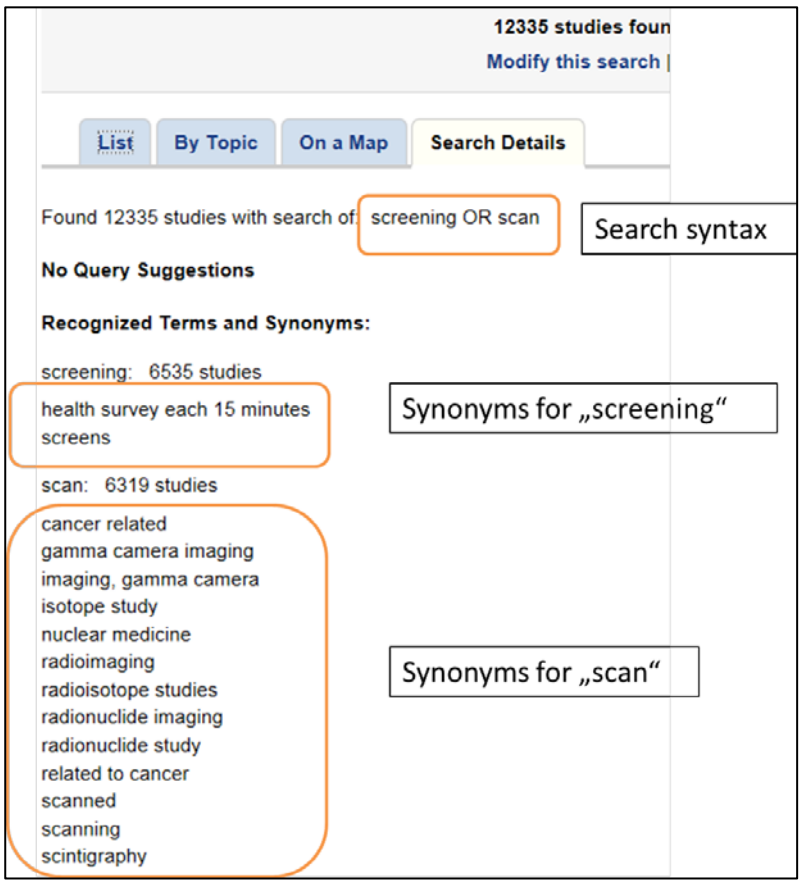


Figure 15: Synonyms for “screening OR scan” using the example of ClinicalTrials.gov

In ICTRP Search portal and in the EU Clinical Trials Register, the synonyms were examined indirectly. For this purpose, the search strategy for ClinicalTrials.gov was extended and adjusted if the number of hits changed. In our example, however, no changes in the strategy were necessary.

Developing search strategies: Adapting the search syntax *(Back to top)*

The terms identified were entered in the different registries using registry-specific search functions. The search can be structured by using brackets in ClinicalTrials.gov and the EU Clinical Trials Register, but not in ICTRP Search Portal. In addition, Boolean operators should always be written in uppercase. Truncation was not used, as this feature turns off the synonym search or is not possible (e.g. in ClinicalTrials.gov).

Study registry	Search syntax	Comment
ClinicalTrials.gov	abdominal aortic aneurysm AND (screening OR scan)	• Brackets can be used in this registry
ICTRP Search Portal	abdominal aortic aneurysm AND screening OR abdominal aortic aneurysm AND scan[2]	• Use of brackets not possible
EU Clinical Trials Register	abdominal aortic aneurysm AND (screening OR scan)	• Brackets can be used in this registry

Table 10: Adapting the search syntax in each study registry

Peer reviewing search strategies[3] *(Back to top)*

Peer reviewing of the draft search strategy was performed by a second person. It was checked whether the search strategies included all terms from the text analysis or were covered by the synonym search in the study registries.

Conducting searches, downloading records and managing references *(Back to top)*

After implementation of the comments on quality assurance, the preparations were completed. The final search strategies could then be applied. Direct export of the results as xml or txt file is offered for all 3 study registries (see Figure 16).

[2] In the report, 2 separate search steps were undertaken to enter the syntax and the duplicates removed in EndNote. The search above yields the same results but is more convenient.

[3] The process of quality assurance of search strategies in study registries has recently been revised. Therefore the example does not show the current status.

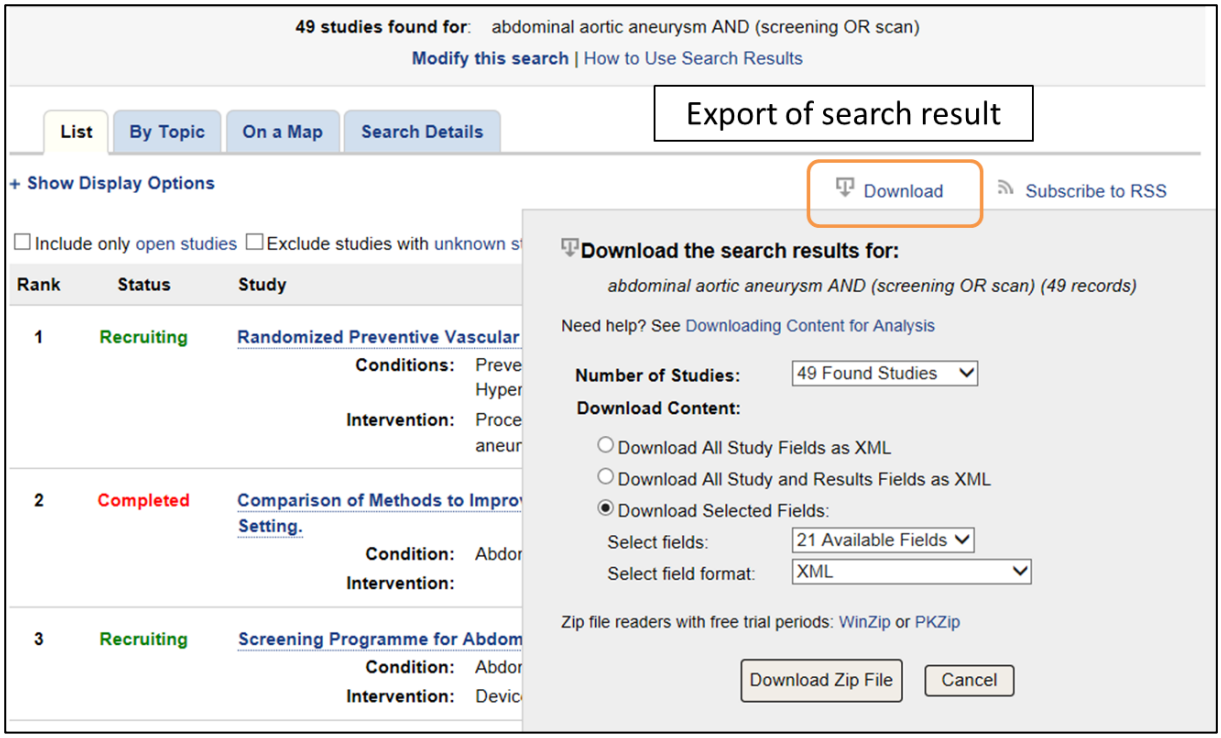


Figure 16: Export function using the example of ClinicalTrials.gov

These files were then imported in EndNote using an import filter. The duplicates were then removed based on the registry numbers (see Figure 17).

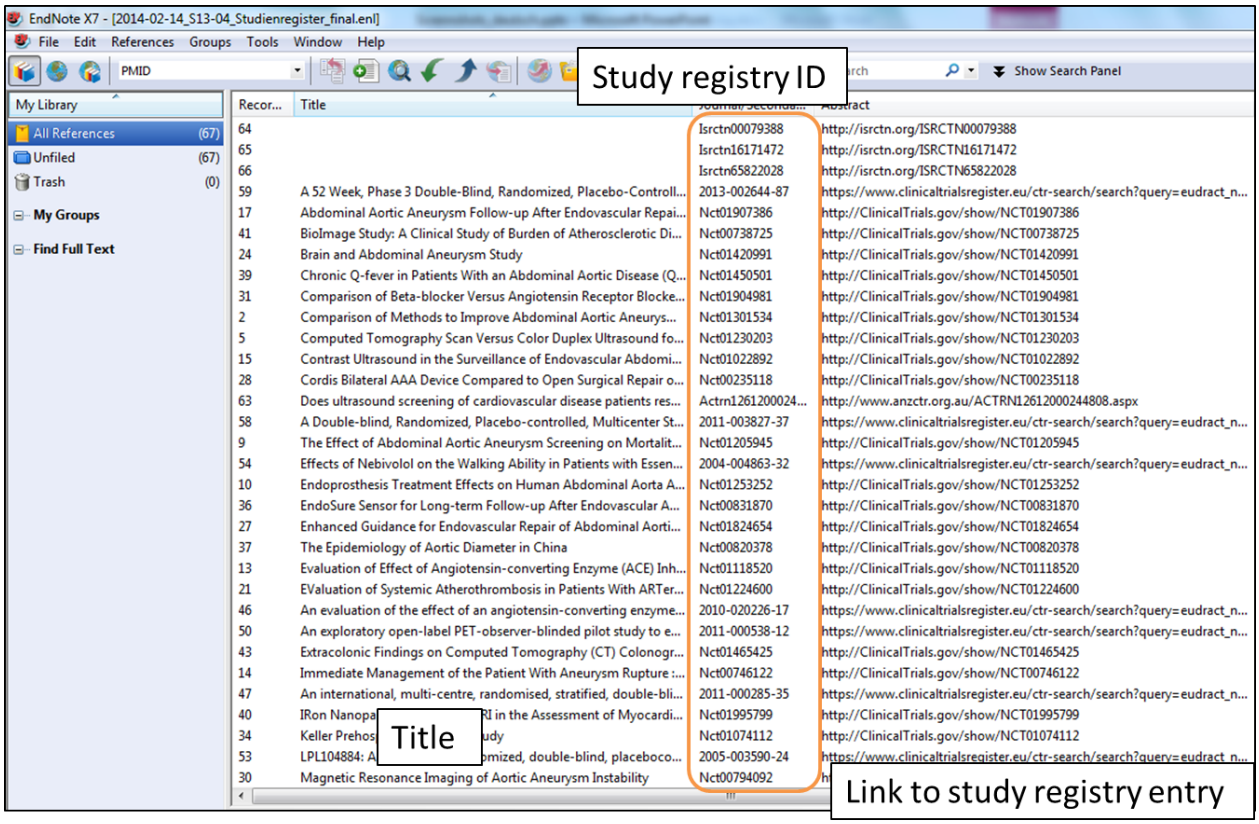


Figure 17: Result of the search in study registries after import into EndNote

Screening citations (technical process) *(Back to top)*

In a 1-step procedure the references were screened and assessed by two reviewers independently of one another. IQWiG´s own screening tool was used for this purpose (webTSDB).

67 studies were assessed for relevance; a total of 3 completed studies and 2 ongoing studies were identified.

Documenting and reporting the search process *(Back to top)*

Internal documentation

Documentation was performed throughout the process. The xml and txt files were saved. In addition, the search results were documented by screenshot and saved for all searches and pages as pdf (see Figure 18).

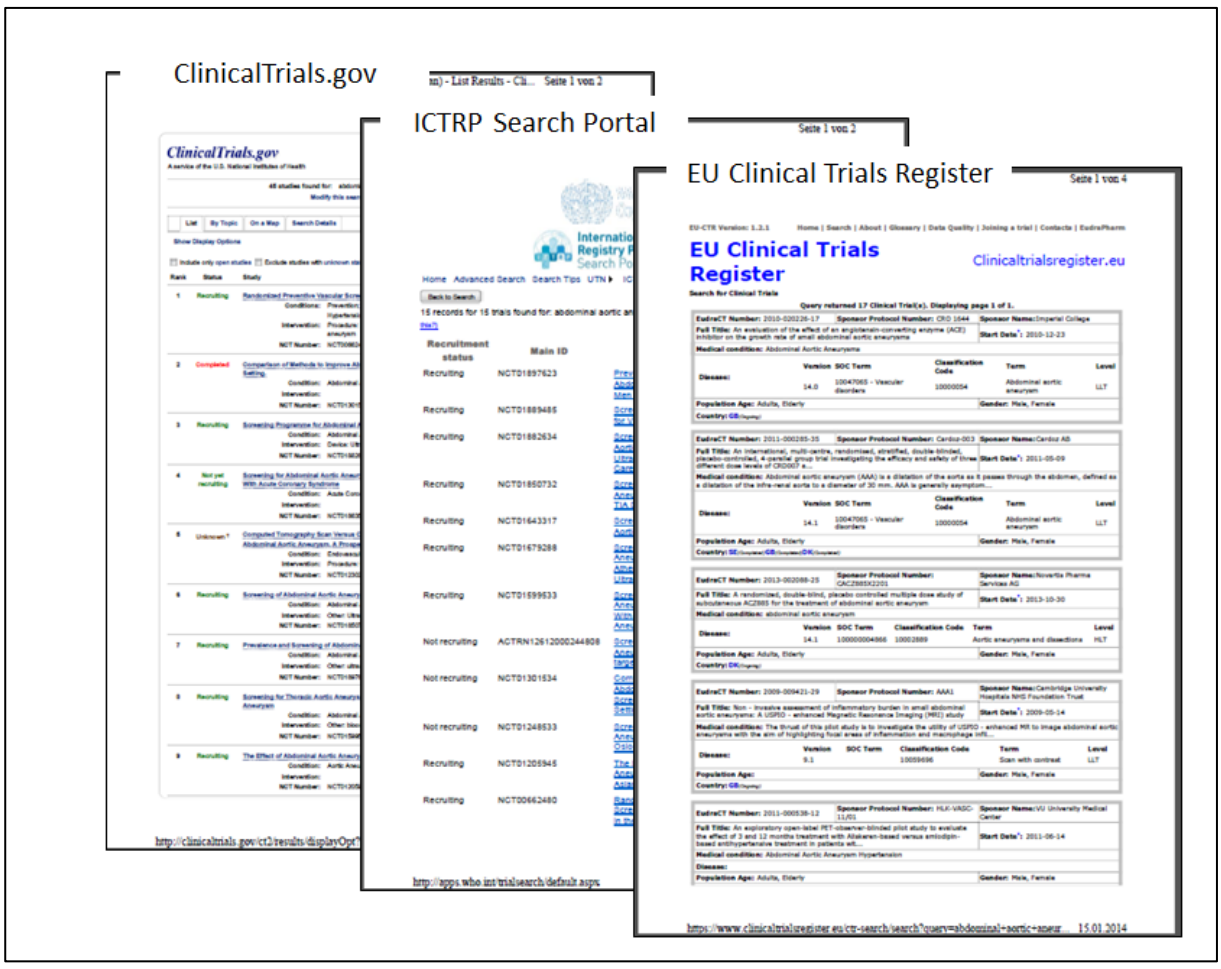
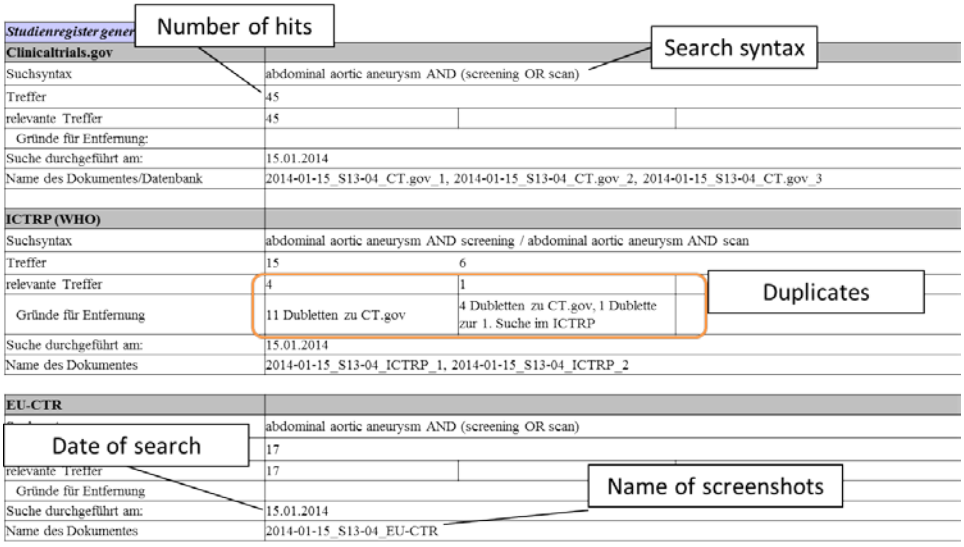


Figure 18: Screenshots of search results in study registries

The search strategies, the number of hits, the date of the search, the duplicate check, and the naming of screenshots were saved for all study registries in EXCEL (see Figure 19).



Studienregister gener			
Clinicaltrials.gov			
Suchsyntax	abdominal aortic aneurysm AND (screening OR scan)		
Treffer	45		
relevante Treffer	45		
Gründe für Entfernung:			
Suche durchgeführt am:	15.01.2014		
Name des Dokumentes/Datenbank	2014-01-15_S13-04_CT.gov_1, 2014-01-15_S13-04_CT.gov_2, 2014-01-15_S13-04_CT.gov_3		
ICTRP (WHO)			
Suchsyntax	abdominal aortic aneurysm AND screening / abdominal aortic aneurysm AND scan		
Treffer	15	6	
relevante Treffer	4	1	
Gründe für Entfernung	11 Dubletten zu CT.gov	4 Dubletten zu CT.gov, 1 Dublette zur 1. Suche im ICTRP	
Suche durchgeführt am:	15.01.2014		
Name des Dokumentes	2014-01-15_S13-04_ICTRP_1, 2014-01-15_S13-04_ICTRP_2		
EU-CTR			
	abdominal aortic aneurysm AND (screening OR scan)		
	17		
relevante Treffer	17		
Gründe für Entfernung			
Suche durchgeführt am:	15.01.2014		
Name des Dokumentes	2014-01-15_S13-04_EU-CTR		

Figure 19: Documentation of the search in study registries

Reporting

All study registries searched were listed in the methods section of the report.

All completed and ongoing studies, together with the study registry ID, study name, citation, and information on whether the results of the study are available in the study registry, were presented in the results section of the report (see Figure 20).

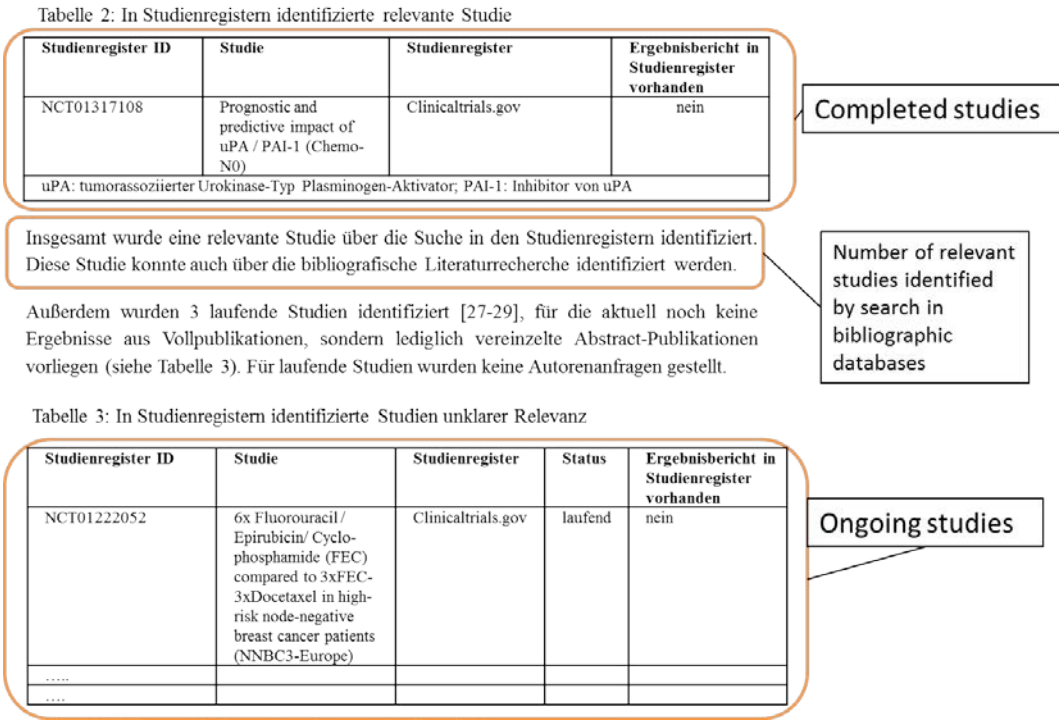


Tabelle 2: In Studienregistern identifizierte relevante Studie

Studienregister ID	Studie	Studienregister	Ergebnisbericht in Studienregister vorhanden
NCT01317108	Prognostic and predictive impact of uPA / PAI-1 (Chemo-N0)	Clinicaltrials.gov	nein

uPA: tumorassoziierter Urokinase-Typ Plasminogen-Aktivator; PAI-1: Inhibitor von uPA

Außerdem wurden 3 laufende Studien identifiziert [27-29], für die aktuell noch keine Ergebnisse aus Vollpublikationen, sondern lediglich vereinzelte Abstract-Publikationen vorliegen (siehe Tabelle 3). Für laufende Studien wurden keine Autorenanfragen gestellt.

Tabelle 3: In Studienregistern identifizierte Studien unklarer Relevanz

Studienregister ID	Studie	Studienregister	Status	Ergebnisbericht in Studienregister vorhanden
NCT01222052	6x Fluorouracil / Epirubicin/ Cyclo-phosphamide (FEC) compared to 3xFEC-3xDocetaxel in high-risk node-negative breast cancer patients (NNBC3-Europe)	Clinicaltrials.gov	laufend	nein
.....				
....				

Figure 20: Documentation of the studies from the study registry search in the report

In addition, the search strategies for all study registries, the provider, URL, and input interface (e.g. Basic Search in ClinicalTrials.gov) were presented in the appendix of the report (see Figure 21).

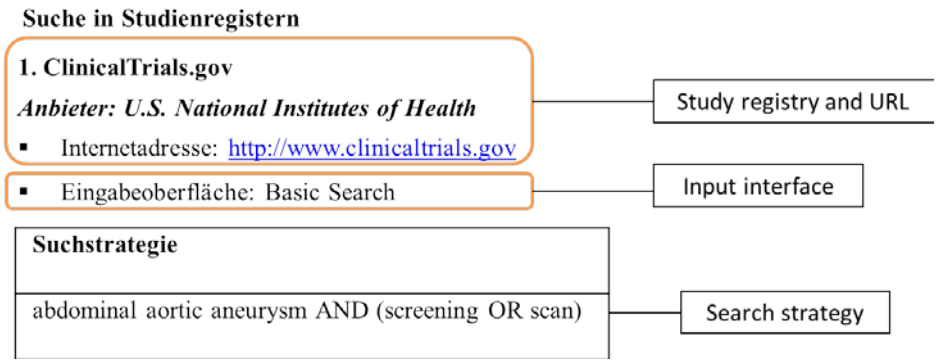


Figure 21: Reporting the search strategy of the report using the example of ClinicalTrials.gov

Updating searches *(Back to top)*

If the report is published after January 2015 (12 months after the initial search), an update search will be performed concurrently to the search in bibliographical databases.

The procedure is as follows: The results of the initial search and update search are compared in EndNote or Excel. The duplicate check is performed using the study registration numbers (see Figure 22). Alternatively, the results can be compared using the documented screenshots.

The study status is checked again for studies identified as “ongoing” in the initial search. If the status has changed to “complete”, the studies are considered for assessment. The further procedure regarding screening, documenting and reporting corresponds to the procedure in the initial search.

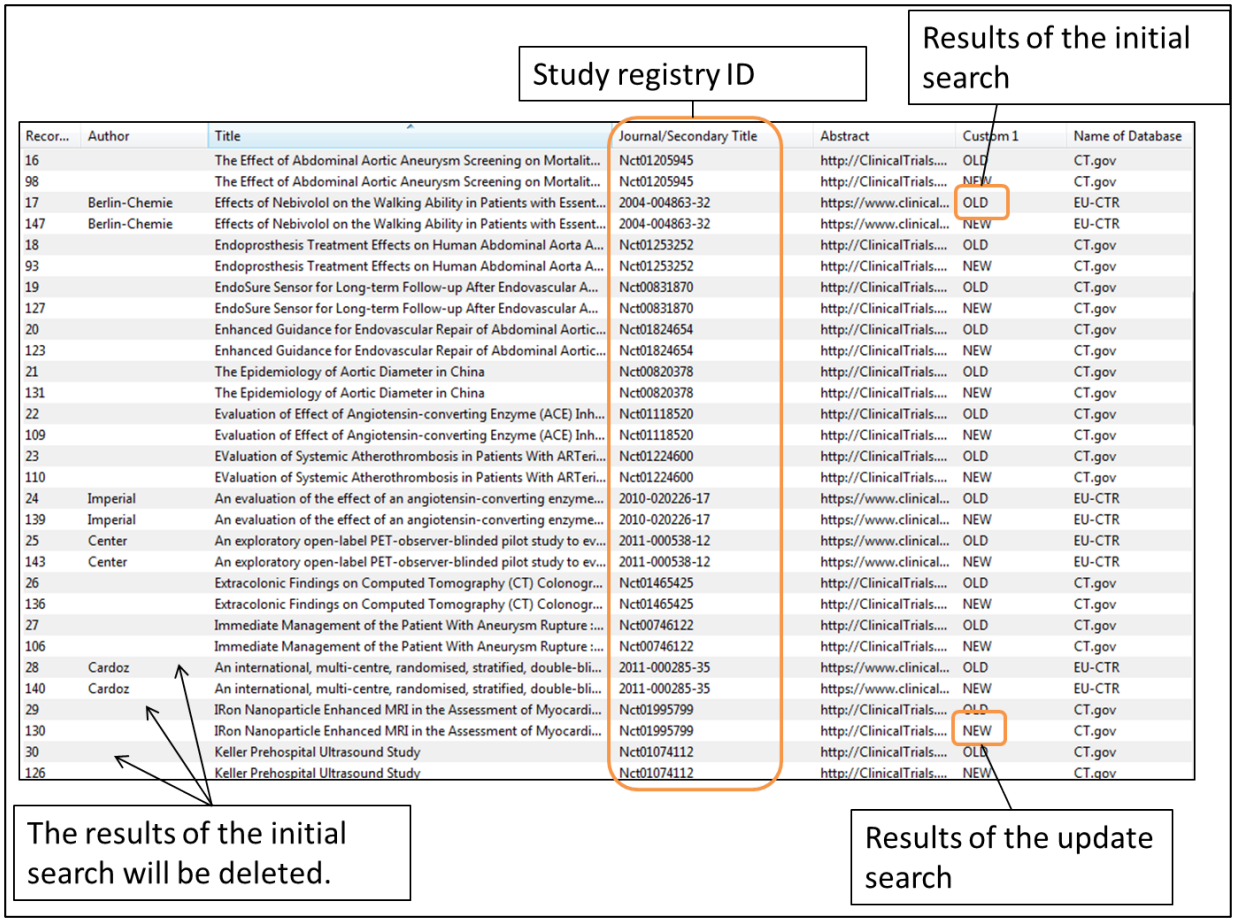


Figure 22: Duplicate check of the search in study registries in EndNote