



**eunethta**

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

**METHODOLOGICAL GUIDELINES**

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

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The primary objective of EUnetHTA methodological 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.

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## Disclaimer

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## Acronyms - Abbreviations

AHRQ – Agency for Healthcare Research and Quality

AMSTAR – A Measurement Tool to Assess Systematic Reviews

CENTRAL – Cochrane Central Register of Controlled Trials

CRD – Centre for Reviews and Dissemination

CSR – Clinical Study Report

EMA – European Medicines Agency

EU-CTR – EU Clinical Trials Register

FDA – Food and Drug Administration

HTA – Health Technology Assessment

ICMJE – International Committee of Medical Journal Editors

ICTRP – International Clinical Trials Registry Platform

IFPMA – International Federation of Pharmaceutical Manufacturers & Associations

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

PMC – PubMed Central

PMID – PubMed identifier

PRESS Checklist – Peer Review of Electronic Search Strategies Checklist

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

REA – Relative Effectiveness Assessment

RCT – Randomized Controlled Trial

RMS – Reference Management Software

SOP – Standard Operating Procedure

SuRe Info – Summarized Research in Information Retrieval for HTA

SR – Systematic Review

## Definitions of central terms and concepts

### **Accession number**

An accession number is a specific (mostly multi-digit) unique 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 different accession numbers.

### **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.

### **Bias**

A bias is a “systematic error, or deviation from the truth, in results. Biases can lead to under-estimation or over-estimation of the true intervention effect and can vary in magnitude: some are small (and trivial compared with the observed effect) and some are substantial (so that an apparent finding may be due entirely to bias) [1]”. Different types of bias exist in clinical research, for example, selection, performance, detection, attrition, and non-reporting bias (a detailed overview is provided in the Cochrane Handbook [1]).

### **Further search techniques**

Different search techniques are available. Their common feature is that one or more relevant articles (so-called key articles) are used as a starting point to identify further relevant articles.

Snowballing: Screening the reference lists of key articles (backward citations) or checking which other articles have cited the key articles (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.

“Similar articles” function of the database: 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.

### **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.

## **PubMed Segments**

PubMed consists of various segments (subsets) and users can limit a search to a particular segment [2]. Only the MEDLINE segment has been indexed with MeSH terms and has undergone a quality control procedure.

Verbatim extract from [2]:

Table 1: Status subsets [2]

<b>Status Tag</b>	<b>Citation Status</b>
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	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.
PubMed	Citations that 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.

## **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). High-quality filters should be validated using an independent set of relevant references. They are often developed with different characteristics, for example, maximized sensitivity (“broad”), maximized specificity (“narrow”), and optimized search filters (“minimizing difference”).

## **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 or adjacency operator: Two search terms have a specified number of words between each other.

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, using a function known as wildcard; some interfaces only allow to search for a certain number of variations of the truncated word (e.g. truncation in PubMed is restricted to 600 variations).

“Explode” function: Automatically combines the subject heading via OR with all related narrower subject headings.

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

Search fields: Fields of records 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).

### ***Search interface***

Bibliographic databases can often be accessed via different providers / 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. Access to Embase is exclusively fee-based (e.g. via Embase.com, OvidSP or ProQuest). These 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.

### ***Search terms***

Search terms: All terms used in a search, i.e. subject headings, publication types and free-text terms (see below). It should be noted that publication types and subject headings may differ between databases.

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.

Publication types: Describes the type of material the article represents. Examples: "Review", "Clinical Trial" or "Letter". Like subject headings, publication types differ between databases.

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.

### ***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 the true sensitivity, a gold standard must be predefined, for example, by hand searching or relative recall of included studies from multiple SRs.

# Summary and table with main recommendations

## Problem statement

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

The aim of this methodological guideline is to provide an up-to-date and transparent overview of the whole information retrieval process.

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.

## Methods

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

The guideline was primarily based on empirical evidence. 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. A second author performed quality assurance by checking the extracted text and its suitability for the guideline.

Annexe 4 contains a summary of EUnetHTA standards in information retrieval.

Table 2: Recommendations

<b>Recommendations</b>	<b>The recommendation is based on arguments presented in the following parts of the guideline text</b>
1 <sup>st</sup> recommendation: Information specialists should form an integral part of the assessment team of an HTA / SR from the beginning of the project.	2.2.2
2 <sup>nd</sup> recommendation: An SR should regularly include a search for unpublished literature to identify both unpublished studies and unpublished data from published studies.	2.2.3, 5
3 <sup>rd</sup> recommendation: Besides MEDLINE, other bibliographic databases such as Embase and CENTRAL should be searched to identify all published relevant studies on the topic of interest.	3.1.4
4 <sup>th</sup> recommendation: Individual search strategies must be developed for selected databases / interfaces using both free-text terms and, if available, subject headings. If the search in the main databases (MEDLINE, Embase) is restricted to RCTs, validated highly sensitive search filters should be used.	3.1.5
5 <sup>th</sup> recommendation: Search strategies should undergo peer reviewing to ensure high-quality search strategies.	3.1.6, 3.2.5
6 <sup>th</sup> recommendation: The search process should be documented in real time and reported in a transparent manner.	3.1.9, 3.2.8
7 <sup>th</sup> recommendation: If information retrieval is based on existing SRs, only the studies included in these SRs are used in the assessment report. An update search for primary studies should be conducted for the period not covered by the SRs.	4

# 1. Introduction

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

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

Information retrieval for SRs needs to be performed in a thorough, 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.

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.

### Aspects of the guideline

Bibliographic databases are the main sources for information retrieval in SRs 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.)

Further information sources, such as unpublished company documents, regulatory documents, queries to authors and further search techniques will also be presented. In addition, a layered searching approach for performing an assessment on the basis of existing SRs will be described.

Since preliminary searches for SRs 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, more objective approaches will also be presented [7,8]. The latter are increasingly important approaches in information retrieval for SRs [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.

## Excluded aspects

The description of searches for studies on specific aspects or domains such as diagnostic accuracy, economic evaluations (for HTAs), ethical analysis, or legal aspects 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 [16].

The assessment of a submission dossier is not covered by this guideline. Detailed information on the procedure can be found in the internal EUnetHTA standard operating procedure (SOP) “PT-03-InfRetr”.

## 1.2. Related EUnetHTA documents

The EUnetHTA Companion Guide [17] (restricted to EUnetHTA partners, requires a password) contains the following SOPs on information retrieval for the production of rapid relative effectiveness assessments on other technologies (Rapid REA).

- Review of information retrieval in the project plan by a dedicated reviewer (information specialist) (OT-02-CheckInfRetrPP)
- Information retrieval (OT-03-InfRetr)
- Review of information retrieval in the draft assessment by a dedicated reviewer (information specialist) (OT-03-InfRetr)
- Queries to authors (OT-03-QueAut)
- Scoping, developing 1<sup>st</sup> Draft of the Project Plan and Submission Dossier (OT-02-ScoDevDPPSubDos)

## 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 [1]
- Institute of Medicine's Standards for Systematic Reviews [18]
- AHRQ Methods for Effective Health Care [19] (for unpublished literature)
- PRESS: Peer Review of Electronic Search Strategies [10,20] (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.

Furthermore, the guideline authors performed various search techniques, such as snowballing, PubMed's related citation search, and simple searches 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. Review protocol

The protocol specifies the methods that will be used to create a systematic review. It includes the rationale for the review, primary outcomes, inclusion criteria, search methods, data extraction, data synthesis and other aspects [5,18].

The PRISMA statement requires the creation of a protocol. The protocol should also be publicly available: "Without a protocol that is publicly accessible, it is difficult to judge between appropriate and inappropriate modifications [21]". PRISMA-P was developed to support quality and consistency in the protocol [22].

### **2.2.2. Expertise in searching**

Information specialists should form an integral part of the assessment team of an SR from the beginning of the project [5,18]. Search strategy development requires expertise and skills in search methodology [9]. Navigating through different information sources is a complex task [18], especially as the structure and functionalities of the databases and their interfaces are continually modified.

The tasks of information specialists are manifold [23-28]. They are responsible for the development and peer review of search strategies, as well as the actual conduct of the search [11,18,29]. 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 [30,31], and are responsible for the implementation of software solutions in information management [31].

The call for the routine involvement of information specialists in SRs is supported by research findings: Firstly, their involvement significantly increases the use of recommended search methods [32]. Secondly, search strategies developed and reported by information specialists are conducted and reported more comprehensively and are thus easier to reproduce [33-35]. These search strategies also contain fewer consequential errors [36].

### **2.2.3. Addressing reporting bias (including publication bias)**

Searches in bibliographic databases aim primarily to identify published studies (see Section 3.1). However, much research is never published or is published with delay [37-40], and published studies tend to overestimate the effectiveness of interventions and underestimate harms [37,38].

To reduce publication and outcome reporting bias, an SR should regularly include a search for unpublished literature to identify both unpublished studies and unpublished data from published studies (see Sections 3.2, 0 and 0).

In this context it should be noted that only clinical study reports (CSRs) provide (almost) complete information on a study [41], whereas the information provided in study registries and journal publications is often insufficient for the assessment of a study [42]. However, registries and publications may supplement each other [43] or registries can be used to verify published data [19].

Various analyses have shown inconsistencies between the information provided in different sources and publications, e.g. regarding inclusion criteria, endpoints investigated or rates of adverse events [43-45]. This may lead to differing assessments of the same study.

To further address reporting bias, the International Committee of Medical Journal Editors (ICMJE) mandates a data sharing plan included in each paper since 2018 [46]. Leading general medical journals like The BMJ and PLOS Medicine already have a policy expressly requiring data sharing as a condition for publication of clinical trials [47].

Despite the importance of unpublished data, HTA agencies do not routinely search study registries or send enquiries to companies [48]. In addition, many authors of SRs fail to report and assess publication bias [49-51].

#### **2.2.4. Matching documents and data**

It is often challenging to match all relevant documents (e.g. journal publications, trial registry entries, CSRs) to the correct study. An SR by Bashir et al. [52] reported that the linkage of trial registries and their corresponding publications requires extensive manual processes.

The Open Trials database [53] aims to identify and match all publicly available data and documents of a study and publish them online.

### 3. Comprehensive information retrieval

The aim of comprehensive information retrieval is to identify as many studies and related documents as possible that are relevant to the research question. For this purpose, a systematic search in several databases and further information sources and search techniques is required [3].

#### 3.1. Bibliographic databases

##### 3.1.1. Process of searching bibliographic databases

The figure shows the typical process of searching bibliographic databases (Figure 1), which may vary. The steps will be explained in the following sections in detail. In addition, a practical example can be found in Annexe 3.

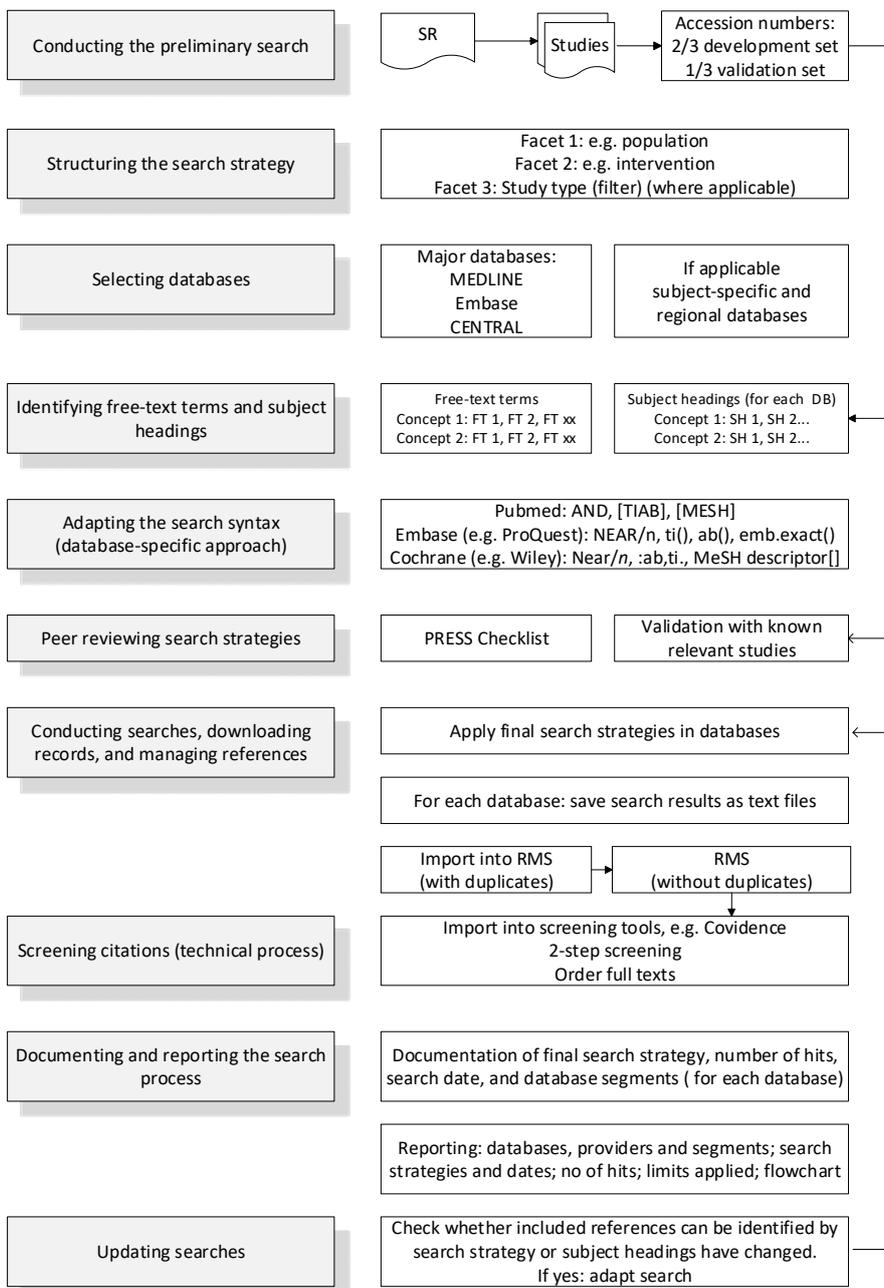


Figure 1: Search in bibliographic databases

### 3.1.2. 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 [30], i.e. understanding the key questions [4], identifying existing SRs [5,54,55], identifying a first set of potentially relevant primary studies [56], and estimating the resources necessary to perform the SR [54]. An SR on the research question under assessment may already exist; in this case, the existing SR may already answer the the research question or be suitable as a basis for information retrieval (see section 4). Secondly, the results of the preliminary search can be used in the development of the search strategy, for instance, by generating a list of search terms from the analysis of identified relevant articles [4,57,58] which can subsequently be used in the development of the search strategy.

Two main methods for conducting preliminary searches are described in the literature. With the first method, SRs on the topic of interest are systematically searched for in preselected information sources [5,54,55,59] such as the Cochrane Database of Systematic Reviews, Epistemonikos, KSR Evidence or the HTA database (under development) and, if relevant, the websites of HTA agencies (e.g. NICE and AHRQ). In order to avoid duplication of work, ongoing HTA reports and SRs should be identified (e.g. via the POP database [60] and PROSPERO [61]) to check whether the planned project is already being addressed.

The second method comprises an iterative process with different search techniques such as “snowballing” (backward or forward citations) [62,63] and checking the “similar articles” link in PubMed [63] or Embase (see 3.4.3). The starting point is a key 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 [4,58].

The most effective way of conducting a preliminary search is first to search for SRs. The techniques described in the second method above (e.g. “snowballing”) are used to search directly for primary studies if the first search produced no relevant or only poor-quality reviews [58].

*See example: Conducting preliminary searches (bib. databases)*

### 3.1.3. 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. The Patient(s) or Population(s) / Intervention(s) / Comparison(s) / Outcome(s) / Study design(s) (PICOS) is often a useful approach [3] to help to structure the search. The research question is commonly broken into concepts, and only the most important ones are used to develop the search strategy [64]. 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 may include the population, intervention(s), and types of study design [3]. Outcomes are usually not included in a systematic search, as they are generally inadequately reported in abstracts of journal publications [65]. For more complex review questions, it may be necessary to use several combinations of search concepts to capture a review topic [9,66] or to use other search approaches to capture relevant studies (see section 3.1.2).

The search terms are allocated to the individual search concepts or facets, 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” and the individual concepts are combined with the “AND” operator [3]. In this context, the use of separate lines for each subject heading and for free-text terms facilitates the quality assurance of search strategies since it enhances the readability of search strategies and therefore helps to avoid errors.

Validated study filters should be used for the search concepts on study design (see Section 3.1.5.1).

If search strategies are limited, for example, by language or publication year, this should be justified in the methods section of the SR. However, such limits should be used with caution, as they may introduce bias [4,10]. Moreover, they should only be considered if they can be reliably applied in the individual databases.

*See example: Structuring the search strategy (bib. databases)*

### **3.1.4. Choosing information sources**

The production of an SR requires a systematic search in several bibliographic databases. This is because journal inclusion rates differ between databases [67,68]. Furthermore, the time and quality of indexing differs [68-71], meaning that a reference might be more difficult to find or be found with delay in some databases, but not in others.

There is insufficient empirical evidence 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]. Recent analyses of retrieval rates of relevant studies indicate that most of the published studies can be found in a limited number of databases [72-75].

It is also recommended that an additional search for non-indexed information be undertaken e.g. in PubMed, to ensure that all references, especially the most recent ones, have been identified.

Depending on the topic of the SR, regional or subject-specific databases may also be relevant [3-5,18,76]. However, the additional impact of searching in regional databases has been insufficiently investigated, and many such databases provide restricted functionalities [77,78]. However, for some objectives the use of subject-specific databases may identify additional relevant studies (e.g. on complementary and alternative medicine) [79,80]. A list of regional and subject-specific databases is provided in the Technical Supplement of the Cochrane Handbook [81].

*See example: Choosing information sources (bib. databases)*

### **3.1.5. Developing search strategies**

#### *3.1.5.1. Identifying search terms*

A combination of subject headings (including publication type) and free-text terms is required in the development of search strategies [82-84]. Different approaches to identify search terms are described in the literature [7,85]. The conceptual approach [86,87] is recommended by the pertinent literature. Sources used in this approach include the MeSH database [88] or Emtree, medical dictionaries, scanning of relevant publications or

consultations with experts to identify a wide range of subject headings and free-text terms [5,56]. In addition, one or more key articles are commonly chosen as a starting point to identify further relevant terms using methods such as “pearl growing” [64]. This process is usually repeated until no further relevant material is found [89].

More objective approaches to develop a search strategy use text-analytic procedures to identify free-text terms and subject headings through a frequency analysis [90-92]. In this context relevant articles already known [7,8,93,94] or newly identified through broad searches [89,95] are systematically analysed for word frequency by a text-analytic software package. These software packages vary in cost and functionality. A list of text-analytic tools can be found in the Systematic Review Toolbox, a web-based catalogue [96].

In the next step, identified terms are assigned to the individual concepts of the search strategy, independently of which approach was chosen to identify subject headings and free-text terms [10,64]. To avoid redundancies, free-text terms should be truncated at the word stem [97] 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 for topics or study designs need not be identified if validated, high-quality filters for study design are available [4]. Study filters and topic-based filters are provided in the literature [98] by the InterTASC Information Specialists' Sub-Group [99] and can be evaluated before the search using appraisal checklists [100,101].

If the search is restricted to RCTs, validated and highly sensitive study filters, yielding a sensitivity of  $\geq 95\%$ , should be used. These include the study filters of the Cochrane Collaboration [81] and of the Health Information Research Unit of McMaster University [102]. The RCT classifiers provided by RobotSearch [126] and Cochrane [127,128] are also appropriate tools for limiting search results [129].

If, besides RCTs, non-randomized studies are considered in the assessment, the search cannot usually be restricted to certain study types, as no high-quality study filters are available in this regard [103].

Likewise, the use of study filters is not recommended to identify studies on diagnostic accuracy unless further search techniques, such as screening reference lists, are applied [104].

RCTs of drugs can be identified with a simple standardized search using the truncated generic drug name in all search fields (e.g. formoterol\*.mp.); this achieves a sensitivity of more than 99% in MEDLINE or Embase [105].

The search for references not yet indexed in PubMed/MEDLINE is a major challenge, as no subject headings have yet been assigned. For this purpose, free-text terms and study filters may need to be adapted [106,107] as searches are usually optimized for a combined subject headings and free-text search.

*See example: Identifying search terms (bib. databases)*

### 3.1.5.2. *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. Each database should be searched separately. Alternatively, cross-database searches are only acceptable if the search strategy is applicable to each database [31]. For this purpose, the free-text terms previously identified can usually be applied across databases [5].

Subject headings must be specifically adapted for each database [3-5,10,108]. In this context it is advisable to adapt the search strategy developed first (commonly in MEDLINE [24]) to the requirements of the other databases [4,10,108]. 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 [97,109]. Tools to help with the conversion of search strategies (e.g. from PubMed to another interface) are now available with the Medline Transpose [110] and the Polyglot Search Syntax Translator [111].

*See example: Adapting the search syntax (bib. databases)*

### 3.1.6. **Peer reviewing search strategies**

A high-quality search strategy is required to ensure the accuracy and completeness of the evidence base used in an SR [10,11]. Due to their complexity, search strategies in bibliographic databases are prone to error [29].

The “Peer Review of Electronic Search Strategies” (PRESS) checklist was developed to support the peer review process [20]. 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 [112,113]. The peer review process using the checklist should be completed before the search strategy is run [18,29,112].

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 [12], i.e. it tests whether relevant references identified beforehand (see Section 3.1.2) can be found by the search strategy used.

*See example: Peer reviewing search strategies (bib. databases)*

### 3.1.7. **Conducting searches, downloading records, and managing references**

After development, search strategies should be saved individually in each database for later use. After conducting the search in the selected databases, all references retrieved are downloaded, combined, and prepared for the screening process. For this purpose, the use of reference management software (RMS) such as EndNote [114], RefWorks [115] or Mendeley [116] is recommended [117-119]. These software programs enable the efficient management of references, including in-text citation [120].

Searching several databases produces duplicates. Qi et al. [121] and Bramer et al. [122] have developed methods for removing duplicates, which involve a stepwise semi-automatic comparison of references. 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; it is then possible to exclude these records from a search in Embase.

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 Ovid it is also possible to conduct separate searches in each database with individual search strategies and then deduplicate [31]. The individual database searches can be run simultaneously by limiting the search result to the respective databases using Ovid database codes [123]. Once this is done the duplicates can be removed by Ovid.

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

### **3.1.8. Screening citations (technical process)**

After the references have been saved in a RMS, 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 [5,18].

The selection of references is usually administered in the RMS or by manual handling of paper copies [5]. In practice this is often problematic, particularly if the search produces a large number of hits. Internet-based systems such as Covidence, EPPI-Reviewer, Rayyan, DistillerSP and Abstrackr have therefore been developed [96] 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 [5,18]. The screening of titles and abstracts usually involves two reviewers to reduce the possibility of missing relevant publications [124]. The selection of studies to be included in the SR also should always be performed by at least two reviewers [3]. Current automation approaches aim to prioritize screening results in order to sort relevant references at the start of the screening process [125].

In the study selection process, information specialists are increasingly involved in data management between different software applications [9,24]. 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 Docline, 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 [130].

*See example: Screening citations (bib. databases)*

### **3.1.9. Documenting 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 [5,18]. 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 [31]. Many databases offer facilities to save search strategies [31].

When exporting search results from the databases, the references should first be saved as text or RIS files and not imported directly into the RMS. This ensures the safe storage of search results [31]. In addition, information on the databases and interfaces searched should be documented, including the search dates and the search periods covered [5,31]. The complete documentation process is described in detail by Rader et al. [31].

*See example: Documenting and reporting (bib. databases)*

### **3.1.10. Updating searches**

The literature search is usually conducted at the initial stage of the production of an SR. As a consequence, the results of a literature search may be outdated before the review is published [131-133]. The available evidence suggests that the last search in a review should be conducted less than 12 months before publication [3,132]. If the assessment is to serve as a basis for healthcare decision-making, this period should be as short as possible. Ideally, the last search in a EUnetHTA assessment should therefore be conducted less than 6 months before publication. For this reason, search updates are often conducted before the planned publication date.

Auto alerts [5] and other surveillance search techniques [134] 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 [12]. Furthermore, it should be assessed whether other databases need to be searched [135] and whether the annual update of MeSH terms has led to any changes.

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 [136]. A second 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. A third technique is to download all references from the update search and directly deduplicate them with the references from the initial search (e.g. using EndNote).

*See example: Updating searches (bib. databases)*

## 3.2. Study registries

### 3.2.1. General aspects

The importance of study registries has increased markedly over the last years. In 2005, the ICMJE specified that the prospective registration of clinical studies was a prerequisite for publication [137].

In 2007, the United States introduced mandatory registration of studies and summary results in ClinicalTrials.gov for most Food and Drug Administration (FDA)-regulated drugs and devices [138]. If a protocol, statistical analysis plan (SAP), and data sharing statement are available for a study, ClinicalTrials.gov provides links to these documents [46,139,140]. Tse et al. [141] provide a summary of the legal basis of ClinicalTrials.gov, highlighting issues that need to be considered.

In 2011 the European Medicines Agency (EMA) established the EU Clinical Trials Register (EU-CTR) [142] for most studies submitted during the drug approval process, and the posting of summary results became mandatory in July 2014 [143]. Compliance with the requirement to report results on the EU-CTR can be monitored with the EU Trials Tracker [144].

Depending on the topic investigated, between 15% (diagnostic or prognostic tests [145]) and nearly 100% (newly approved drugs [146,147]) of studies are registered in study registries.

#### Structure of study registries

Study registries are generally web-based databases that are publicly available. They contain key information from the study protocol, including outcomes, and/or summary results [19].

Different types of individual registries have been established (see Table 3). In addition, meta-registries such as the ICTRP Search Portal [148] contain regularly updated data from individual registries or access individual registries directly at the time of the search query.

Table 3: Types of study registries

Types of study registries	Examples
National registry	German Clinical Trials Register [149] Nederlands Trial Register [150] Spanish Clinical Studies Registry [151]
Regulatory registry	ClinicalTrials.gov [152] EU Clinical Trials Register (Europe) [142]
Industry registry	GlaxoSmithKline Clinical Study Register [153] Forest Clinical Trial Registry [154]
Disease-specific registry	ALOIS: A Comprehensive Register of Dementia Studies [155]
Meta-registry	ICTRP Search Portal of the WHO [148]

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, contain errors [156] or be changed after registration [157,158]. In addition, the study status may be outdated [159,160]. Therefore, when searching in study registries, it is recommended to search for ongoing, discontinued and completed studies, as well as study results summaries. Whether the SR actually reports ongoing studies should be discussed at the beginning of a project.

Furthermore, many studies are still registered retrospectively instead of prospectively [44,161-165]. It should also be noted that registries have previously been closed down at short notice (e.g. [clinicalstudyresults.org](http://clinicalstudyresults.org) [166] or the web crawler of the IFPMA Clinical Trials Portal [167]).

Previously, systematic reviews did not routinely search study registries [48,168], despite the fact that additional relevant studies may be identified in these sources [169-171].

### **3.2.2. 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) [172]. It is advisable to search using the most specific concept terms first, as this will probably generate the lowest number of hits. 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)*

### **3.2.3. Choosing information sources**

Several registries should be searched, as no single registry contains all studies [159,172,173]. As a minimum, the ICTRP Search Portal and ClinicalTrials.gov should be searched [3,19,172]. 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 [159,174]. However, it only offers limited search functions [172] and often produces error messages [175]. For this reason, major registries such as ClinicalTrials.gov should always be searched directly [172].

For SRs of drugs, the relevant company registry [171] and EU-CTR, should also be searched.

Only a few suitable disease-specific study registries exist. These registries are frequently established for temporary research programmes and are often no longer updated when funding ceases. Consequently, they are not very useful and should only be searched in exceptional cases [176].

*See example: Choosing information sources (study registries)*

### **3.2.4. Developing search strategies**

#### **3.2.4.1. Identifying search terms**

The trial registry search should use terms from the strategy used for the bibliographic database searching. Known terms of a search concept should be considered in a sensitive search [172]. It should be noted that registries such as ClinicalTrials.gov (see [177] for an example) and the ICTRP Search Portal offer a search for synonyms. Both provide a list of

synonyms for search terms, which enables a reduction in the number of search terms. This is helpful because study registries only provide limited search functions [146].

A recent analysis has shown that the use of the generic drug name is sufficient in searches for newly approved drugs (since 2005) in ClinicalTrials.gov. In the ICTRP Search Portal and EU-CTR, the drug code should also be included [146]. In Clinicaltrials.gov, simple search terms are usually sufficient when searching for the therapeutic indication, as the “search for synonyms” function performs well in this registry. In the ICTRP Search Portal and EU-CTR [146], a more comprehensive approach is recommended.

*See example: Identifying search terms (study registries)*

#### **3.2.4.2. 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, brackets cannot be used to structure searches of the ICTRP Search Portal. Instead, Boolean operators are applied in an automatic order (NOT, AND, OR). In addition, complex search queries may generate error messages. 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 [172].

The York Health Economics Consortium provides a comprehensive overview of the search functions of different registries [178].

If appropriate, a sensitive search should be conducted as a single concept search using the “basic search” function [172].

*See example: Adapting the search syntax (study registries)*

#### **3.2.5. Peer reviewing search strategies**

The peer review of study registry search strategies 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 [172]. A set of relevant registry entries can be compiled, by using relevant studies picked up in the preliminary search (see Section 3.1.2). It is then tested whether the final search strategy actually identifies these entries. However, it is not always possible to link the relevant studies to corresponding registry entries, as not all journal articles include study identifiers such as National Clinical Trial numbers [172].

*See example: Peer reviewing search strategies (study registries)*

### **3.2.6. 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 [178], which can be imported into a RMS using an import filter [31], and processed for screening.

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)*

### **3.2.7. Screening citations (technical process)**

The screening of search results is similar to the procedure applied for bibliographic databases. Using a screening tool (see Section 3.1.8), the registry entries should be independently 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)*

### **3.2.8. Documenting 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.

*See example: Documenting and reporting (study registries)*

### **3.2.9. 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 not to use 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 RMS 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)*

### 3.3. 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 (CSRs), which are submitted to regulatory agencies during the approval procedure for a drug.

These documents are generally prepared following the International Conference on Harmonisation's Guideline for Industry: Structure and Content of Clinical Study Reports (ICH E3) [179] and provide detailed information on the methods and results of a study [180]. They contain far more relevant information than journal publications or registry reports [43,179,180]. Although CSRs are considerably longer than journal publications [181] and require specific expertise with regard to data extraction and assessment, they are indispensable for gaining an unbiased picture of the available research evidence [37,43,179-182].

Pharmaceutical companies are increasing data transparency. However, an analysis of pharmaceutical company policies showed that transparency commitments vary greatly between companies [183]. Since 2013, GlaxoSmithKline (GSK) has published CSRs of all GSK drugs approved or discontinued from 2000 and onwards [184]. CSRs, anonymized individual patient data and/or supporting documents from clinical studies can be requested from pharmaceutical companies via data sharing portals such as the Clinical Study Data Request website [185] or the Yale University Open Data Access Project (YODA) [186]. However, such requests are sometimes rejected [187-189] or the studies listed are incomplete [190].

#### *Search process*

As CSRs are not routinely published by regulatory agencies, pharmaceutical companies or medical device manufacturers, the latter two should be asked to provide unpublished information [19]. This should follow a standardized approach using template letters or forms.

For example, IQWiG currently applies the following approach for this purpose [191]: before requesting data, an agreement is reached between the authors of the SR and the relevant company concerning the transmission of information on the drug or medical device of interest. 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. English-language sample contracts between IQWiG and pharmaceutical companies or medical device manufacturers are available on the IQWiG website [192,193].

### 3.4. Further information sources and search techniques

In addition to the primary search sources named in sections 3.1, 3.2 and 3.3, project-specific information sources and search techniques should be considered. Some examples are briefly presented in the following sections.

#### 3.4.1. Regulatory documents

Websites of regulatory agencies are rarely included as information sources in systematic searches [194,195] although they now publish various documents from the approval process. Jefferson et al. [196] identified criteria that can be used to determine whether CSRs or other documents from regulatory agencies should be considered in an SR.

##### 1. Complete clinical study reports

In 2014, the EU Parliament passed a law specifying the publication of complete CSRs for all clinical trials conducted in the EU (as well as outside the EU for paediatric trials) [197]. The corresponding database is planned to go online in 2020.

In addition, EMA introduced Policy 0070 on data transparency, which became effective in October 2016 [198,199]. Regulatory documents, including CSRs on all drugs submitted for approval, have since been available on the Agency's website "European Medicines Agency – Clinical data" [200]. However, publication of clinical data is temporarily suspended and the database is currently not up to date. Nevertheless, it should be checked whether CSR on the subject are available at the EMA.

Regulatory agencies in other countries such as Canada [201] have also started to publish CSRs and these documents should be considered in individual cases. The FDA, on the other hand, is only testing the voluntary publication of CSRs in a pilot programme [202].

##### 2. Documents from regulatory agencies

Until recently, regulatory agencies did not publish complete CSRs but made available related documents from the approval process (e.g. FDA Medical and Statistical Review documents). These documents can offer important insights into clinical studies [19,203] and may also include a list of studies that are potentially relevant for an SR. However, similar to other sources such as reports from study registries, regulatory documents do not usually contain all relevant information on a study [182].

In Europe, information on centrally authorized drugs (e.g. European public assessment reports) can be found on the EMA website [204]. In the United States, the Medical and Statistical Reviews of drugs approved by the FDA can be found via Drugs@FDA [205].

Regulatory agencies in other countries such as Canada [206] or Japan [207] also publish potentially relevant documents and should be considered in individual cases.

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) [208]. However, this source is not publicly accessible yet. Information on medical devices is sometimes made available by individual countries, for example, in the NICE list of interventional procedures in the UK [209]. In the United States, information on FDA-approved devices, including data used for approval, is available via Devices@FDA [210].

## *Search process*

A **search** for the drug or medical device is conducted on the websites of the relevant regulatory agencies. If no relevant documents are found, it is advisable to conduct a search in Google (e.g. for “FDA advisory committee” AND “active ingredient” / medical device).

Navigating in CSRs can be challenging, as the documents contain several hundred to several thousand pages. However, the structured design of this type of document allows for fast access to the relevant information. The “Restoring Invisible & Abandoned Trials” (RIAT) Support Center provides extensive material for handling CSRs [211].

Turner [212] and Ladanie et al. [213] provided a detailed overview on how to access and process FDA documents. Also Le Cleach et al. [214] have published step-by-step instructions to searching the Drugs@FDA database and EMA website in the supplement of their article. However, navigating on the FDA website and searching in documents can be challenging [156,215]. The OpenTrialsFDA website makes it easier to search through FDA documents. [216].

The **internal documentation** for regulatory sources used in an SR includes information on the website, the search date, and the search terms used.

### **3.4.2. 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 [4,18,217].

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 [218]. 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 [218]. Sending a request to each study author may therefore be considered sufficient. In this context, contact with authors via social networks such as LinkedIn and ResearchGate seems to be gaining importance [219].

When reviewers contact study 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 response from study authors [4,217].

Systematically contacting study authors of all identified relevant studies may also be considered to identify additional unpublished, ongoing or difficult to locate studies that may be useful for the review [220].

### **3.4.3. Further search techniques**

The conventional search approach of applying Boolean operators (see Section “Definitions of central terms and concepts”) to subject heading and free-text queries continues to dominate literature reviews, as it remains an effective method for searching the major online bibliographic databases [221]. However, sensitivity and specificity issues relating to

Boolean searching have led researchers to investigate a variety of alternative search approaches. Checking reference lists (backward citations), citation tracking (forward citations), using the “similar articles” function in the database (see section “Definitions of central terms and concepts”), hand searching and methods of automated retrieval implemented in databases are some examples.

Verifying the studies identified solely by additional search techniques (e.g. checking reference lists) can validate the effectiveness of searches in bibliographic databases [59]. If these searches miss relevant articles, revising the search strategy and rerunning the search should be considered [222].

Optional citation tracking can be used. Although there is only limited evidence of the effectiveness of these approaches, the available evidence indicates that using so-called “indirect citation relationships”, such as checking co-citations [223] (i.e. the reference lists of articles citing key articles) and using the “similar articles” function would seem to be an efficient search approach [63].

Further information on this topic can be found in the chapter “Value of using different search approaches” on SuRe Info in [63].

Section 2.3.2 provides information on the application of the above-mentioned search techniques in preliminary searches.

#### **3.4.4. 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 [224]. Conference abstracts often provide limited details of study methodology, and may contain limited reporting of outcome data [225]. There can be differences between data presented in an abstract and that included in the full publication [5,226,227]. In addition, McAuley et al. [228] showed that the inclusion of abstracts had no relevant impact on pooled estimates of meta-analyses across different medical fields. For these reasons, it is not recommended to routinely search for abstracts and reviewers should always try to obtain the full report or further study details, before considering whether to include the results in the review [5,225].

However, especially if systematic literature searches for published studies yield no or very few citations or the available evidence is conflicting, searching conference abstracts and proceedings may be considered to identify additional studies [225,229]. 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 [225].

If the assessment 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 3.5. The assessment 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 [225].

### **3.4.5. Dissertation and reports**

Searching for dissertations and other reports seems helpful only in exceptional cases (e.g. religion and mental health [230]). Numerous databases exist for these types of documents (e.g. BL EThOS, DART Europe, ProQuest Dissertations & Theses Database, OpenGrey, NIH RePORTER). However, it is not recommended to routinely search these sources. It has been shown that “searching for and retrieving unpublished dissertations involves considerable time and effort” [231] and there seems to be little impact on the results or the conclusion of a review [231,232].

### **3.5. Reporting the search process**

With PRISMA-S [233,234], a consensus will soon be available on how information retrieval for systematic reviews should be documented. The requirements specified in PRISMA-S include details on databases and additional information sources used, search restrictions and filters applied, as well as the documentation of full search strategies.

In addition, the study selection process should be displayed in a flowchart in the results section of the SR [4,5,18] (see PRISMA for a template [21,235]). Furthermore, the references of the studies included and excluded (for articles read in full text) should be presented in separate reference lists [236]. In contrast to journal publications, HTA reports do not have space restrictions, and should therefore document the search process as precisely as necessary [18].

## 4. Layered searching approach based on SRs

Information retrieval for SRs on clinical effectiveness is generally based on primary studies. In some cases (e.g. if a preliminary search identifies up-to-date, high-quality and relevant SRs on the topic of interest), a layered searching approach [237,238] can be applied. In this approach, the relevant SRs are used as the main source for the primary studies considered in the assessment. In addition, an update search for primary studies is conducted [238].

1) First, SRs are searched for in a focused search. In focused information retrieval it is not necessary to conduct a search for SRs that is targeted towards completeness. Restrictions and adaptations can be undertaken in the development of search strategies (e.g. less sensitive study filters), in the peer review and execution of search strategies, in study selection (e.g. screening by only reviewer), and in the reporting of information retrieval.

If screening identifies SR(s) fulfilling the inclusion criteria of the assessment report, the information specialist checks the quality of information retrieval (including methods used for study selection) in these documents by means of a checklist (e.g. Item 3 of AMSTAR (A Measurement Tool to Assess Systematic Reviews) [236]).

One (or potentially several) high-quality and current SR(s) is/are then chosen, and the primary studies considered in these SRs are extracted and then checked for meeting the inclusion criteria of the report.

2) Subsequently, an update search for primary studies published in the period not covered by the SR(s) is usually conducted (from the date of the last search to present) (see Section 3). The original search strategy from the SR can be used or a new search strategy be developed.

3) In the case that certain research questions of the report are not completely covered by the SR, a search for the specific questions is carried out without time limit (see section 3).

If important information sources in the SR/HTA are missing or were not searched comprehensively (e.g. study registries), these sources can be searched additionally within the framework of information retrieval for the assessment without limiting the search period (see Section 3).

## 5. Conclusion

The information sources listed in the present guideline show different strengths and weaknesses. For instance, a search in bibliographic databases is generally a routine task for an information specialist. However, many studies are never published and cannot be found in these databases. The production of an SR thus requires the regular search of additional information sources, even though this usually involves additional effort.

CSRs deliver the most comprehensive information on clinical studies and information sources providing these documents should therefore be included in a search. They minimize the problem of reporting bias and are thus indispensable for gaining an unbiased picture of the available research evidence. As CSRs 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 agencies 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 study 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.

Further search techniques, such as checking reference lists or using the “similar articles” function of relevant publications, can be used as additional information sources. If searches conducted in bibliographic databases have failed to identify relevant published studies included in the reference lists, search strategies should be reviewed and, if necessary, adjusted.

A search for conference abstracts may be of only limited use and is primarily conducted to identify further studies.

The types of information sources considered in an SR 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 (a measurement tool for the “Assessment of Multiple Systematic Reviews” [236]) 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).

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

## Annexe 1. Bibliography

1. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ et al. Cochrane handbook for systematic reviews of interventions: version 6.0 [internet]. 2019 [cited: 05.11.2019]. Available from: <https://training.cochrane.org/handbook>
2. National Center for Biotechnology Information. PubMed help: status subsets [internet]. [cited: 18.03.2019]. Available from: [https://www.ncbi.nlm.nih.gov/books/NBK3827/table/pubmedhelp.T.status\\_subsets/](https://www.ncbi.nlm.nih.gov/books/NBK3827/table/pubmedhelp.T.status_subsets/)
3. Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf MI et al. Chapter 4: searching for and selecting studies [internet]. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ et al (Eds). Cochrane handbook for systematic reviews of interventions: version 6. 07.2019 [cited: 14.11.2019]. Available from: <https://training.cochrane.org/handbook>
4. Relevo R, Balshem H. Finding evidence for comparing medical interventions: methods guide for comparative effectiveness reviews; AHRQ publication no. 11-EHC021-EF [internet]. 01.2011 [cited: 27.05.2019]. Available from: [https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/methods-guidance-finding-evidence\\_methods.pdf](https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/methods-guidance-finding-evidence_methods.pdf)
5. Centre for Reviews and Dissemination. CRD's guidance for undertaking reviews in health care. York: CRD; 2009. Available from: [https://www.york.ac.uk/media/crd/Systematic\\_Reviews.pdf](https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf)
6. Waffenschmidt S, Janzen T, Hausner E, Kaiser T. Simple search techniques in PubMed are potentially suitable for evaluating the completeness of systematic reviews. *J Clin Epidemiol* 2013; 66(6): 660-665.
7. Hausner E, Waffenschmidt S, Kaiser T, Simon M. Routine development of objectively derived search strategies. *Syst Rev* 2012; 1: 19.
8. Simon M, Hausner E, Klaus SF, Dunton N. Identifying nurse staffing research in Medline: development and testing of empirically derived search strategies with the PubMed interface. *BMC Med Res Methodol* 2010; 10: 76.
9. Lefebvre C, Glanville J, Wieland LS, Coles B, Weightman AL. Methodological developments in searching for studies for systematic reviews: past, present and future? *Syst Rev* 2013; 2: 78.
10. Sampson M, McGowan J, Lefebvre C, Moher D, Grimshaw J. PRESS: Peer Review of Electronic Search Strategies. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2008. Available from: [http://www.cadth.ca/media/pdf/477\\_PRESS-Peer-Review-Electronic-Search-Strategies\\_tr\\_e.pdf](http://www.cadth.ca/media/pdf/477_PRESS-Peer-Review-Electronic-Search-Strategies_tr_e.pdf)
11. Sampson M, McGowan J, Cogo E, Grimshaw J, Moher D, Lefebvre C. An evidence-based practice guideline for the peer review of electronic search strategies. *J Clin Epidemiol* 2009; 62(9): 944-952.
12. Sampson M, McGowan J. Inquisitio Validus Index Medicus: a simple method of validating MEDLINE systematic review searches. *Res Syn Meth* 2011; 2(2): 103-109.

13. Yoshii A, Plaut DA, McGraw KA, Anderson MJ, Wellik KE. Analysis of the reporting of search strategies in Cochrane systematic reviews. *J Med Libr Assoc* 2009; 97(1): 21-29.
14. Sampson M, McGowan J, Tetzlaff J, Cogo E, Moher D. No consensus exists on search reporting methods for systematic reviews. *J Clin Epidemiol* 2008; 61(8): 748-754.
15. EPPI-Centre. EPPI-Reviewer 4 [internet]. [cited: 22.12.2016]. Available from: <http://eppi.ioe.ac.uk/cms/Default.aspx?alias=eppi.ioe.ac.uk/cms/er4>
16. Isojärvi J, Ormstad SS. Summarized research in information retrieval for HTA [internet]. [cited: 22.12.2016]. Available from: <http://www.sure-info.org>
17. European Network for Health Technology Assessment. EUnetHTA Companion Guide [internet]. 27.02.2019 [cited: 16.05.2019]. Available from: <https://companionguide.eunetha.be/doku.php>
18. Eden J, Levit L, Berg A, Morton S (Ed). Finding what works in health care: standards for systematic reviews. Washington: National Academies Press; 2011. Available from: [http://books.nap.edu/catalog.php?record\\_id=13059](http://books.nap.edu/catalog.php?record_id=13059)
19. Balshem H, Stevens A, Ansari M, Norris S, Kansagara D, Shamliyan T et al. Finding grey literature evidence and assessing for outcome and analysis reporting biases when comparing medical interventions: AHRQ and the Effective Health Care Program; methods guide for comparative effectiveness reviews; AHRQ publication no. 13(14)-EHC096-EF [internet]. 11.2013 [cited: 18.03.2019]. Available from: [https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/methods-guidance-reporting-bias\\_methods.pdf](https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/methods-guidance-reporting-bias_methods.pdf)
20. Mc Gowan J, Sampson M, Salzwedel DM, Cogo E, Foester V, Lefebvre C. PRESS: Peer Review Electronic Search Strategies; 2015 guideline explanation and elaboration (PRESS E&E) [internet]. 01.2016 [cited: 22.12.2016]. Available from: [https://www.cadth.ca/sites/default/files/pdf/CP0015\\_PRESS\\_Update\\_Report\\_2016.pdf](https://www.cadth.ca/sites/default/files/pdf/CP0015_PRESS_Update_Report_2016.pdf)
21. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *PLoS Med* 2009; 6(7): e1000097.
22. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; 4: 1.
23. Spencer AJ, Eldredge JD. Roles for librarians in systematic reviews: a scoping review. *J Med Libr Assoc* 2018; 106(1): 46-56.
24. McGowan J, Sampson M. Systematic reviews need systematic searchers. *J Med Libr Assoc* 2005; 93(1): 74-80.
25. Harris MR. The librarian's roles in the systematic review process: a case study. *J Med Libr Assoc* 2005; 93(1): 81-87.
26. Beverley CA, Booth A, Bath PA. The role of the information specialist in the systematic review process: a health information case study. *Health Info Libr J* 2003; 20(2): 65-74.

27. Metzendorf MI, Featherstone RM. Ensuring quality as the basis of evidence synthesis: leveraging information specialists' knowledge, skills, and expertise. *Cochrane Database Syst Rev* 2018; (4): ED000125.
28. Fenton C, Littlewood A, Bridges C, Doney L, Hampson L, Higgins G et al. *Cochrane information specialists' handbook* [internet]. 2018 [cited: 06.06.2019]. Available from: <https://training.cochrane.org/resource/cochrane-information-specialists-handbook>
29. Sampson M, McGowan J. Errors in search strategies were identified by type and frequency. *J Clin Epidemiol* 2006; 59(10): 1057-1063.
30. Rethlefsen ML, Murad MH, Livingston EH. Engaging medical librarians to improve the quality of review articles. *JAMA* 2014; 312(10): 999-1000.
31. Rader T, Mann M, Stansfield C, Cooper C, Sampson M. Methods for documenting systematic review searches: a discussion of common issues. *Res Syn Meth* 2014; 5(2): 98-115.
32. Koffel JB. Use of recommended search strategies in systematic reviews and the impact of librarian involvement: a cross-sectional survey of recent authors. *PLoS One* 2015; 10(5): e0125931.
33. Golder S, Loke Y, McIntosh HM. Poor reporting and inadequate searches were apparent in systematic reviews of adverse effects. *J Clin Epidemiol* 2008; 61(5): 440-448.
34. Rethlefsen ML, Farrell AM, Osterhaus Trzasko LC, Brigham TJ. Librarian co-authors correlated with higher quality reported search strategies in general internal medicine systematic reviews. *J Clin Epidemiol* 2015; 68(6): 617-626.
35. Meert D, Torabi N, Costella J. Impact of librarians on reporting of the literature searching component of pediatric systematic reviews. *J Med Libr Assoc* 2016; 104(4): 267-277.
36. Zhang L, Sampson M, McGowan J. Reporting the role of the expert searcher in Cochrane reviews. *Evid Based Libr Inf Pract* 2006; 1(4): 3-16.
37. McGauran N, Wieseler B, Kreis J, Schüller YB, Kölsch H, Kaiser T. Reporting bias in medical research: a narrative review. *Trials* 2010; 11: 37.
38. Song F, Parekh S, Hooper L, Loke YK, Ryder J, Sutton AJ et al. Dissemination and publication of research findings: an updated review of related biases. *Health Technol Assess* 2010; 14(8): iii-xi, 1-220.
39. Canestaro WJ, Hendrix N, Bansal A, Sullivan SD, Devine EB, Carlson JJ. Favorable and publicly funded studies are more likely to be published: a systematic review and meta-analysis. *J Clin Epidemiol* 2017; 92: 58-68.
40. Van Aert RCM, Wicherts JM, Van Assen M. Publication bias examined in meta-analyses from psychology and medicine: a meta-meta-analysis. *PLoS One* 2019; 14(4): e0215052.
41. Köhler M, Haag S, Biester K, Brockhaus AC, McGauran N, Grouven U et al. Information on new drugs at market entry: retrospective analysis of health technology assessment reports versus regulatory reports, journal publications, and registry reports. *BMJ* 2015; 350: h796.

42. Glasziou P, Altman DG, Bossuyt P, Boutron I, Clarke M, Julious S et al. Reducing waste from incomplete or unusable reports of biomedical research. *Lancet* 2014; 383(9913): 267-276.
43. Wieseler B, Kerekes MF, Vervoelgyi V, McGauran N, Kaiser T. Impact of document type on reporting quality of clinical drug trials: a comparison of registry reports, clinical study reports, and journal publications. *BMJ* 2012; 344: d8141.
44. Pranic S, Marusic A. Changes to registration elements and results in a cohort of Clinicaltrials.gov trials were not reflected in published articles. *J Clin Epidemiol* 2016; 70: 26-37.
45. Jones CW, Keil LG, Holland WC, Caughey MC, Platts-Mills TF. Comparison of registered and published outcomes in randomized controlled trials: a systematic review. *BMC Med* 2015; 13: 282.
46. Taichman DB, Sahni P, Pinborg A, Peiperl L, Laine C, James A et al. Data sharing statements for clinical trials: a requirement of the International Committee of Medical Journal Editors. *PLoS Med* 2017; 14(6): e1002315.
47. Naudet F, Sakarovitch C, Janiaud P, Cristea I, Fanelli D, Moher D et al. Data sharing and reanalysis of randomized controlled trials in leading biomedical journals with a full data sharing policy: survey of studies published in *The BMJ* and *PLOS Medicine*. *BMJ* 2018; 360: k400.
48. Kreis J, Panteli D, Busse R. How health technology assessment agencies address the issue of unpublished data. *Int J Technol Assess Health Care* 2014; 30(1): 34-43.
49. Koletsi D, Valla K, Fleming PS, Chaimani A, Pandis N. Assessment of publication bias required improvement in oral health systematic reviews. *J Clin Epidemiol* 2016; 76: 118-124.
50. Atakpo P, Vassar M. Publication bias in dermatology systematic reviews and meta-analyses. *J Dermatol Sci* 2016; 82(2): 69-74.
51. Hedin RJ, Umberham BA, Detweiler BN, Kollmorgen L, Vassar M. Publication bias and nonreporting found in majority of systematic reviews and meta-analyses in anesthesiology journals. *Anesth Analg* 2016; 123(4): 1018-1025.
52. Bashir R, Bourgeois FT, Dunn AG. A systematic review of the processes used to link clinical trial registrations to their published results. *Syst Rev* 2017; 6(1): 123.
53. Goldacre B, Gray J. OpenTrials: towards a collaborative open database of all available information on all clinical trials. *Trials* 2016; 17: 164.
54. Forsetlund L, Kirkehei I, Harboe I, Odgaard-Jensen J. A comparison of two search methods for determining the scope of systematic reviews and health technology assessments. *Int J Technol Assess Health Care* 2012; 28(1): 59-64.
55. Statens Beredning för Medicinsk Utvärdering. Utvärdering av metoder i hälso- och sjukvården: en handbok. Stockholm: SBU; 2012. Available from: <http://www.sbu.se/upload/ebm/metodbok/SBUshandbok.pdf>

56. Khan K, Kunz R, Kleijnen J, Antes G. Systematic reviews to support evidence-based medicine: how to review and apply findings of healthcare research. London: Royal Society of Medicine Press; 2003.
57. Booth A. Unpacking your literature search toolbox: on search styles and tactics. *Health Info Libr J* 2008; 25(4): 313-317.
58. Sayers A. Tips and tricks in performing a systematic review. *Br J Gen Pract* 2007; 57(545): 999.
59. Whitlock EP, Lin JS, Chou R, Shekelle P, Robinson KA. Using existing systematic reviews in complex systematic reviews. *Ann Intern Med* 2008; 148(10): 776-782.
60. European Network for Health Technology Assessment. EUnetHTA POP database [internet]. [cited: 22.12.2016]. Available from: <http://eunetha.dimdi.de/PopDB>
61. Centre for Reviews and Dissemination. PROSPERO [internet]. [cited: 22.12.2016]. Available from: <http://www.crd.york.ac.uk/PROSPERO/>
62. Cooper C, Booth A, Britten N, Garside R. A comparison of results of empirical studies of supplementary search techniques and recommendations in review methodology handbooks: a methodological review. *Syst Rev* 2017; 6: 234.
63. Hausner E, Waffenschmidt S. Value of using different search approaches [internet]. 29.05.2019 [cited: 29.05.2019]. Available from: <http://vortal.htai.org/?q=node/993>
64. Schlosser RW, Wendt O, Bhavnani S, Nail-Chiwetalu B. Use of information-seeking strategies for developing systematic reviews and engaging in evidence-based practice: the application of traditional and comprehensive Pearl Growing; a review. *Int J Lang Commun Disord* 2006; 41(5): 567-582.
65. Jin L, Hua F, Cao Q. Reporting quality of randomized controlled trial abstracts published in leading laser medicine journals: an assessment using the CONSORT for abstracts guidelines. *Lasers Med Sci* 2016; 31(8): 1583-1590.
66. Huang X, Lin J, Demner-Fushman D. Evaluation of PICO as a knowledge representation for clinical questions. In: American Medical Informatics Association (Ed). AMIA 2006 Symposium Proceedings; 11.-15.11.2006; Washington DC, USA. Bethesda: Curran Associates; 2006. p. 359-363.
67. Whiting P, Westwood M, Burke M, Sterne J, Glanville J. Systematic reviews of test accuracy should search a range of databases to identify primary studies. *J Clin Epidemiol* 2008; 61(4): 357.
68. Crumley ET, Wiebe N, Cramer K, Klassen TP, Hartling L. Which resources should be used to identify RCT/CCTs for systematic reviews: a systematic review. *BMC Med Res Methodol* 2005; 5: 24.
69. Betrán AP, Say L, Gülmezoglu AM, Allen T, Hampson L. Effectiveness of different databases in identifying studies for systematic reviews: experience from the WHO systematic review of maternal morbidity and mortality. *BMC Med Res Methodol* 2005; 5: 6.

70. Lemeshow AR, Blum RE, Berlin JA, Stoto MA, Colditz GA. Searching one or two databases was insufficient for meta-analysis of observational studies. *J Clin Epidemiol* 2005; 58(9): 867-873.
71. Sampson M, Barrowman NJ, Moher D. Should meta-analysts search Embase in addition to Medline? *J Clin Epidemiol* 2003; 56(10): 943-955.
72. Hartling L, Featherstone R, Nuspl M, Shave K, Dryden DM, Vandermeer B. The contribution of databases to the results of systematic reviews: a cross-sectional study. *BMC Med Res Methodol* 2016; 16: 127.
73. Aagaard T, Lund H, Juhl C. Optimizing literature search in systematic reviews: are MEDLINE, EMBASE and CENTRAL enough for identifying effect studies within the area of musculoskeletal disorders? *BMC Med Res Methodol* 2016; 16(1): 161.
74. Halladay CW, Trikalinos TA, Schmid IT, Schmid CH, Dahabreh IJ. Using data sources beyond PubMed has a modest impact on the results of systematic reviews of therapeutic interventions. *J Clin Epidemiol* 2015; 68(9): 1076-1084.
75. Goossen K, Tenckhoff S, Probst P, Grummich K, Mihaljevic AL, Buchler MW et al. Optimal literature search for systematic reviews in surgery. *Langenbecks Arch Surg* 2018; 403(1): 119-129.
76. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [internet]. 10.2014 [cited: 22.12.2016]. Available from: <http://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/developing-NICE-guidelines-the-manual.pdf>
77. De Freitas AE, Herbert RD, Latimer J, Ferreira PH. Searching the LILACS database for Portuguese- and Spanish-language randomized trials in physiotherapy was difficult. *J Clin Epidemiol* 2005; 58(3): 233-237.
78. Waffenschmidt S, Hausner E, Kaiser T. An evaluation of searching the German CCMed database for the production of systematic reviews. *Health Info Libr J* 2010; 27(4): 262-267.
79. Stevinson C, Lawlor DA. Searching multiple databases for systematic reviews: added value or diminishing returns? *Complement Ther Med* 2004; 12(4): 228-232.
80. Pilkington K. Searching for CAM evidence: an evaluation of therapy-specific search strategies. *J Altern Complement Med* 2007; 13(4): 451-459.
81. Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf MI et al. Technical supplement to chapter 4: searching for and selecting studies [internet]. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ et al (Eds). *Cochrane handbook for systematic reviews of interventions: version 6*. 2019 [cited: 18.12.2019]. Available from: <https://training.cochrane.org/handbook>
82. Jenuwine ES, Floyd JA. Comparison of Medical Subject Headings and text-word searches in MEDLINE to retrieve studies on sleep in healthy individuals. *J Med Libr Assoc* 2004; 92(3): 349-353.
83. Kastner M, Wilczynski NL, Walker-Dilks C, McKibbin KA, Haynes B. Age-specific search strategies for Medline. *J Med Internet Res* 2006; 8(4): e25.

84. Gehanno JF, Rollin L, Le Jean T, Louvel A, Darmoni S, Shaw W. Precision and recall of search strategies for identifying studies on return-to-work in Medline. *J Occup Rehabil* 2009; 19(3): 223-230.
85. O'Mara-Eves A, Brunton G, McDaid D, Kavanagh J, Oliver S, Thomas J. Techniques for identifying cross-disciplinary and 'hard-to-detect' evidence for systematic review. *Res Syn Meth* 2014; 5(1): 50-59.
86. Crumley E, Blackhall K. Setting up search strategies for systematic reviews (or, how many ways can you spell diarrhea?). *Bib Medica Can* 2003; 24(4): 167-168.
87. Jenkins M. Evaluation of methodological search filters: a review. *Health Info Libr J* 2004; 21(3): 148-163.
88. U.S. National Library of Medicine. MeSH [internet]. [cited: 09.07.2019]. Available from: <https://www.ncbi.nlm.nih.gov/mesh>
89. Thompson J, Davis J, Mazerolle L. A systematic method for search term selection in systematic reviews. *Res Syn Meth* 2014; 5(2): 87-97.
90. Stansfield C, O'Mara-Eves A, Thomas J. Text mining for search term development in systematic reviewing: a discussion of some methods and challenges. *Res Syn Meth* 2017; 8(3): 355-365.
91. Paynter RA, Bañez LL, E. B, Erinoff E, Lege-Matsuura J, Potter S et al. EPC methods: an exploration of the use of text-mining software in systematic reviews; AHRQ publication no 16-EHC023-EF [internet]. 04.2016 [cited: 22.12.2016]. Available from: [https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/text-mining\\_white-paper.pdf](https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/text-mining_white-paper.pdf)
92. Glanville J, Wood H. Text mining opportunities: white paper [internet]. 05.2018 [cited: 24.05.2019]. Available from: [https://www.cadth.ca/sites/default/files/pdf/methods/2018-05/MG0013\\_CADTH\\_Text-Mining\\_Opportunities\\_Final.pdf](https://www.cadth.ca/sites/default/files/pdf/methods/2018-05/MG0013_CADTH_Text-Mining_Opportunities_Final.pdf)
93. Mesgarpour B, Mesgarpour M, Müller M, Herkner H. Developing software for combining search queries to design efficient search strategies [internet]. In: *Cochrane Colloquium Abstracts: 19th Cochrane Colloquium; 19.-22.10.2011; Madrid, Spain.* [cited: 22.12.2016]. Available from: <http://abstracts.cochrane.org/2011-madrid/developing-software-combining-search-queries-design-efficient-search-strategies>
94. Damarell RA, Tieman J, Sladek RM, Davidson PM. Development of a heart failure filter for Medline: an objective approach using evidence-based clinical practice guidelines as an alternative to hand searching. *BMC Med Res Methodol* 2011; 11: 12.
95. Petrova M, Sutcliffe P, Fulford KW, Dale J. Search terms and a validated brief search filter to retrieve publications on health-related values in Medline: a word frequency analysis study. *J Am Med Inform Assoc* 2011; 19(3): 479-488.
96. Marshall C. Systematic Review Toolbox [internet]. [cited: 01.04.2019]. Available from: <http://systematicreviewtools.com/>
97. Younger P, Boddy K. When is a search not a search? A comparison of searching the AMED complementary health database via EBSCOhost, OVID and DIALOG. *Health Info Libr J* 2009; 26(2): 126-135.

98. Damarell RA, May N, Hammond S, Sladek RM, Tieman JJ. Topic search filters: a systematic scoping review. *Health Info Libr J* 2019; 36(1): 4-40.
99. InterTASC Information Specialists' Sub-Group. The InterTASC Information Specialists' Sub-Group Search Filter Resource [internet]. [cited: 22.12.2016]. Available from: <http://www.york.ac.uk/inst/crd/intertasc/index.htm>
100. Bak G, Mierzwinski-Urban M, Fitzsimmons H, Morrison A, Maden-Jenkins M. A pragmatic critical appraisal instrument for search filters: introducing the CADTH CAI. *Health Info Libr J* 2009; 26(3): 211-219.
101. Glanville J, Bayliss S, Booth A, Dundar Y, Fernandes H, Fleeman ND et al. So many filters, so little time: the development of a search filter appraisal checklist. *J Med Libr Assoc* 2008; 96(4): 356-361.
102. Wong SSL, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. *J Med Libr Assoc* 2006; 94(4): 451-455.
103. Hausner E, Metzendorf MI, Richter B, Lotz F, Waffenschmidt S. Study filters for non-randomized studies of interventions consistently lacked sensitivity upon external validation. *BMC Med Res Methodol* 2018; 18: 171.
104. Relevo R. Chapter 4: effective search strategies for systematic reviews of medical tests. *J Gen Intern Med* 2012; 27(Suppl 1): S28-S32.
105. Waffenschmidt S, Guddat C. Searches for randomized controlled trials of drugs in MEDLINE and EMBASE using only generic drug names compared with searches applied in current practice in systematic reviews. *Res Syn Meth* 2015; 6(2): 188-194.
106. Janzen T, Hausner E, Waffenschmidt S. Entwicklung und Evaluation von RCT- und SR-Filtern für die Suche nach nicht verschlagworteten Datensätzen in PubMed [internet]. In: *Entscheiden trotz Unsicherheit: 14. Jahrestagung des Deutschen Netzwerks Evidenzbasierte Medizin; 15.-16.03.2013; Berlin, Deutschland. 11.03.2013* [cited: 22.12.2016]. Available from: <http://www.egms.de/static/de/meetings/ebm2013/13ebm059.shtml>
107. Damarell RA, Tieman JJ, Sladek RM. OvidSP Medline-to-PubMed search filter translation: a methodology for extending search filter range to include PubMed's unique content. *BMC Med Res Methodol* 2013; 13: 86.
108. DeLuca JB, Mullins MM, Lyles CM. Developing a comprehensive search strategy for evidence based systematic reviews. *Evid Based Libr Inf Pract* 2008; 3(1): 3-32.
109. Bradley SM. Examination of the clinical queries and systematic review "hedges" in EMBASE and MEDLINE. *Journal of the Canadian Health Libraries Association* 2010; 31(2): 27-37.
110. Wanner A, Baumann N. Design and implementation of a tool for conversion of search strategies between PubMed and Ovid MEDLINE. *Res Synth Methods* 2019; 10(2): 154-160.
111. Bond University, Centre for Evidence-Based Practice. Systematic review accelerator: polyglot search [internet]. [cited: 16.05.2019]. Available from: <http://crebp-sra.com/#/polyglot>

112. Relevo R, Paynter R. Peer review of search strategies: methods research report; AHRQ publication no. 12-EHC068-EF [internet]. 06.2012 [cited: 22.12.2016]. Available from: [http://effectivehealthcare.ahrq.gov/ehc/products/342/1131/Peer-Review-of-Search-Strategies\\_FinalMethodsReport\\_20120607.pdf](http://effectivehealthcare.ahrq.gov/ehc/products/342/1131/Peer-Review-of-Search-Strategies_FinalMethodsReport_20120607.pdf)
113. Spry C, Mierzwinski-Urban M. The impact of the peer review of literature search strategies in support of rapid review reports. *Res Synth Methods* 2018; 9(4): 521-526.
114. Thomson Reuters. Endnote [internet]. [cited: 22.12.2016]. Available from: <http://endnote.com>
115. ProQuest. RefWorks [internet]. [cited: 22.12.2016]. Available from: <https://www.refworks.com/>
116. Mendeley. Mendeley [internet]. [cited: 22.12.2016]. Available from: <https://www.mendeley.com>
117. Kern MK, Hensley MK. Citation management software. *Reference and User Services Quarterly* 2011; 50(3): 204-208.
118. Gilmour R, Cobus-Kuo L. Reference management software: a comparative analysis of four products. *Issues in Science and Technology Librarianship* 2011; (66): DOI: 10.5062/F5064Z5060KZF.
119. Lorenzetti DL, Ghali WA. Reference management software for systematic reviews and meta-analyses: an exploration of usage and usability. *BMC Med Res Methodol* 2013; 13: 141.
120. Hernandez DA, El-Masri MM, Hernandez CA. Choosing and using citation and bibliographic database software (BDS). *Diabetes Educ* 2008; 34(3): 457-474.
121. Qi X, Yang M, Ren W, Jia J, Wang J, Han G et al. Find duplicates among the PubMed, EMBASE, and Cochrane Library Databases in Systematic Review. *PLoS One* 2013; 8(8): e71838.
122. Bramer WM, Giustini D, De Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. *J Med Libr Assoc* 2016; 104(3): 240-243.
123. Wolters Kluwer. Ovid database shortnames [internet]. 2014 [cited: 22.12.2016]. Available from: [http://resourcecenter.ovid.com/site/support/ovid\\_db\\_shortnames.jsp](http://resourcecenter.ovid.com/site/support/ovid_db_shortnames.jsp)
124. Waffenschmidt S, Bühn S, Knelangen M, Sieben W, Pieper D. Single screening versus conventional double screening for study selection in systematic reviews: a methodological systematic review [in press]. *BMC Med Res Methodol* 2019.
125. O'Mara-Eves A, Thomas J, McNaught J, Miwa M, Ananiadou S. Using text mining for study identification in systematic reviews: a systematic review of current approaches. *Syst Rev* 2015; 4: 5.
126. RobotSearch RCT classifier [internet]. [cited: 09.07.2019]. Available from: <https://robotsearch.vortext.systems>

127. Cochrane Register of Studies. Quick ref guides RCT classifier example: for authors [internet]. [cited: 01.04.2019]. Available from: <https://community.cochrane.org/sites/default/files/uploads/inline-files/E5%20RCT%20classifier%20example%20-%20for%20authors.pdf>
128. Wallace BC, Noel-Storr A, Marshall IJ, Cohen AM, Smalheiser NR, Thomas J. Identifying reports of randomized controlled trials (RCTs) via a hybrid machine learning and crowdsourcing approach. *J Am Med Inform Assoc* 2017; 24(6): 1165-1168.
129. Marshall IJ, Noel-Storr A, Kuiper J, Thomas J, Wallace BC. Machine learning for identifying randomized controlled trials: an evaluation and practitioner's guide. *Res Syn Meth* 9(4): 602-614.
130. Booth A, Papaioannou D, Sutton A. Systematic approaches to a successful literature review. London: Sage; 2012.
131. Shojania KG, Sampson M, Ansari MT, Ji J, Garritty C, Doucette S et al. Updating systematic reviews: AHRQ publication no 07-0087 [internet]. 09.2007 [cited: 22.12.2016]. (AHRQ Technical Reviews; volume 16). Available from: <http://www.ncbi.nlm.nih.gov/books/NBK44099/pdf/TOC.pdf>
132. Shojania KG, Sampson M, Ansari MT, Ji J, Doucette S, Moher D. How quickly do systematic reviews go out of date? A survival analysis. *Ann Intern Med* 2007; 147(4): 224-233.
133. Sampson M, Shojania KG, Garritty C, Horsley T, Ocampo M, Moher D. Systematic reviews can be produced and published faster. *J Clin Epidemiol* 2008; 61(6): 531-536.
134. Sampson M, Shojania KG, McGowan J, Daniel R, Rader T, Iansavichene AE et al. Surveillance search techniques identified the need to update systematic reviews. *J Clin Epidemiol* 2008; 61(8): 755-762.
135. Sampson M. Leverage your evidence: analyze the evidence base of your systematic review to inform the update search [internet]. In: Cochrane Colloquium Abstracts: 17th Cochrane Colloquium; 11.-14.10.2009; Singapore. [cited: 22.12.2016]. Available from: <http://abstracts.cochrane.org/2009-singapore/leverage-your-evidence-analyze-evidence-base-your-systematic-review-inform-update>
136. Bergerhoff K, Ebrahim S, Paletta G. Fishing for citations: catching them all? Do we need to consider 'In Process Citations' for search strategies? [internet]. In: Cochrane Colloquium Abstracts: 12th Cochrane Colloquium; 02.-06.10.2004; Ottawa, Canada. [cited: 22.12.2016]. Available from: <http://abstracts.cochrane.org/2004-ottawa/do-we-need-consider-process-citations-search-strategies>
137. De Angelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R et al. Is this clinical trial fully registered? A statement from the International Committee of Medical Journal Editors. *Ann Intern Med* 2005; 143(2): 146-148.
138. Food and Drug Administration. Food and Drug Administration Amendments Act of 2007: public law 110-85 [internet]. 27.09.2007 [cited: 22.12.2016]. Available from: <http://www.gpo.gov/fdsys/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf>

139. National Institutes of Health, Department of Health and Human Services. Clinical trials registration and results information submission: final rule. Fed Regist 2016; 81(183): 64981-65157.
140. Zarin DA, Tse T, Williams RJ, Carr S. Trial reporting in ClinicalTrials.gov: the final rule. N Engl J Med 2016; 375(20): 1998-2004.
141. Tse T, Fain KM, Zarin DA. How to avoid common problems when using ClinicalTrials.gov in research: 10 issues to consider. BMJ 2018; 361: k1452.
142. European Medicines Agency. EU Clinical Trials Register [internet]. [cited: 22.12.2016]. Available from: <https://www.clinicaltrialsregister.eu/ctr-search/search>
143. European Medicines Agency. Posting of clinical trial summary results in European Clinical Trials Database (EudraCT) to become mandatory for sponsors as of 21 July 2014 [internet]. 19.06.2014 [cited: 22.12.2016]. Available from: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2014/06/news\\_detail\\_002127.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/06/news_detail_002127.jsp&mid=WC0b01ac058004d5c1)
144. Goldacre B, DeVito NJ, Heneghan C, Irving F, Bacon S, Fleminger J et al. Compliance with requirement to report results on the EU Clinical Trials Register: cohort study and web resource. BMJ 2018; 362: k3218.
145. Korevaar DA, Bossuyt PM, Hooft L. Infrequent and incomplete registration of test accuracy studies: analysis of recent study reports. BMJ Open 2014; 4(1): e004596.
146. Knelangen M, Hausner E, Metzendorf MI, Sturtz S, Waffenschmidt S. Trial registry searches for randomized controlled trials of new drugs required registry-specific adaptation to achieve adequate sensitivity. J Clin Epidemiol 2018; 94: 69-75.
147. Miller JE, Korn D, Ross JS. Clinical trial registration, reporting, publication and FDAAA compliance: a cross-sectional analysis and ranking of new drugs approved by the FDA in 2012. BMJ Open 2015; 5(11): e009758.
148. World Health Organization. International Clinical Trials Search Portal [internet]. [cited: 22.12.2016]. Available from: <http://apps.who.int/trialsearch>
149. Deutsches Institut für Medizinische Dokumentation und Information. Deutsches Register Klinischer Studien (DRKS) [internet]. [cited: 30.09.2019]. Available from: [https://www.drks.de/drks\\_web/](https://www.drks.de/drks_web/)
150. Dutch Cochrane Center. Nederlands Trial Register [internet]. [cited: 22.12.2016]. Available from: <http://www.trialregister.nl/trialreg/index.asp>
151. Spanish Agency of Medicines and Health Products. Spanish Clinical Studies Registry [internet]. [cited: 14.05.2019]. Available from: <https://reec.aemps.es/reec/public/web.html>
152. U.S. National Library of Medicine. ClinicalTrials.gov [internet]. [cited: 22.12.2016]. Available from: <http://clinicaltrials.gov>
153. GlaxoSmithKline. GSK Clinical Study Register [internet]. [cited: 22.12.2016]. Available from: <http://www.gsk-clinicalstudyregister.com>

154. Forest Laboratories. Forest Laboratories Clinical Trials Registry [internet]. [cited: 22.12.2016]. Available from: <http://www.forestclinicaltrials.com>
155. Cochrane Dementia and Cognitive Improvement Group. ALOIS: a comprehensive register of dementia studies [internet]. [cited: 22.12.2016]. Available from: <http://www.medicine.ox.ac.uk/alois>
156. Chan AW. Out of sight but not out of mind: how to search for unpublished clinical trial evidence. *BMJ* 2012; 344: d8013.
157. Ramagopalan SV, Skingsley AP, Handunnetthi L, Magnus D, Klingel M, Pakpoor J et al. Funding source and primary outcome changes in clinical trials registered on ClinicalTrials.gov are associated with the reporting of a statistically significant primary outcome: a cross-sectional study. *F1000Res* 2015; 4: 80.
158. Ramagopalan S, Skingsley AP, Handunnetthi L, Klingel M, Magnus D, Pakpoor J et al. Prevalence of primary outcome changes in clinical trials registered on ClinicalTrials.gov: a cross-sectional study. *F1000Res* 2014; 3: 77.
159. Chi C. Shall we search all trial registers? A comparative study of the sensitivity of five trial registers used by the Cochrane Skin Group [internet]. In: Cochrane Colloquium Abstracts: 20th Cochrane Colloquium; 30.09.-03.10.2012; Auckland, New Zealand. [cited: 22.12.2016]. Available from: <http://abstracts.cochrane.org/2012-auckland/shall-we-search-all-trial-registers-comparative-study-sensitivity-five-trial-registers>
160. Alturki R, Schandelmaier S, Olu KK, Von Niederhausern B, Agarwal A, Frei R et al. Premature trial discontinuation often not accurately reflected in registries: comparison of registry records with publications. *J Clin Epidemiol* 2017; 81: 56-63.
161. Dal-Re R, Ross JS, Marusic A. Compliance with prospective trial registration guidance remained low in high-impact journals and has implications for primary endpoint reporting. *J Clin Epidemiol* 2016; 75: 100-107.
162. Boccia S, Rothman KJ, Panic N, Flacco ME, Rosso A, Pastorino R et al. Registration practices for observational studies on ClinicalTrials.gov indicated low adherence. *J Clin Epidemiol* 2016; 70: 176-182.
163. Smail-Faugeron V, Fron-Chabouis H, Durieux P. Clinical trial registration in oral health journals. *J Dent Res* 2015; 94(3 Suppl): 8S-13S.
164. Su CX, Han M, Ren J, Li WY, Yue SJ, Hao YF et al. Empirical evidence for outcome reporting bias in randomized clinical trials of acupuncture: comparison of registered records and subsequent publications. *Trials* 2015; 16: 28.
165. De Oliveira GS Jr, Jung MJ, McCarthy RJ. Discrepancies between randomized controlled trial registry entries and content of corresponding manuscripts reported in anesthesiology journals. *Anesth Analg* 2015; 121(4): 1030-1033.
166. Veitch E. Silent takedown of the pharma trials database...and more [internet]. In: PLOS Medical Journals' Community Blog. 23.03.2012 [cited: 22.12.2016]. Available from: <http://blogs.plos.org/speakingofmedicine/2012/03/23/silent-takedown-of-the-pharma-trials-database%E2%80%A6and-more>

167. International Federation of Pharmaceutical Manufacturers & Associations. IFPMA Clinical Trials Portal discontinued, visitors will be re-directed to the WHO International Clinical Trials Registry Platform [internet]. [cited: 15.07.2014]. Available from: <http://www.ifpma.org/ethics/clinical-trials-disclosure.html>
168. Van Enst WA, Scholten RJ, Hooft L. Identification of additional trials in prospective trial registers for Cochrane systematic reviews. *PLoS One* 2012; 7(8): e42812.
169. Jones CW, Keil LG, Weaver MA, Platts-Mills TF. Clinical trials registries are under-utilized in the conduct of systematic reviews: a cross-sectional analysis. *Syst Rev* 2014; 3: 126.
170. Keil LG, Platts-Mills TF, Jones CW. Systematic reviews published in emergency medicine journals do not routinely search clinical trials registries: a cross-sectional analysis. *Ann Emerg Med* 2015; 66(4): 424-427.e2.
171. Potthast R, Vervölgyi V, McGauran N, Kerekes MF, Wieseler B, Kaiser T. Impact of inclusion of industry trial results registries as an information source for systematic reviews. *PLoS One* 2014; 9(4): e92067.
172. Glanville J, Duffy S, McCool R, Varley D. Searching ClinicalTrials.gov and the International Clinical Trials Registry Platform to inform systematic reviews: what are the optimal search approaches? *J Med Libr Assoc* 2014; 102(3): 177-183.
173. Tai FM, Willson ML, Gherzi D. Implications of searching multiple trial registries: how should we search ClinicalTrials.gov and WHO ICTRP? [internet]. In: *Cochrane Colloquium Abstracts: 20th Cochrane Colloquium; 30.09.-03.10.2012; Auckland, New Zealand.* [cited: 22.12.2016]. Available from: <http://abstracts.cochrane.org/2012-auckland/implications-searching-multiple-trial-registries-how-should-we-search>
174. Hardt JL, Metzendorf MI, Meerpohl JJ. Surgical trials and trial registers: a cross-sectional study of randomized controlled trials published in journals requiring trial registration in the author instructions. *Trials* 2013; 14: 407.
175. Hausner E. Problems encountered with ICTRP Search Portal; Comment on: "Van Enst WA, Scholten RJ, Hooft L. Identification of additional trials in prospective trial registers for Cochrane systematic reviews (PLoS One 2012; 7(8): e42812)." [internet]. 23.07.2014 [cited: 22.12.2016]. Available from: <http://www.plosone.org/annotation/listThread.action?root=81099>
176. Hausner E, Kaiser T. Suche in Studienregistern: Ablauf und Dokumentation. *Z Evid Fortbild Qual Gesundhwes* 2010; 104(4): 292-297.
177. Menezes AS, Barnes A, Scheer AS, Martel G, Moloo H, Boushey RP et al. Clinical research in surgical oncology: an analysis of ClinicalTrials.gov. *Ann Surg Oncol* 2013; 20(12): 3725-3731.
178. York Health Economics Consortium. Finding clinical trials, research registers and research results [internet]. [cited: 22.12.2016]. Available from: <https://sites.google.com/a/york.ac.uk/yhectrialsregisters>
179. Wieseler B, Wolfram N, McGauran N, Kerekes MF, Vervölgyi V, Kohlepp P et al. Completeness of reporting of patient-relevant clinical trial outcomes: comparison of

unpublished clinical study reports with publicly available data. PLoS Med 2013; 10(10): e1001526.

180. Doshi P, Jefferson T, Del Mar C. The imperative to share clinical study reports: recommendations from the Tamiflu experience. PLoS Med 2012; 9(4): e1001201.

181. Doshi P, Jefferson T. Clinical study reports of randomised controlled trials: an exploratory review of previously confidential industry reports. BMJ Open 2013; 3(2): e002496.

182. Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database Syst Rev 2014; (4): CD008965.

183. Goldacre B, Lane S, Mahtani KR, Heneghan C, Onakpoya I, Bushfield I et al. Pharmaceutical companies' policies on access to trial data, results, and methods: audit study. BMJ 2017; 358: j3334.

184. GlaxoSmithKline. Clinical study report compounds [internet]. [cited: 22.12.2016]. Available from: <http://www.gsk-clinicalstudyregister.com/compounds/a-f/clinicalstudyreport>

185. Clinical Study Data Request. ClinicalStudyDataRequest.com [internet]. [cited: 22.12.2016]. Available from: <https://www.clinicalstudydatarequest.com>

186. Center for Outcomes Research and Evaluation. The Yoda Project [internet]. [cited: 02.08.2017]. Available from: <http://yoda.yale.edu/>

187. Mayo-Wilson E, Doshi P, Dickersin K. Are manufacturers sharing data as promised? BMJ 2015; 351: h4169.

188. Navar AM. Use of open access platforms for clinical trial data. JAMA 2016; 315(12): 1283-1284.

189. Murugiah K, Ritchie JD, Desai NR, Ross JS, Krumholz HM. Availability of clinical trial data from industry-sponsored cardiovascular trials. J Am Heart Assoc 2016; 5(4): e003307.

190. Boutron I, Dechartres A, Baron G, Li J, Ravaud P. Sharing of data from industry-funded registered clinical trials. JAMA 2016; 315(24): 2729-2730.

191. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [internet]. 10.07.2017 [cited: 20.03.2019]. Available from: [https://www.iqwig.de/download/General-Methods\\_Version-5-0.pdf](https://www.iqwig.de/download/General-Methods_Version-5-0.pdf)

192. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. IQWiG bietet Medizinprodukteherstellern Vereinbarung für mehr Transparenz an [internet]. 14.11.2017 [cited: 17.11.2017]. Available from: <https://www.iqwig.de/de/presse/pressemitteilungen/pressemitteilungen/iqwig-bietet-medizinprodukteherstellern-vereinbarung-fur-mehr-transparenz-an.8159.html>

193. Institute for Quality and Efficiency in Health Care. Agreement upon manufacturer data [internet]. 26.08.2005 [cited: 17.11.2017]. Available from: [https://www.iqwig.de/en/press/press\\_releases/press\\_releases/agreement\\_upon\\_manufacturer\\_data.2246.html](https://www.iqwig.de/en/press/press_releases/press_releases/agreement_upon_manufacturer_data.2246.html)

194. Schroll JB, Bero L, Gøtzsche PC. Searching for unpublished data for Cochrane reviews: cross sectional study. *BMJ* 2013; 346: f2231.
195. McDonagh MS, Peterson K, Balshem H, Helfand M. US Food and Drug Administration documents can provide unpublished evidence relevant to systematic reviews. *J Clin Epidemiol* 2013; 66(10): 1071-1081.
196. Jefferson T, Doshi P, Boutron I, Golder S, Heneghan C, Hodgkinson A et al. When to include clinical study reports and regulatory documents in systematic reviews. *BMJ Evid Based Med* 2018; 23(6): 210-217.
197. European Parliament, Council Of The European Union. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. *Official Journal of the European Union* 2014; L158(1): 1-76.
198. European Medicines Agency. Clinical data publication [internet]. [cited: 14.01.2019]. Available from: <https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/clinical-data-publication>
199. European Medicines Agency. European Medicines Agency policy on publication of clinical data for medicinal products for human use [internet]. 02.10.2014 [cited: 17.11.2017]. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2014/10/WC500174796.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf)
200. European Medicines Agency. Clinical data [internet]. [cited: 02.08.2017]. Available from: <https://clinicaldata.ema.europa.eu/web/cdp/home>
201. Health Canada. Search for clinical information on drugs and medical devices [internet]. 12.03.2019 [cited: 23.05.2019]. Available from: <https://clinical-information.canada.ca/search/ci-rc>
202. Doshi P. FDA to begin releasing clinical study reports in pilot programme. *BMJ* 2018; 360: k294.
203. Jefferson T, Doshi P, Thompson M, Heneghan C. Ensuring safe and effective drugs: who can do what it takes? *BMJ* 2011; 342: c7258.
204. European Medicines Agency. Medicines [internet]. [cited: 14.05.2019]. Available from: <https://www.ema.europa.eu/en/medicines>
205. Food and Drug Administration. Drugs@FDA [internet]. [cited: 22.12.2016]. Available from: <http://www.accessdata.fda.gov/scripts/cder/daf/>
206. Health Canada. The Drug and Health Product Register [internet]. 30.01.2019 [cited: 20.03.2019]. Available from: <https://hpr-rps.hres.ca/index.php>
207. Pharmaceuticals and Medical Devices Agency Japan. Approved products [internet]. [cited: 22.12.2016]. Available from: <http://www.pmda.go.jp/english/service/approved.html>
208. European Commission. Market surveillance and vigilance: Eudamed2; European Databank on Medical Devices [internet]. [cited: 14.05.2019]. Available from:

[https://ec.europa.eu/growth/sectors/medical-devices/current-directives/market-surveillance\\_en#eudamed](https://ec.europa.eu/growth/sectors/medical-devices/current-directives/market-surveillance_en#eudamed)

209. National Institute for Health and Care Excellence. Find guidance [internet]. [cited: 22.12.2016]. Available from: <http://www.nice.org.uk/guidance>

210. Food and Drug Administration. Devices@FDA [internet]. [cited: 22.12.2016]. Available from: <http://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm>

211. Restoring Invisible & Abandoned Trials. RIAT Support Center [internet]. [cited: 05.04.2019]. Available from: <https://restoringtrials.org/>

212. Turner EH. How to access and process FDA drug approval packages for use in research. *BMJ* 2013; 347: f5992.

213. Ladanie A, Ewald H, Kasenda B, Hemkens LG. How to use FDA drug approval documents for evidence syntheses. *BMJ* 2018; 362: k2815.

214. Le Cleach L, Doney E, Katz KA, Williams HC, Trinquart L. Research techniques made simple: workflow for searching databases to reduce evidence selection bias in systematic reviews. *J Invest Dermatol* 2016; 136(12): e125-e129.

215. Schroll JB, Abdel-Sattar M, Bero L. The Food and Drug Administration reports provided more data but were more difficult to use than the European Medicines Agency reports. *J Clin Epidemiol* 2015; 68(1): 102-107.

216. Goldacre B, Turner E. You can now search FDA approval documents easily at [fda.opentrials.net](http://fda.opentrials.net). *BMJ* 2017; 356: j677.

217. Mullan RJ, Flynn DN, Carlberg B, Tleyjeh IM, Kamath CC, LaBella ML et al. Systematic reviewers commonly contact study authors but do so with limited rigor. *J Clin Epidemiol* 2009; 62(2): 138-142.

218. Young T, Hopewell S. Methods for obtaining unpublished data. *Cochrane Database Syst Rev* 2011; (11): MR000027.

219. Godard-Sebillotte C, Le Berre M, Karunanathan S, Hong QN, Vedel I. A digital media strategy to obtain unpublished data for a systematic review yields a very high author response rate. *J Clin Epidemiol* 2018; 104: 141-143.

220. Reveiz L, Cardona AF, Ospina EG, De Agular S. An e-mail survey identified unpublished studies for systematic reviews. *J Clin Epidemiol* 2006; 59(7): 755-758.

221. Hinde S, Spackman E. Bidirectional citation searching to completion: an exploration of literature searching methods. *Pharmacoeconomics* 2015; 33(1): 5-11.

222. Horsley T, Dingwall O, Sampson M. Checking reference lists to find additional studies for systematic reviews. *Cochrane Database Syst Rev* 2011; (1): MR000026.

223. Janssens AC, Gwinn M. Novel citation-based search method for scientific literature: application to meta-analyses. *BMC Med Res Methodol* 2015; 15: 84.

224. Scherer RW, Meerpohl JJ, Pfeifer N, Schmucker C, Schwarzer G, Von Elm E. Full publication of results initially presented in abstracts. *Cochrane Database Syst Rev* 2018; (11): MR000005.
225. Dundar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson P. Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies. *Health Technol Assess* 2006; 10(5): iii-iv, ix-145.
226. Toma M, McAlister FA, Bialy L, Adams D, Vandermeer B, Armstrong PW. Transition from meeting abstract to full-length journal article for randomized controlled trials. *JAMA* 2006; 295(11): 1281-1287.
227. Saldanha IJ, Scherer RW, Rodriguez-Barraquer I, Jampel HD, Dickersin K. Dependability of results in conference abstracts of randomized controlled trials in ophthalmology and author financial conflicts of interest as a factor associated with full publication. *Trials* 2016; 17: 213.
228. McAuley L, Pham B, Tugwell P, Moher D. Does the inclusion of grey literature influence estimates of intervention effectiveness reported in meta-analyses? *Lancet* 2000; 356(9237): 1228-1231.
229. Scherer RW, Saldanha IJ. How should systematic reviewers handle conference abstracts? A view from the trenches. *Syst Rev* 2019; 8(1): 264.
230. Wright JM, Cottrell DJ, Mir G. Searching for religion and mental health studies required health, social science, and grey literature databases. *J Clin Epidemiol* 2014; 67(7): 800-810.
231. Vickers AJ, Smith C. Incorporating data from dissertations in systematic reviews. *Int J Technol Assess Health Care* 2000; 16(2): 711-713.
232. Hartling L, Featherstone R, Nuspl M, Shave K, Dryden DM, Vandermeer B. Grey literature in systematic reviews: a cross-sectional study of the contribution of non-English reports, unpublished studies and dissertations to the results of meta-analyses in child-relevant reviews. *BMC Med Res Methodol* 2017; 17: 64.
233. Rethlefsen M, Koffel J, Kirtley S, Waffenschmidt S, Ayala A. PRISMA-S draft 1: checklist table format 1.0.pdf [internet]. 20.03.2019 [cited: 28.05.2019]. Available from: <https://doi.org/10.17605/OSF.IO/7NCYS>
234. Rethlefsen M, Koffel J, Kirtley S, Waffenschmidt S, Ayala A. Preferred Reporting Items for Systematic review and Meta-Analysis Searches (PRISMA-S) 2019: elaboration and explanation; version 1.0 [internet]. 10.04.2019 [cited: 28.05.2019]. Available from: <https://doi.org/10.31219/osf.io/sfc38>
235. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; 339: b2700.
236. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007; 7: 10.

237. Tricco AC, Langlois EV, Straus SE. Rapid reviews to strengthen health policy and systems: a practical guide [internet]. Available from: <http://apps.who.int/iris/bitstream/10665/258698/1/9789241512763-eng.pdf?ua=1>
238. Robinson KA, Whitlock EP, O'Neil ME, Anderson JK, Hartling L, Dryden DM et al. Integration of existing systematic reviews: research white paper; AHRQ publication no. 14-EHC016-EF [internet]. 06.2014 [cited: 23.05.2019]. Available from: [https://www.ncbi.nlm.nih.gov/books/NBK216379/pdf/Bookshelf\\_NBK216379.pdf](https://www.ncbi.nlm.nih.gov/books/NBK216379/pdf/Bookshelf_NBK216379.pdf)
239. Cosford PA, Leng GC. Screening for abdominal aortic aneurysm. Cochrane Database Syst Rev 2007; (2): CD002945.
240. Agenzia Nazionale per i Servizi Sanitari Regionali. Abdominal aorta aneurysm screening [internet]. In: HTA Core Model Online. 31.01.2013 [cited: 22.12.2016]. Available from: <http://mekat.thl.fi/htacore/106.aspx>
241. Takagi H, Goto SN, Matsui M, Manabe H, Umemoto T. A further meta-analysis of population-based screening for abdominal aortic aneurysm. J Vasc Surg 2010; 52(4): 1103-1108.
242. Health Information Research Unit. Search filters for MEDLINE in Ovid syntax and the PubMed translation [internet]. 30.04.2013 [cited: 22.12.2016]. Available from: [http://hiru.mcmaster.ca/hiru/HIRU\\_Hedges\\_MEDLINE\\_Strategies.aspx](http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx)
243. Hausner E, Ebrahim S, Herrmann-Frank A, Janzen T, Kerekes MF, Pischedda M et al. Study selection by means of a web-based Trial Selection DataBase (webTSDB) [internet]. In: Cochrane Colloquium Abstracts: 19th Cochrane Colloquium; 19.-22.10.2011; Madrid, Spain. [cited: 22.12.2016]. Available from: <http://abstracts.cochrane.org/2011-madrid/study-selection-means-web-based-trial-selection-database-webtsdb>

## Annexe 2. Documentation of the literature search

### Auto alert

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

#	Searches
1	(Semi-automated or data mining or (Capture adj3 recapture) or machine learning).ab,ti.
2	(search adj3 (strateg* or term* or filter*)).ab,ti.
3	(query or queries).ab,ti.
4	search*.ti.
5	or/1-4
6	exp "Information Storage and Retrieval"/
7	"Medical Subject Headings"/
8	"Abstracting and Indexing as Topic"/
9	Documentation/
10	reporting.ab,ti.
11	(bibliographic databas* or Pubmed).ab,ti.
12	(MeSH or controlled vocabulary or indexing).ab,ti.
13	or/6-12
14	"Review Literature as Topic"/
15	exp "Evidence-Based Practice"/
16	"Technology Assessment, Biomedical"/
17	or/14-16
18	and/5,13,17
19	exp *"Information Storage and Retrieval"/
20	4 and (16 or 19)
21	(Medline or PubMed).ti.
22	(Clinical Queries or Haynes or hedge or search).ti,ab.
23	and/21-22
24	or/18,20,23

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

#	Searches
1	exp Databases, Bibliographic/
2	(medline* or pubmed* or embase* or cochrane* or cinahl* or psycinfo* or amed* or google* or pedro*).ti.
3	1 or 2
4	exp "Information Storage and Retrieval"/
5	(systematic and search*).ab,ti.
6	or/4-5
7	review*.ab,ti.
8	Review Literature as Topic/
9	Meta-Analysis as Topic/
10	Evidence-Based Medicine/
11	*Randomized Controlled Trials as Topic/
12	or/7-11
13	and/3,6,12

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

#	Searches
1	clinicaltrials*.ti.
2	unpublished.ti.
3	(handsearch* or hand search* or reference list*).ti.
4	((full or abstract or bias) adj3 publication).ti.
5	or/1-4
6	Registries/
7	*Databases, Factual/
8	(clinicaltrials* or trial* registr* or ICTRP or European Medicines Agency).ti,ab.
9	6 or 7 or 8
10	Clinical Trials as Topic/
11	*Randomized Controlled Trials as Topic/
12	9 and (10 or 11)
13	5 or 12

## Annexe 3. 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 of 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 SRs 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 [239]) was identified that precisely covers the research question (Figure 2).

The screenshot displays the Cochrane Library search interface. At the top, there are tabs for 'Search', 'Search manager', and 'Medical terms (MeSH)'. A 'Simple search' box is highlighted, containing the search term 'Ultrasound screening and abdominal aortic aneurysms'. Below the search box, there are buttons for 'Save search', 'View searches', and 'Search help'. A 'Clear all' button is also visible. The search results are displayed in a table with columns for 'Cochrane Reviews' (2), 'Cochrane Protocols' (0), 'Trials' (48), 'Editorials' (0), and 'Special collections' (0). The results are filtered by 'Relevancy' and 'Results per page' is set to 25. The first result is 'Screening for abdominal aortic aneurysm' by Paul A Cosford, Gillian C Leng, and Justyn Thomas, published in the Cochrane Database of Systematic Reviews, Issue 4 of 12, April 2019. The second result is 'Medical treatment for small abdominal aortic aneurysms' by Guy Rughani, Lindsay Robertson, and Mike Clarke, published in the Cochrane Database of Systematic Reviews, Issue 12, September 2012.

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 SRs [240,241].

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 SRs 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 SRs 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 SR.

The search was structured as follows

Concept 1 (indication): abdominal aortic aneurysm

Concept 2 (intervention): ultrasound screening

Concept 3 (study type): 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.

Other subject-specific or regional databases were not selected.

Table 4: Databases and interfaces

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

## 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.

Left	Indication	Hits	Right
abdominal	AORTIC	25	aneurysm/s
	ABDOMINAL	25	aortic aneurysm/s, aorta
abdominal aortic, aortic	ANEURYSM	23	abdominal aorta
abdominal aortic, aortic	ANEURYSMS	15	
abdominal	AORTA	5	

Words commonly occur in this group of words

Figure 3: Common terms for concept 1

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

Table 5: Phrases and consequences for implementation using the example of MEDLINE via OvidSP

<b>Phrases from Figure 3</b>	<b>Consequences</b>	<b>Example of the search syntax in Ovid</b>
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(s)	<ul style="list-style-type: none"> <li>• “Aneurysm” is used both in the singular and plural form: this term is therefore truncated.</li> <li>• “Aorta” is also used in addition to “aortic”; the word stem “aort” is thus also truncated.</li> </ul>	abdominal adj1 aort* adj1 aneurysm* (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* <b>adj3</b> aneurysm* (final)

### 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).

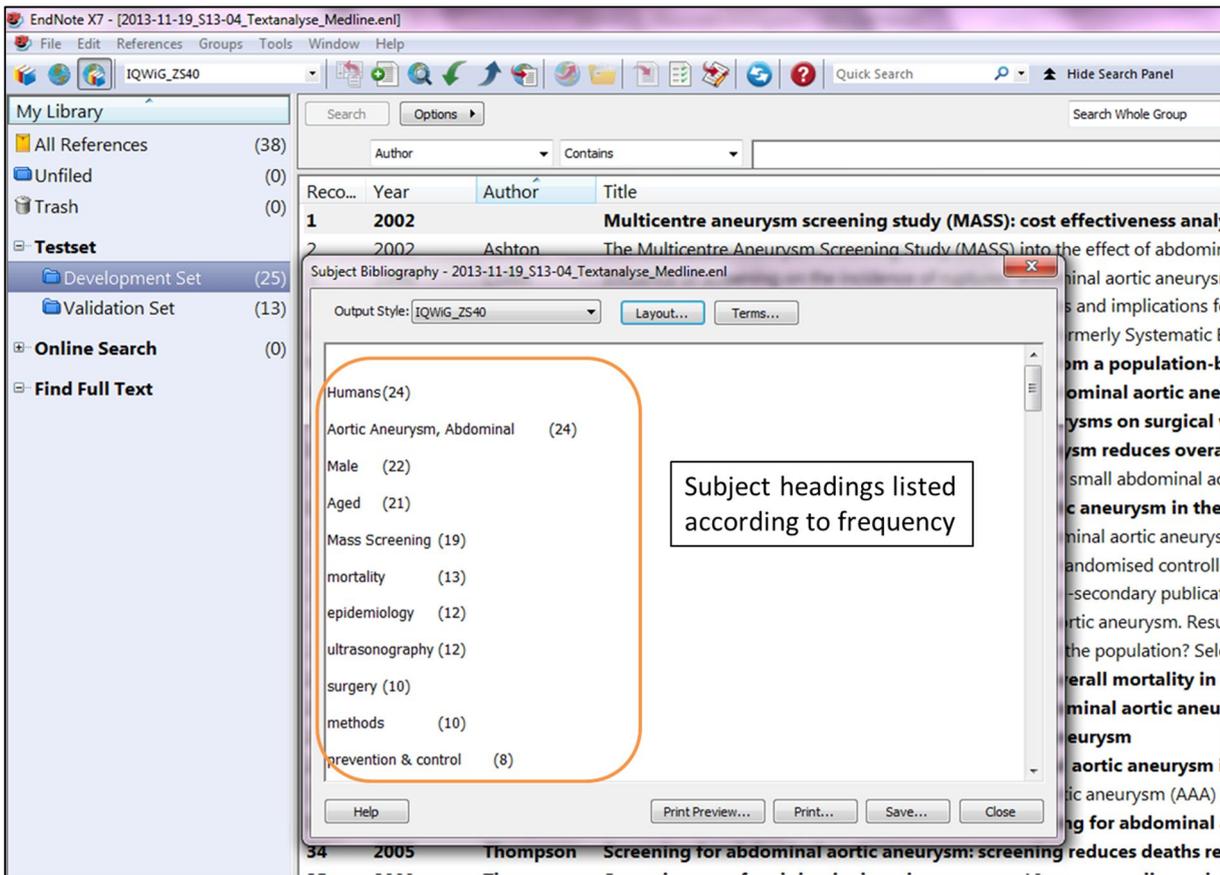


Figure 4: Analysis of subject headings in EndNote via the “Subject Bibliography” function

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

Subject heading	Frequency	
Indication	Hits	Notes
Aortic Aneurysm, Abdominal	24	No narrower subject headings

Information about „subordinate terms“

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) [81].

### 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 6 shows the proximity operators differ depending on the interface. The subject headings were identified separately for each database (see Table 7).

Our example shows the implementation for concept 1:

Table 6: Database- and interface-specific tags for free-text terms

Database (interface)	Free-text terms
MEDLINE and 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 7: Database- and interface-specific tags for subject headings

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[ <i>sb</i> ]”.

The search strategy was organized according to the search concepts used in the 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 8).

Our example shows the implementation for MEDLINE:

Table 8: Structure of search strategy in MEDLINE (Ovid)

#	Searches	Results
1	Aortic Aneurysm, Abdominal/	13646
2	(abdominal* adj1 aort* adj3 aneurysm*).ti,ab.	14046
3	or/1-2 <b>[Concept 1]</b>	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 <b>[Concept 2]</b>	567366
9	randomized controlled trial.pt.	396032
10	controlled clinical trial.pt.	90636
...		
15	or/ 9-15 <b>[Study filter: RCT]</b>	391739
16	and/3,8,15 <b>[Concept 1 AND Concept 2 AND Study filter]</b>	520

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 [20]).

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. The study filter was not changed as no other validated study filter would have found this reference either (HIRU Clinical Queries filters – High sensitivity strategy [102,242], Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision) [81]).

<input type="checkbox"/>	16	14 not 15 [CHSS - sensitivity-maximizing version]	2903085	Advanced	Display	More >>
<input type="checkbox"/>	17	meta analysis.mp.pt.	80620	Advanced	Display	More >>
<input type="checkbox"/>	18	search*.tw.	247360	Advanced	Display	More >>
<input type="checkbox"/>	19	review.pt.	1905103	Advanced	Display	More >>
<input type="checkbox"/>	20	or/17-19 [Wong - Strategy minimizing difference between sensitivity and specificity]	2101835	Advanced	Display	More >>
<input type="checkbox"/>	21	or/16,20	4602378	Advanced	Display	More >>
<input type="checkbox"/>	22	and/9,21	538	Number of hits		More >>
<input type="checkbox"/>	23	("17514666" or "7497157" or "17443519" or "11336846" or "10392481" or "11748949" or "16893663" or "10375481" or "15545293" or "7648155" or "11202589" or "10321373" or "10671927").ui. [Validation Set]	14	Advanced	Display	More >>
<input type="checkbox"/>	24	22 and 23	13	Identified references from validation set		More >>
<input type="checkbox"/>	25	23 not 24	1	References not identified from validation set		More >>

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, saved search strategies could be applied. PubMed was searched for non-indexed references followed by MEDLINE, Embase and the Cochrane Library.

The text files with the references were designated in a standardized manner: date of search, name of project and database (e.g. 2015-07-09\_S1555\_Medline.txt) and the references then imported to 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; [243]). In the first screening step, 623 of the 703 references could be excluded on the abstract and title level, and 80 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 9).

The screenshot shows three overlapping windows of search strategy documentation:

- Medline (Ovid):** Shows search steps 1 through 25, including terms like 'Aortic Aneurysm, Abdominal/' and 'Screening\* .ti,ab'. It includes a table with 25 rows for search steps.
- Embase (Ovid):** Shows search steps 1 through 21, including terms like 'Abdominal Aorta Aneurysm' and 'Screening Test/'. It includes a table with 21 rows for search steps.
- The Cochrane Library:** Shows a table with 17 rows of search results, including columns for ID, Search, and Hits. The results include MeSH descriptors and various search combinations.

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

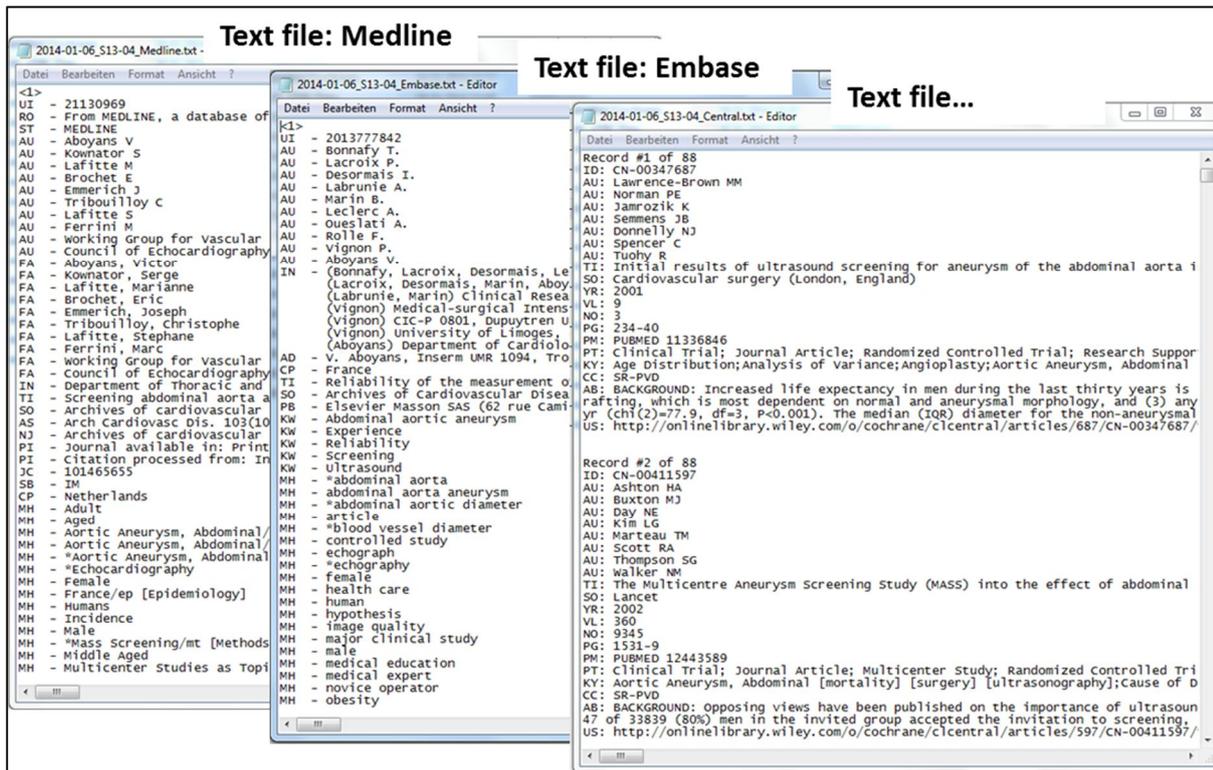


Figure 8: Documentation of the references in the individual bibliographic databases (as text files)

Table 9: Documentation of the search process in Excel

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
...	...	...	...
<b>Total hits</b>			<b>951</b>
Duplicates			249
<b>Hits without duplicates</b>			<b>702</b>

## 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).

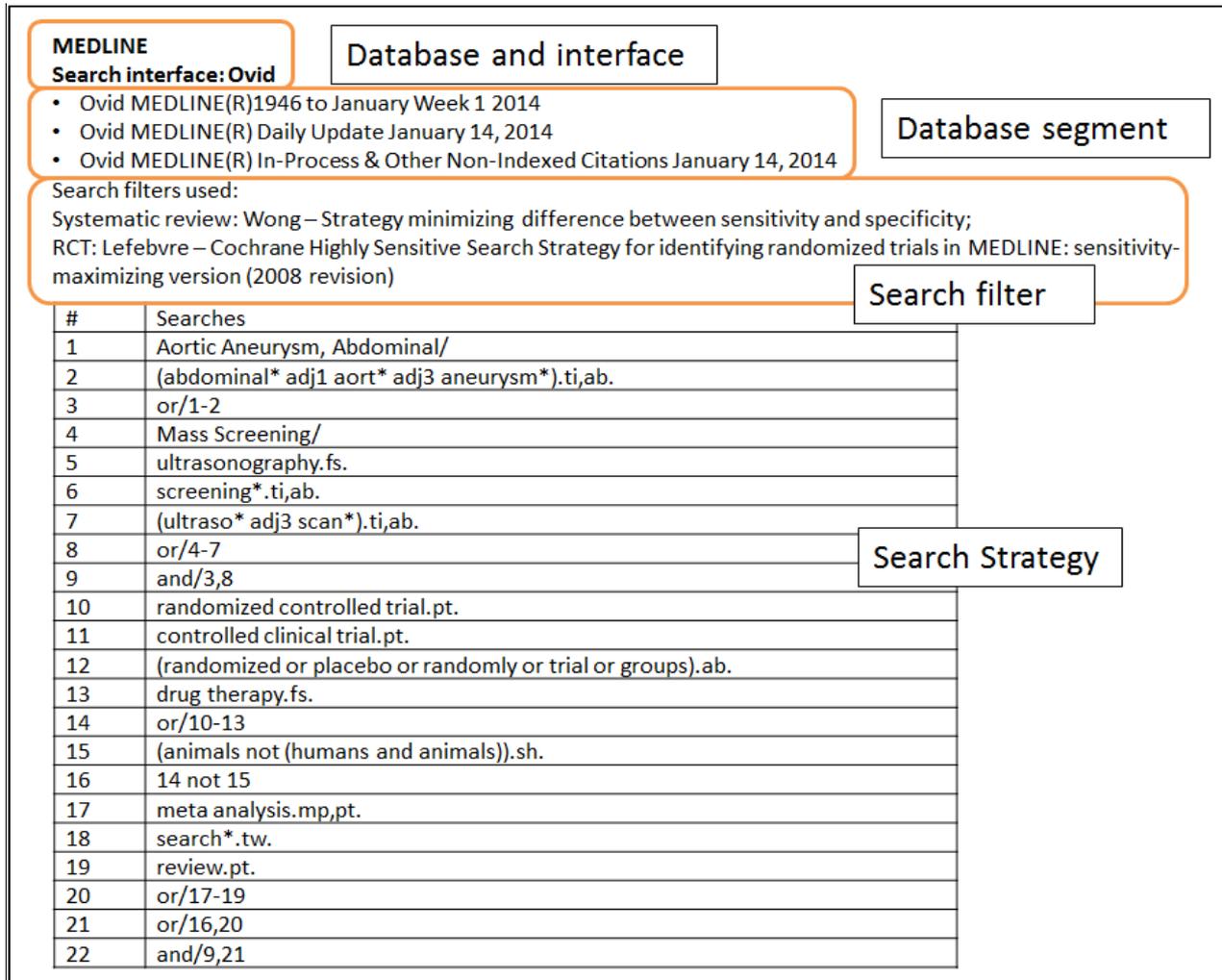


Figure 9: Reporting of the search strategy of the report using the example of MEDLINE

The results of the search, the check for duplicates, and the selection of studies following PRISMA [235] were presented in the results section of the report (see Figure 10).

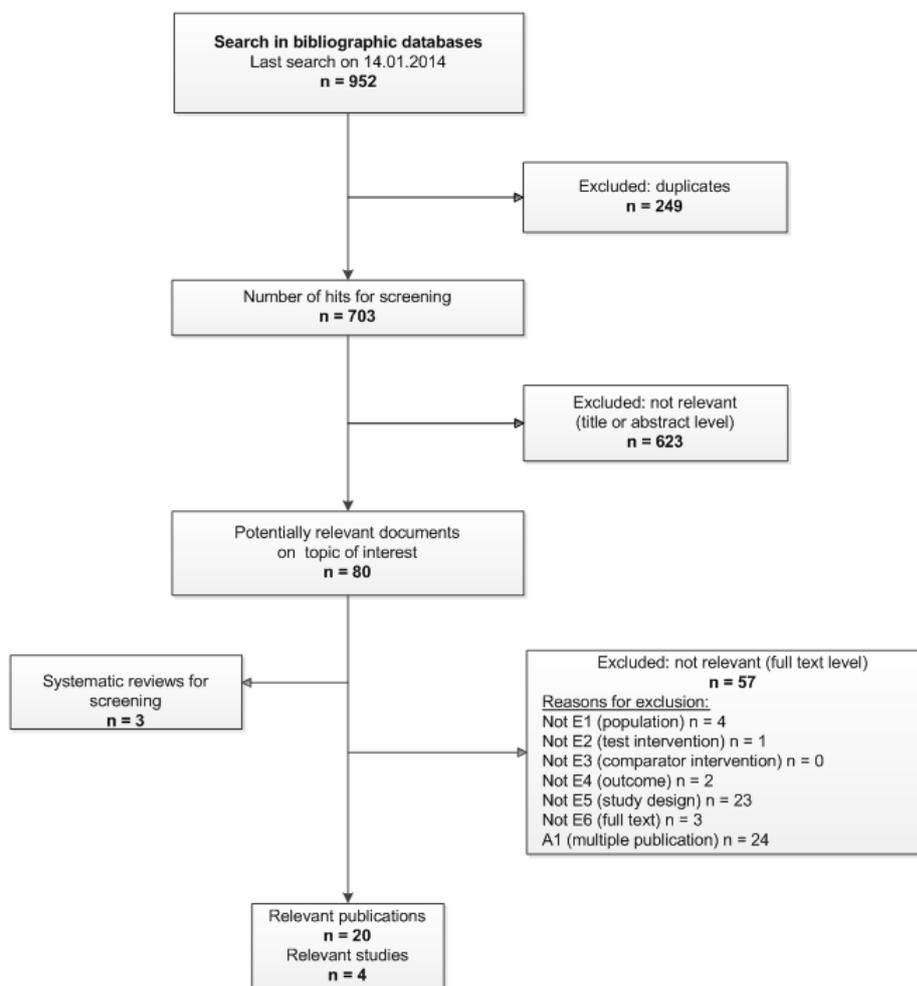


Figure 10: Flowchart for bibliographic database search in the results section of the report

In addition, the report contains the citations of all included studies and all excluded studies, together with the reasons for exclusion, (see Table 10 and Figure 11).

Table 10: Reporting of studies included in the HTA report

Study	Available documents	
	Full publication <sup>a</sup> (in publicly accessible journals)	Study registry entries
Chichester	[25-30]	[24]
MASS	[31,32,34-36]	[33]
Viborg	[38-43]	[37]
Western Australia	[44,46,47]	[45]

a: The errata relevant to the study are also cited.

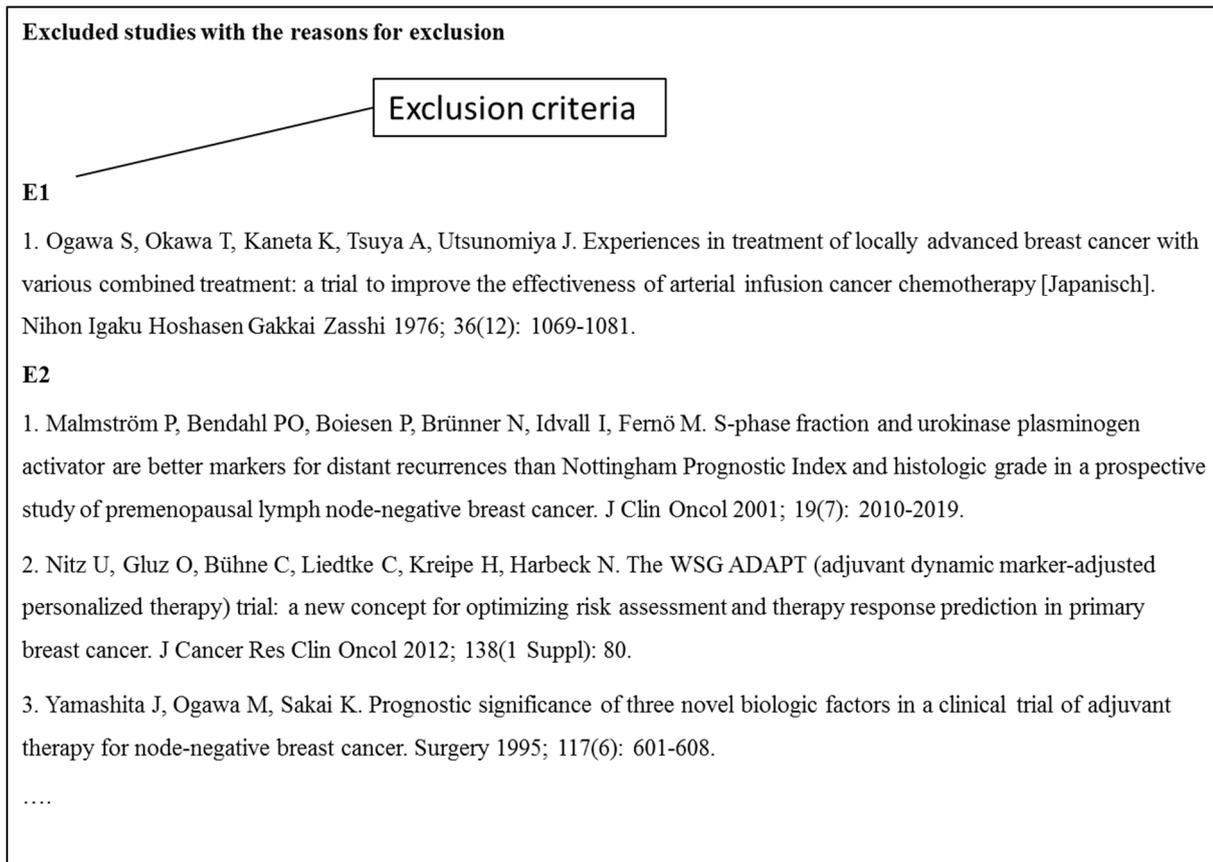


Figure 11: Reporting of studies excluded from the HTA report

## Updating searches *(Back to top)*

An update search was performed in December 2014. The procedure was as follows: First, we checked in which databases the 20 relevant publications were found and whether they could be identified with the search strategies. It was checked whether, for instance, references contained in MEDLINE could be identified with the MEDLINE strategy. Any changes in subject headings of the individual databases were also considered.

To remove the duplicates of the initial search from the update search, a search string was created in MEDLINE, Embase and PubMed using all accession numbers of the respective references from the initial search. This search string and the search strategy were linked with “NOT” to obtain the results of the update search (Figure 12). In the Cochrane Library, this approach is only possible for references from MEDLINE and Embase. The remaining duplicates were then removed in EndNote.

The further search process followed the standards in “Conducting searches, downloading records and managing references” (see 2.4.6).

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

21	or/16,20	4649590	Update search
22	and/9,21	544	Advanced Display
23	(["1913408" or "1481294" or "8093508" or "7664011" or "9853437" or "9853436" or "10873733" or "21130969" or "21086623" or "16890847" or "22163325" or "20478680" or "16996941" or "3066407" or "8634854" or "8379351" or "9345237" or "16467752" or "21810825" or "7936338" or "1925354" or "1829179" or "21236619" or "23260442" or "15185182" or "12514572" or "11718410" or "15176708" or "10541616" or "15943504" or "12443589" or "17514666" or .... "16293428" or "2200328" or "18082528" or "14677480" or "22231532" or "8021114" or "17303997" or "21485471" or "11496273" or "16881275" or "15886653" or "15354629" or "18575030" or "21043165" or "21622013" or "9234101" or "9034919" or "20570470" or "9854557" or "9501808" or "17152201" or "23692903" or "15943501" or "9711956" or "23602862" or "7494369" or "17145427" or "17180573" or "10828236").ui.	513	Advanced Display Delete
24	22 not 23	31	New added references

Selected | Save Selected | Combine selections with: And Or | RSS | Save Search History

Figure 12: 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 concepts 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.

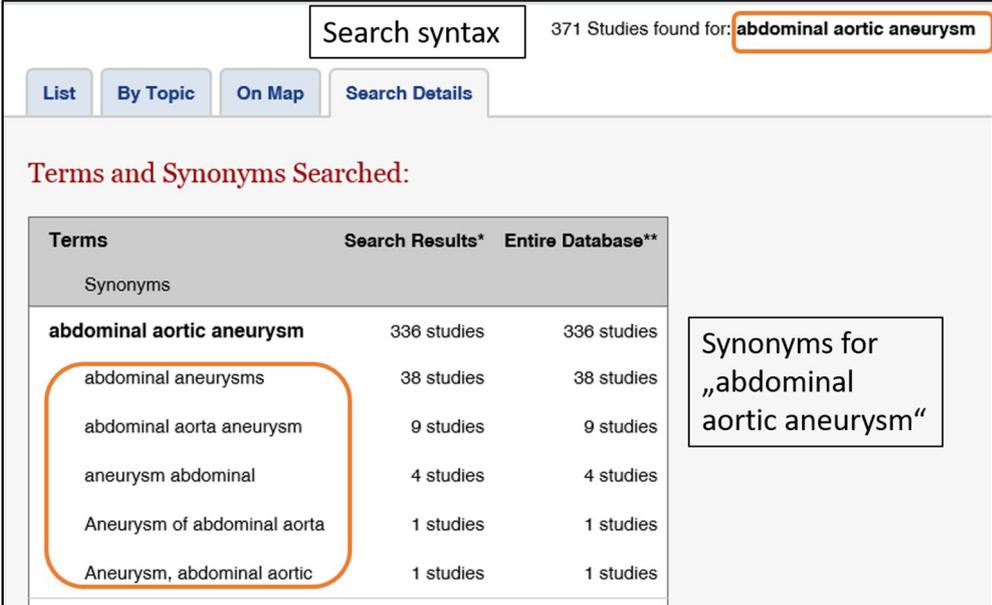
Table 11: Study registries

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

### 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 13). No further adjustment was therefore necessary.



Search syntax 371 Studies found for: **abdominal aortic aneurysm**

List By Topic On Map Search Details

**Terms and Synonyms Searched:**

Terms	Search Results*	Entire Database**
Synonyms		
<b>abdominal aortic aneurysm</b>	336 studies	336 studies
abdominal aneurysms	38 studies	38 studies
abdominal aorta aneurysm	9 studies	9 studies
aneurysm abdominal	4 studies	4 studies
Aneurysm of abdominal aorta	1 studies	1 studies
Aneurysm, abdominal aortic	1 studies	1 studies

Synonyms for „abdominal aortic aneurysm“

Figure 13: 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 14).

30704 Studies found for **screening OR scan** Search syntax

List By Topic On Map Search Details

**Terms and Synonyms Searched:**

Terms	Search Results*	Entire Database**
Synonyms		
<b>screening</b>	16,789 studies	16,789 studies
<span style="border: 1px solid black; border-radius: 5px; padding: 2px;">Screens</span>	3,665 studies	3,665 studies
<b>scan</b>	15,321 studies	15,321 studies
<span style="border: 1px solid black; border-radius: 15px; padding: 2px;">Scanning</span>	2,133 studies	2,133 studies
Cancer related	957 studies	957 studies
Nuclear Medicine	580 studies	581 studies
Related to Cancer	494 studies	494 studies
scanned	463 studies	463 studies
Scintigraphy	462 studies	462 studies
Radionuclide Imaging	53 studies	53 studies
isotope studies	18 studies	18 studies
Gamma Camera Imaging	14 studies	14 studies
radioimaging	11 studies	11 studies
radionuclide studies	4 studies	4 studies

Synonyms for „screening“

Synonyms for „scan“

Figure 14: 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).

Table 12: Adapting the search syntax in each study registry

Study registry	Search syntax	Comment
<b>ClinicalTrials.gov</b>	abdominal aortic aneurysm AND (screening OR scan)	<ul style="list-style-type: none"> <li>• Brackets can be used in this registry</li> </ul>
<b>ICTRP Search Portal</b>	abdominal aortic aneurysm AND screening OR abdominal aortic aneurysm AND scan <sup>1</sup>	<ul style="list-style-type: none"> <li>• Use of brackets not possible</li> </ul>
<b>EU Clinical Trials Register</b>	(abdominal aortic aneurysm) AND (screening OR scan)	<ul style="list-style-type: none"> <li>• Brackets can be used in this registry</li> </ul>

### Peer reviewing search strategies<sup>2</sup> [\(Back to top\)](#)

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 and the final search strategies applied. Direct export of the results as xml or txt file is offered for all 3 study registries (see Figure 15).

---

<sup>1</sup> 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.

<sup>2</sup> The process of quality assurance of search strategies in study registries has recently been revised. Therefore the example does not show the current status.

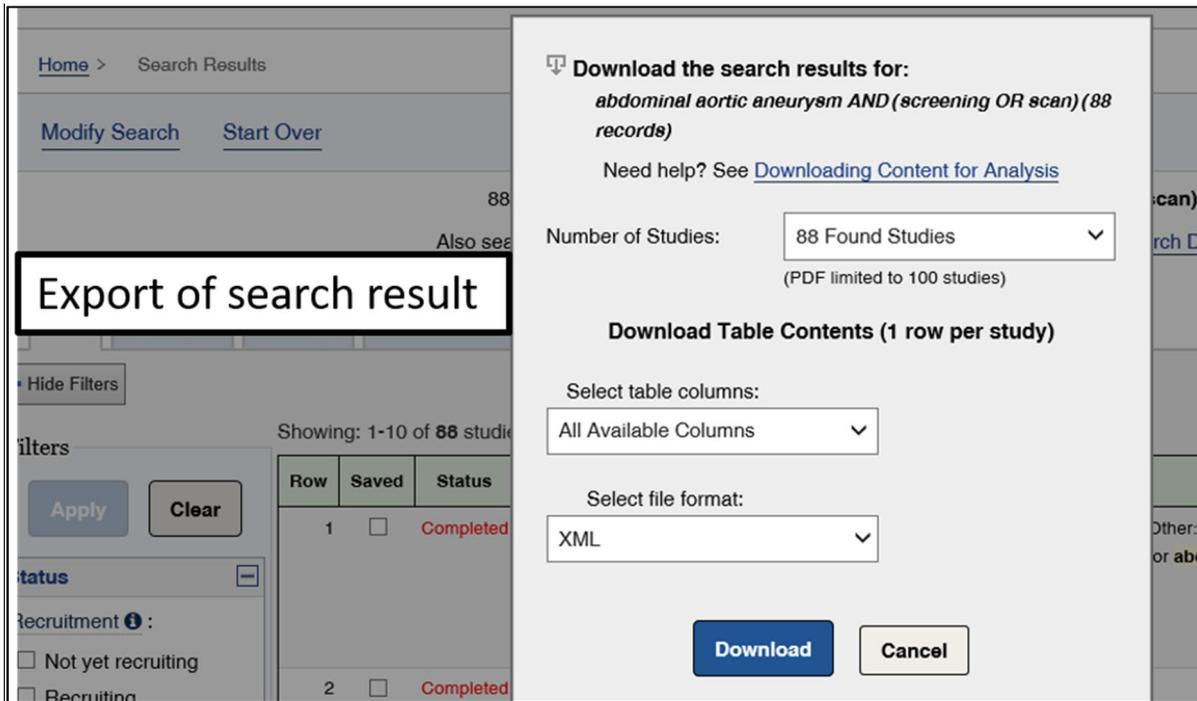


Figure 15: Export function using the example of ClinicalTrials.gov

These files were then imported in EndNote using an import filter. The duplicates were removed based on the registry numbers (see Figure 16).

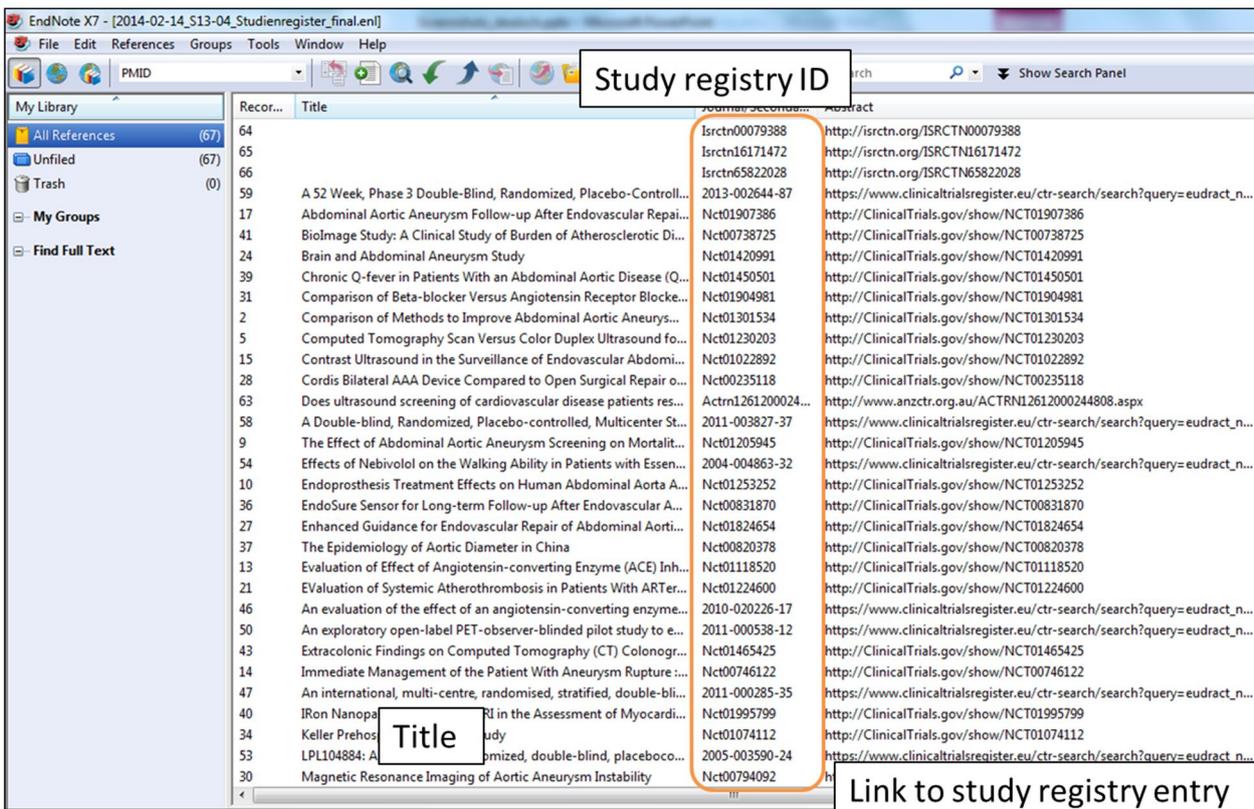


Figure 16: Result of the search in study registries after import into EndNote

## 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. (see Figure 17).

The figure displays three overlapping screenshots of search results from different clinical trial registries:

- ClinicalTrials.gov:** Shows XML search results for the query 'abdominal aortic aneurysm'. The results include details for study NCT00662480, such as title, conditions, and sponsor information.
- ICTRP Search Portal:** Shows a search result for 'Screening of Abdominal Aortic Aneurysm' (Trial ID NCT016792). It lists details like the primary sponsor (Cardoz AB), registration date, and target size.
- EU Clinical Trials Register:** Shows a list of study entries with details such as Eudract Number, Sponsor Name, Full Title, Start Date, and Medical Condition. Examples include studies for abdominal aortic aneurysm and inflammatory burden.

Figure 17: Screenshots of search results in study registries

The search strategies, the number of hits, the search date and the duplicate check were saved for all study registries in EXCEL (see Figure 18).

Studienregister gener	
Clinicaltrials.gov	
Search syntax	abdominal aortic aneurysm AND (screening OR scan)
Number of hits	45
Relevant hits	45
Reason for exclusion:	
Date of search	15.01.2014
Name of screenshots	2014-01-15_S13-04_CT.gov_1, 2014-01-15_S13-04_CT.gov_2, 2014-01-15_S13-04_CT.gov_3

EU-CTR	
Search syntax	abdominal aortic aneurysm AND (screening OR scan)
Number of hits	17
Relevant hits	17
Reason for exclusion:	
Date of search	15.01.2014
Name of screenshots	2014-01-15_S13-04_EU-CTR

Figure 18: 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 19).

Table 5: Relevant studies identified in study registries

Study registry ID	Study name	Study registry [Citation]	Results of the study available
ISRCTN00079388	Chichester	ISRCTN [30]	No
ISRCTN65822028	Viborg	ISRCTN [42]	No
ISRCTN16171472	Western Australian	ISRCTN [53]	No
ISRCTN37381646	MASS	ISRCTN [54]	No

Completed studies

Table 6: Studies of unknown relevance identified in study registries

Study registry ID	Study name	Study registry [Citation]	Status	Results of the study available
NCT01205945	The Effect of Abdominal Aortic Aneurysm Screening on Mortality in Asian Population	Clinicaltrials.gov [66]	ongoing	No
NCT00662480	The Viborg vascular screening trial (VIVA)	ClinicalTrials.gov [67]	ongoing	No

Ongoing studies

Figure 19: 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 20).

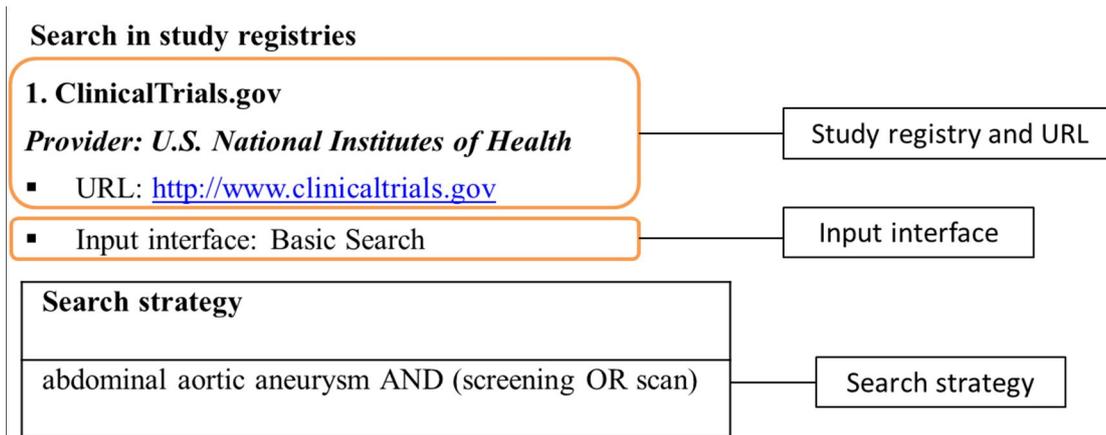


Figure 20: Reporting the search strategy of the report using the example of ClinicalTrials.gov

### Updating searches *(Back to top)*

An update search was performed concurrently to the search in bibliographical databases. The procedure was as follows: The results of the initial search and update search were compared in EndNote or Excel. The duplicate check was performed using the study registration numbers (see Figure 21).

The study status was checked again for studies identified as “ongoing” in the initial search. If the status had changed to “complete”, the studies were considered for assessment. The further procedure regarding screening, documenting and reporting corresponded to the procedure in the initial search.

Recor...	Author	Title	Journal/Secondary Title	Abstract	Custom 1	Name of Database
16		The Effect of Abdominal Aortic Aneurysm Screening on Mortalit...	Nct01205945	http://ClinicalTrials....	OLD	CT.gov
98		The Effect of Abdominal Aortic Aneurysm Screening on Mortalit...	Nct01205945	http://ClinicalTrials....	NEW	CT.gov
17	Berlin-Chemie	Effects of Nebivolol on the Walking Ability in Patients with Essent...	2004-004863-32	https://www.clinical...	OLD	EU-CTR
147	Berlin-Chemie	Effects of Nebivolol on the Walking Ability in Patients with Essent...	2004-004863-32	https://www.clinical...	NEW	EU-CTR
18		Endoprosthesis Treatment Effects on Human Abdominal Aorta A...	Nct01253252	http://ClinicalTrials....	OLD	CT.gov
93		Endoprosthesis Treatment Effects on Human Abdominal Aorta A...	Nct01253252	http://ClinicalTrials....	NEW	CT.gov
19		EndoSure Sensor for Long-term Follow-up After Endovascular A...	Nct00831870	http://ClinicalTrials....	OLD	CT.gov
127		EndoSure Sensor for Long-term Follow-up After Endovascular A...	Nct00831870	http://ClinicalTrials....	NEW	CT.gov
20		Enhanced Guidance for Endovascular Repair of Abdominal Aortic...	Nct01824654	http://ClinicalTrials....	OLD	CT.gov
123		Enhanced Guidance for Endovascular Repair of Abdominal Aortic...	Nct01824654	http://ClinicalTrials....	NEW	CT.gov
21		The Epidemiology of Aortic Diameter in China	Nct00820378	http://ClinicalTrials....	OLD	CT.gov
131		The Epidemiology of Aortic Diameter in China	Nct00820378	http://ClinicalTrials....	NEW	CT.gov
22		Evaluation of Effect of Angiotensin-converting Enzyme (ACE) Inh...	Nct01118520	http://ClinicalTrials....	OLD	CT.gov
109		Evaluation of Effect of Angiotensin-converting Enzyme (ACE) Inh...	Nct01118520	http://ClinicalTrials....	NEW	CT.gov
23		Evaluation of Systemic Atherothrombosis in Patients With ARTeri...	Nct01224600	http://ClinicalTrials....	OLD	CT.gov
110		Evaluation of Systemic Atherothrombosis in Patients With ARTeri...	Nct01224600	http://ClinicalTrials....	NEW	CT.gov
24	Imperial	An evaluation of the effect of an angiotensin-converting enzyme...	2010-020226-17	https://www.clinical...	OLD	EU-CTR
139	Imperial	An evaluation of the effect of an angiotensin-converting enzyme...	2010-020226-17	https://www.clinical...	NEW	EU-CTR
25	Center	An exploratory open-label PET-observer-blinded pilot study to ev...	2011-000538-12	https://www.clinical...	OLD	EU-CTR
143	Center	An exploratory open-label PET-observer-blinded pilot study to ev...	2011-000538-12	https://www.clinical...	NEW	EU-CTR
26		Extracolonic Findings on Computed Tomography (CT) Colonogr...	Nct01465425	http://ClinicalTrials....	OLD	CT.gov
136		Extracolonic Findings on Computed Tomography (CT) Colonogr...	Nct01465425	http://ClinicalTrials....	NEW	CT.gov
27		Immediate Management of the Patient With Aneurysm Rupture ...	Nct00746122	http://ClinicalTrials....	OLD	CT.gov
106		Immediate Management of the Patient With Aneurysm Rupture ...	Nct00746122	http://ClinicalTrials....	NEW	CT.gov
28	Cardoz	An international, multi-centre, randomised, stratified, double-bli...	2011-000285-35	https://www.clinical...	OLD	EU-CTR
140	Cardoz	An international, multi-centre, randomised, stratified, double-bli...	2011-000285-35	https://www.clinical...	NEW	EU-CTR
29		IRon Nanoparticle Enhanced MRI in the Assessment of Myocardi...	Nct01995799	http://ClinicalTrials....	OLD	CT.gov
130		IRon Nanoparticle Enhanced MRI in the Assessment of Myocardi...	Nct01995799	http://ClinicalTrials....	NEW	CT.gov
30		Keller Prehospital Ultrasound Study	Nct01074112	http://ClinicalTrials....	OLD	CT.gov
126		Keller Prehospital Ultrasound Study	Nct01074112	http://ClinicalTrials....	NEW	CT.gov

Study registry ID

Results of the initial search

The results of the initial search will be deleted.

Results of the update search

Figure 21: Duplicate check of the search in study registries in EndNote

## Annexe 4. Checklist for information retrieval

On the basis of the methods in sections 3 and 4, the following standards can be derived for the work on EUnetHTA REA. Details can be found in the SOPs.

Table 13: Summary of EUnetHTA standards in information retrieval

Section in the Guideline	Example	EUnetHTA standards
General issues		
2.2.2 Expertise in searching	n.a.	Information retrieval in bibliographic databases and study registries is conducted by an information specialist.  In EUnetHTA the requirements are that a) the HTA agency confirms that the proposed person is an information specialist and b) that the information specialist has experience in developing search strategies and conducting searches for SRs. Details can be found in the SOP (OT-01-CallCollFormAss)
Bibliographic databases		
3.1.1 Process of searching bibliographic databases	n.a.	/
3.1.2 Conducting preliminary searches	Page 58	A preliminary search is conducted during the development of the project plan. Important SRs on the topic of interest are listed in the project plan.
3.1.3 Structuring the search strategy	Page 59	The research question is commonly broken into concepts; only the most important concepts are used to develop the search strategy (usually population, intervention, and study type).
		If language restriction is applied, this should be justified in the methods section of the SR.

		If search strategies are restricted, for example, with regard to the publication period, this is justified in the methods section of the assessment report. Moreover, these strategies are only considered if they can be reliably applied in the individual databases.
3.1.4 Choosing information sources	Page 59	MEDLINE, Embase and Central are searched routinely.
3.1.5 Developing search strategies	Page 60	A combination of subject headings (including publication type) and free-text terms is required in the development of search strategies.
		If the search in the main databases (MEDLINE, Embase) is restricted to RCTs, validated highly sensitive search filters are used.
		If, besides RCTs, non-randomized studies are included in the assessment, search filters cannot usually be used.
		The search syntax is adapted for each database / interface.
3.1.6 Peer reviewing search strategies	Page 64	The peer review of the search strategies is performed using the PRESS checklist.
		The final search strategy is tested against a set of relevant references.
		A second information specialist performs the peer review.
3.1.7 Conducting searches, downloading records, and managing references	Page 66	Reference management software such as EndNote is used.
		Duplicates are removed from the search result.
3.1.8 Screening citations (technical process)	Page 66	Study selection is performed by 2 persons independently of each other.
		A 2-step (title/abstract and full-text level) procedure is performed.
		Internet-based systems such as Covidence or EPPI-Reviewer are preferably used (highly desirable). The HTA agency responsible for the assessment currently requires its own licence for these products.
3.1.9 Documenting the search process	Page 66	The search process is documented in real time.

		Reporting: please see current template / OT-02-InfRetr
3.1.10 Updating searches	Page 71	The last search in an assessment is conducted less than 6 months before the planned publication of the assessment report.
Study registries		
3.2.1 General aspects	n.a.	n.a.
3.2.2 Structuring the search strategy	Page 73	Searches in study registries should be simple, highly sensitive, and (ideally) structured to search for one concept (e.g. intervention or population).
3.2.3 Choosing information sources	Page 73	ClinicalTrials.gov, ICTRP Search Portal and EU Clinical Trials Register (if meaningful) are searched routinely (please see details in OT-02-CheckInfRet).
		ClinicalTrials.gov is always searched directly.
3.2.4 Developing search strategies	Page 73	The functions provided vary considerably and these differences need to be observed (e.g. concerning truncation, use of brackets).
		The search syntax is adapted for each registry.
3.2.5 Peer reviewing search strategies	Page 75	Peer review is performed.
		The final search strategy is tested against a set of relevant study registry entries.
		A second information specialist performs the peer review.
3.2.6 Conducting searches, downloading records and managing references	Page 75	A reference management software (RMS) such as EndNote is used.
		Preferable, multiple entries of the same study in different registries are not deleted (except for entries with identical registration numbers) (highly desirable).
3.2.7 Screening citations (technical process)	Page 77	Study selection is performed by 2 persons independently of each other.

		A 1-step procedure is performed.
		Internet-based systems such as Covidence or EPPI-Reviewer are preferably used (highly desirable). The HTA agency responsible for the assessment currently requires its own licence for these products.
3.2.8 Documenting the search process	Page 77	The same requirements apply as for searches in bibliographic databases.
3.2.9 Updating searches	Page 79	The same requirements apply as for searches in bibliographic databases.
Further information sources and techniques		
3.3 Unpublished company documents	n.a.	Please see SOP “Scoping, developing project plan and submission dossier” (OT-02-ScDevPPSubDos; restricted to EUnetHTA partners, requires a password)
3.4.1 Regulatory documents (optional information source)	n.a.	Other technologies: The Devices@FDA and NICE list of interventional procedures are searched routinely, if meaningful (please OT-02-CheckInfRet).
		Drugs: EMA – Clinical data and Drugs@FDA are searched routinely.
		One person performs the search and potentially assesses the relevance of the study; a second person checks the whole process.
		Reporting: please see current template / OT-02-InfRetr.
3.4.2 Queries to authors (optional information source)	n.a.	Criteria for queries to authors are defined in the project plan.
		If criteria in project plan are fulfilled, queries to authors are sent.
		Queries to authors (and answer(s)) are documented in the assessment report.
		Data obtained by queries to study authors are labelled (e.g. using footnotes).

3.4.3 Further search techniques (checking reference lists)	n.a.	One person screens the reference lists in SRs or studies on the topic of interest and, if applicable, in the submission dossier. A second person checks the whole process.
		Reporting: please see current template / OT-02-InfRetr.
Layered searching approach based on SRs		
4 Layered searching approach based on SR	n.a.	<p>If information retrieval is based on SRs, only the search result is used in the assessment report, but not the data extraction or the evaluation of the primary studies included in the SRs.</p> <p>An update search for primary studies is conducted for the period not covered by the SRs.</p> <p>A quality check of information retrieval reported in SRs is conducted for those SRs fulfilling the inclusion criteria of the assessment report (AMSTAR, Item 3).</p>