eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

GUIDELINE

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

Version 2.0, August 2019

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

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

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1.0	First Version	EUnetHTA JA2 WP7	July 2015
1.1	Editorial changes and minor updates based on recently published literature. The meaning of recommendations was not altered.	EUnetHTA JA3 WP6	December 2016
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2.0	Editorial changes, new annexe (checklist for information retrieval), new section on layered searching approach based on systematic reviews, major revision of the "regulatory documents" chapter	EUnetHTA JA3 WP6	

The version 1.0 of this guideline was reviewed by a group of dedicated reviewers from:

- National Institute for Health and Care Excellence (NICE) / United Kingdom
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- Norwegian Institute of Public Health (NIPHNO) / Norway
- Andalusian Agency for Health Technology Assessment (AETSA) / Spain

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Acronyms - Abbreviations

AHRQ – Agency for Healthcare Research and Quality

AMSTAR – A Measurement Tool to Assess Systematic Reviews

CRD – Centre for Reviews and Dissemination

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

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

1.1.1. 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.

1.1.2. Auto alert

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

1.1.3. Bias

“A bias is a systematic error, or deviation from the truth, in results or inferences. Biases can operate in either direction: different biases can lead to underestimation or overestimation of the true intervention effect [1]”. Different types of bias exist in clinical research, for example, selection, performance, detection, attrition, and reporting bias (a detailed overview is provided in the Cochrane Handbook [1]).

1.1.4. 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.

1.1.5. Limits

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

1.1.6. 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]:

Status Tag	Citation Status
PubMed - as supplied by publisher	Citations recently added to PubMed via electronic submission from a publisher, and are soon to proceed to the next stage, PubMed - in process (see below). This tag is also on citations received before late 2003 if they are from journals not indexed for MEDLINE, or from a journal that was accepted for MEDLINE after the citations' publication date. These citations bibliographic data have not been reviewed.
PubMed - in process	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.

1.1.7. 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”).

1.1.8. 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).

1.1.9. Search interface

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

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

1.1.10. Search terms

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

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

Subject headings: Controlled vocabulary used by bibliographic databases to describe the content of a publication. Most of the major databases have their own controlled vocabulary. Medical Subject Headings (MeSH) are the controlled vocabulary indexing system developed by the NLM for indexing publications in MEDLINE. MeSH is also used in other databases (e.g. CENTRAL). Emtree thesaurus is used in Embase.

Subheadings: Qualifiers that can be used in conjunction with subject headings to limit them to a particular aspect or as a stand-alone to extend a search strategy.

Search string: An individual search query.

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

1.1.11. 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.

Recommendations	The recommendation is based on arguments presented in the following parts of the guideline text
1st 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
2nd 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
3rd 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

4th recommendation: Individual search strategies must be developed for selected databases using both free-text terms and, if available, subject headings.	3.1.5
5th recommendation: Search strategies should undergo peer reviewing to ensure high-quality search strategies.	3.1.6, 3.2.5
6th recommendation: The search process should be documented in real time and reported in a transparent manner.	3.1.9, 3.2.8
7th recommendation: If information retrieval is based on SRs, only the study pool extracted from these SRs is used in the assessment report. An update search for primary studies should be conducted for the period not covered by the SRs.	4

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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 [3], 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 such as safety, diagnostic accuracy, and economic evaluations (for HTAs) will not form part of this guideline.

Summarized Research in Information Retrieval for HTA (SuRe Info) provides research-based evidence on methods to use when searching for these specific aspects [16].

The assessment of a submission file 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 the project plan and submission file (OT-02-ScoDevPPSubFil) - in progress

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 [18]
- Institute of Medicine's Standards for Systematic Reviews [19]
- AHRQ Methods for Effective Health Care [20] (for unpublished literature)
- PRESS: Peer Review of Electronic Search Strategies [10,21] (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 [5,19].

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 [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 [5,19]. Search strategy development requires expertise and skills in search methodology [9]. Navigating through different information sources is a complex task [19], especially as the structure and functionalities of the databases and their interfaces are continually modified.

The tasks of information specialists are manifold [3,23-27]. They are responsible for the development and peer review of search strategies, as well as the actual conduct of the search [11,19,28]. 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 [29,30], and are responsible for the implementation of software solutions in information management [30].

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 [31]. Secondly, search strategies developed and reported by information specialists are conducted and reported more comprehensively and are thus easier to reproduce [32-34]. These search strategies also contain fewer consequential errors [35].

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 [36-39], and published studies tend to overestimate the effectiveness of interventions and underestimate harms [36,37].

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, 3.3 and 3.4).

In this context it should be noted that only clinical study reports (CSRs) provide (almost) complete information on a study [40], whereas the information provided in study registries and journal publications is often insufficient for the assessment of a study. However, registries and publications may supplement each other [41] or registries can be used to verify published data [20].

Various analyses have shown inconsistencies between the information provided in different sources (e.g. regarding inclusion criteria, endpoints investigated or rates of adverse events [41-43]). 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 [44]. 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 [45].

Despite the importance of unpublished data, HTA agencies do not routinely search study registries or send enquiries to companies [46]. In addition, many authors of SRs fail to report and assess publication bias [47-49].

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. [50] reported that the linkage of trial registries and their corresponding publications requires extensive manual processes.
The Open Trials database [51] 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 is required as well as the application of various search techniques [3].

3.1. Bibliographic databases

3.1.1. Process of searching bibliographic databases

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

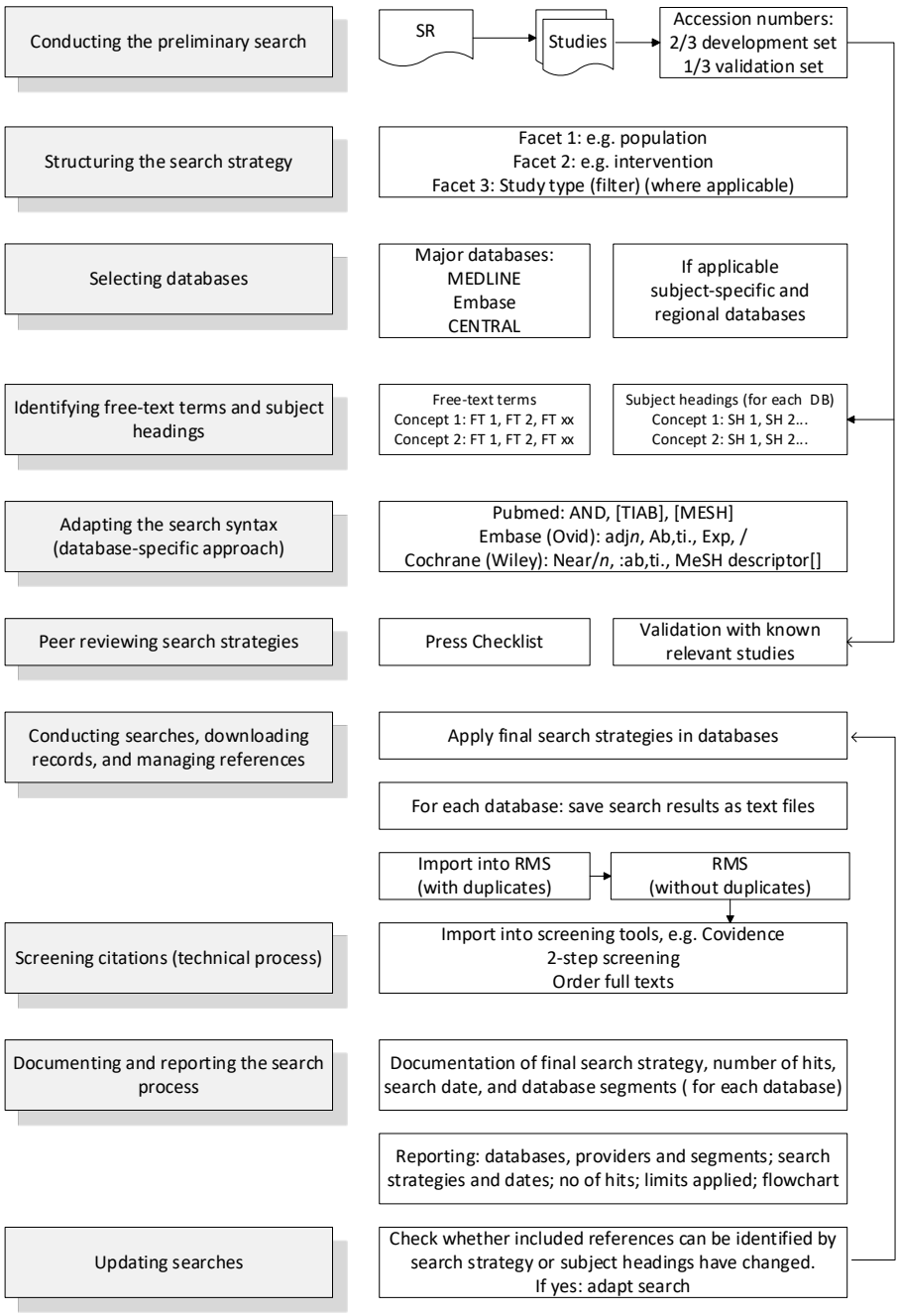

Figure 1: Search in bibliographic databases

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 [29], i.e. understanding the key questions [4], identifying existing SRs [5,52,53], identifying a first set of potentially relevant primary studies [54], and estimating the resources necessary to perform the SR [52]. 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 [4,55,56] and subsequently used in the development of the search strategy.

Two main methods for conducting preliminary searches are described in the literature. With the first method, SRs on the topic of interest are systematically searched for in preselected information sources [5,52,53,57] such as the Cochrane Library, Epistemonikos and, if meaningful, the websites of HTA agencies (e.g. NICE and AHRQ). In order to identify ongoing HTA reports and SRs, further sources should be considered (e.g. the POP database [58] and PROSPERO [59]).

The second method comprises an iterative process with different search techniques such as “snowballing” (backward or forward citations) [60,61] and checking the “similar articles” link in PubMed [61] (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 [4,56].

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 [56].

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 or Population / Intervention / Comparison / Outcome / Study design (PICOS) is often a useful approach [3]. The research question is commonly broken into concepts, and only the most important ones are used to develop the search strategy [62]. 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 [63]. For more complex review questions, it may be necessary to use several combinations of search concepts to capture a review topic [9,64] 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” [3]. In this context, the use of separate lines for each subject heading and free-text term facilitates the quality assurance of search strategies since it enhances the readability of search strategies and therefore helps to avoid errors.

Validated study filters are used for the search concepts on study design (see Section 3.1.5.1). All search concepts are then combined with the “AND” operator [3].

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 [3,4,10]. 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 due to the fact that journal inclusion rates differ between databases [65,66]. Furthermore, the time and quality of indexing differs [66-69], meaning that a reference might be more difficult to find or be found with delay in some databases, but not in others.

However, insufficient empirical evidence is available so far on how many and which databases should be regularly searched. The Cochrane Handbook names MEDLINE, Embase and CENTRAL as the three most important bibliographic databases (for primary studies) [3]. Recent analyses of retrieval rates of relevant studies indicate that most of the published studies can be found in a limited number of databases [70-73].

Furthermore, an additional search for non-indexed information can be conducted e.g. in PubMed or MEDLINE (Ovid), aiming in particular to identify very recent references.

Depending on the objective of the SR, regional or subject-specific databases may also be relevant [3-5,19,74]. However, the additional impact of searching in regional databases has been insufficiently investigated, and many of such databases seem to provide restricted functionalities [75,76]. In contrast, at least for some objectives the use of subject-specific databases may identify additional relevant studies (e.g. on complementary and alternative medicine) [77,78]. A list of regional and subject-specific databases is provided in the Cochrane Handbook [3].

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 [79-81]. Different approaches to identify search terms are described in the literature [7,82]. The conceptual approach [83,84] is recommended by the pertinent literature. Sources used in this approach include the MeSH database [85], medical dictionaries, scanning of relevant publications or consultations with experts to identify a wide range of subject headings and free-text terms [3,5,54]. 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” [62]. This process is usually repeated until no further relevant material is found [86].

More objective approaches to develop a search strategy use text-analytic procedures to identify free-text terms and subject headings through a frequency analysis [87-89]. In this context relevant articles already known [7,8,90,91] or newly identified through broad searches [86,92] are systematically analysed. Different software packages are available that in part clearly differ with regard to costs and functionalities. A list of various tools can be found in the Systematic Review Toolbox, a web-based catalogue [93].

In the next step the terms chosen are assigned to the individual concepts of the search strategy, independently of which approach was chosen to identify subject headings and free-text terms [10,62]. To avoid redundancies, free-text terms should be truncated at the word stem [94] and subject headings and related subordinate subject headings should be summarized with the “explode” function [3,10], if meaningful. The inclusion of further search fields (e.g. substance name, original title), as well as the restriction of subject headings via subheadings or focus (for topic-specific results) must be checked separately for each research question.

Terms related to topic or study design 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 [95] by the InterTASC Information Specialists' Sub-Group [96] and can be evaluated before the search using appraisal checklists [97,98].

If the search is restricted to RCTs, validated and highly sensitive study filters, which should yield a sensitivity of ≥ 95%, should be used. These include the study filters of the Cochrane Collaboration [3] and of the Health Information Research Unit of McMaster University [99].

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 [100].

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 [101].

RCTs of drugs can be identified with a simple standardized search using the truncated generic drug name in all search fields; this achieves a sensitivity of more than 99% in MEDLINE or Embase [102].

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 [103,104] 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. Ideally, each database should be searched separately. Alternatively, cross-database searches may be acceptable if separate search strategies can be applied for each database [30]. 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 [3-5,10,105]. In this context it is advisable to adapt the search strategy developed first (commonly in MEDLINE [24]) to the requirements of the other databases [3,4,10,105]. 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 [94,106]. Tools to help with the conversion of search strategies (e.g. from PubMed to Ovid MEDLINE) are now available with the Medline Transpose [107] and the Polyglot Search Syntax Translator [108].

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 [28].

The “Peer Review of Electronic Search Strategies” (PRESS) checklist was developed to support the peer review process [21]. 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 [109,110]. The peer review process using the checklist should be completed before the search strategy is run [19,28,109].

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 is tested 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. It should be ensured that each strategy fulfils the current quality assurance requirements. 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 [111], RefWorks [112] or Mendeley [113] is recommended [114-116]. These software programs enable the efficient management of references, including in-text citation [117].

Searching several databases produces duplicates. Qi et al. [118] and Bramer et al. [119] 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 and Embase; it is then possible to exclude these records from a search in CENTRAL [3].

Some interfaces also offer the option of directly deleting duplicates in the bibliographic database via a search command (e.g. in Ovid MEDLINE with the command "..dedup x [search line]".

In Ovid it is also possible to conduct separate searches in each database with individual search strategies and then deduplicate [30]. The individual database searches can be run simultaneously by limiting the search result to the respective databases using Ovid database codes [120]. 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 [5,19].

The selection of references is usually administered by a 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 [93] 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 [5,19,121]. The screening of titles and abstracts usually involves two reviewers to reduce the possibility of missing relevant publications [122]. The selection of studies to be included in the SR also should always be performed by at least two reviewers [121]. Current automation approaches mainly aim to prioritize screening results in order to sort relevant references at the start of the screening process [123]. RCT classifiers as made available by RobotSearch [124] seem to represent an appropriate tool for limiting screening results through prioritization [125] and has been endorsed by Cochrane [126,127].

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 [128].

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 [5,19]. The aim is to document the search process as exactly as possible so that all information required for reporting is available [3]. The strategy for each bibliographic database, including the hits per line, should be copied and pasted as run and saved in text format [3,30]. Many databases offer facilities to save search strategies [30].

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 [30]. In addition, information on the databases and interfaces searched should be documented, including the search dates and the search periods covered [5,30]. The complete documentation process is described in detail by Rader et al. [30].

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 [129-131]. The available evidence suggests that the last search in a review should be conducted less than 12 months before publication [130,132]. 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 [133] 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 [134] 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 [135]. 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 [136].

In 2007, the United States introduced mandatory registration of studies and summary results in Clinical.Trials.gov for most Food and Drug Administration (FDA)-regulated drugs and devices [137]. If a protocol, statistical analysis plan (SAP), and data sharing statement are available for a study, ClinicalTrials.gov provides links to these documents [44,138,139]. Tse et al. [140] provide a summary of the legal basis of Clinical.Trials.gov, highlighting issues that need to be considered.

In 2011 the European Medicines Agency (EMA) established the EU Clinical Trials Register (EU-CTR) [141] for most studies submitted during the drug approval process, and the posting of summary results became mandatory in July 2014 [142]. Compliance with the requirement to report results on the EU-CTR can be monitored with the EU Trials Tracker [143].

Depending on the topic investigated, between 15% (diagnostic or prognostic tests [144]) and nearly 100% (newly approved drugs [145,146]) of studies are registered in study registries.

Structure of study registries

Study registries are publicly available and commonly web-based databases or platforms. They contain key information from the study protocol, including outcomes, and/or summary results [20].

Different types of individual registries have been established (see Table 1). In addition, meta-registries such as the ICTRP Search Portal [147] contain regularly updated data from individual registries or access individual registries directly at the time of the search query.

Types of study registries	**Examples**
National registry	German Clinical Trials Register [148] Nederlands Trial Register [149] Spanish Clinical Studies Registry [150]
Regulatory registry	ClinicalTrials.gov [151] EU Clinical Trials Register (Europe) [141]

Industry registry	GlaxoSmithKline Clinical Study Register [152] Forest Clinical Trial Registry [153]
Disease-specific registry	ALOIS: A Comprehensive Register of Dementia Studies [154]
Meta-registry	ICTRP Search Portal of the WHO [147]

Table 1: Types of study registries

The information contained in study registries is generally entered and updated by those responsible for the conduct of the study. However, entries may be incomplete, contain errors [155] or changed after registration [156,157]. In addition, the study status may be outdated [158,159].

Furthermore, many studies are still registered retrospectively instead of prospectively [42,160-164]. It should also be noted that registries have previously been closed down at short notice (e.g. clinicalstudyresults.org [165] or the web crawler of the IFPMA Clinical Trials Portal [166]).

Previous systematic reviews have not routinely searched study registries [46,167], despite the fact that additional relevant studies may be identified in these sources [168-170].

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) [171]. It is advisable to first conduct the search using the terms of the concept that can be most clearly specified and will thus probably generate the lowest number of hits. The scope of the search should only be limited further by adding the second concept if too many hits are retrieved in the first search. Due to the varying quality of the individual registry entries, it is not advisable to apply additional limitations (e.g. with regard to study status or phase).

See example: Structuring the search strategy (study registries)

3.2.3. Choosing information sources

Several registries should be searched, as no registry contains all studies [158,171,172]. The search should include at least the ICTRP Search Portal as well as ClinicalTrials.gov [20,132,171]. 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 [158,173]. However, it only offers limited search functions [171] and often produces error messages [174]. Therefore major registries such as ClinicalTrials.gov should always be searched directly [171].

For SRs of drugs, the relevant company registry [170], as well as the 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 commonly no longer updated

when funding ceases. They are thus not very useful and should only be searched for in exceptional cases [175].

See example: Choosing information sources (study registries)

3.2.4. Developing search strategies

3.2.4.1. Identifying search terms

The syntax for the search in bibliographic databases provides the basis for the selection of search terms for the search in registries. Known terms of a search concept should be considered in a sensitive search [171]. It should be noted that registries such as ClinicalTrials.gov (see [176] 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 necessary because study registries only provide limited search functions [145].

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 ICTRP and EU-CTR, the drug code also needs to be searched for [145]. When searching for the therapeutic indication, simple search terms usually lead to a complete search result only in ClinicalTrials.gov, as the “search for synonyms” function is adequate in this registry. In the ICTRP Search portal and EU-CTR [145], the use of comprehensive search queries 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 [171].

The York Health Economics Consortium provides a comprehensive overview of the search functions of different registries [177].

If meaningful, a sensitive search should be conducted as a single concept search using the “basic search” function [171].

See example: Adapting the search syntax (study registries)

3.2.5. Peer reviewing search strategies

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

A check for completeness of the search should also be performed. For example, Glanville et al. describe an approach for identifying registry entries on known relevant studies [171]. To the relevant studies already identified in bibliographic databases in the preliminary search (see Section 3.1.2) a set of relevant registry entries can thus be determined. It is then tested whether the final search strategy actually identifies these entries. However, not all relevant studies can be linked to the corresponding registry entries since journal articles do not as a rule include study identifiers such as National Clinical Trial numbers [171].

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 [177], which can then be imported into a RMS using an import filter [30]. The search results can then be processed for screening.

If no export function is available, the search results can be copied and pasted into Excel and processed [175].

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 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, but are rarely made publicly available.

These documents are generally prepared following the International Conference on Harmonisation's Guideline for Industry: Structure and Content of Clinical Study Reports (ICH E3) [178] and provide detailed information on the methods and results of a study [179]. They contain far more relevant information than journal publications or registry reports [41,178,179]. Although CSRs are considerably longer than journals publications [180] and require specific expertise with regard to data extraction and assessment, they are indispensable for gaining an unbiased picture of the available research evidence [36,41,178-181].

Pharmaceutical companies are increasing data transparency. However, an analysis of pharmaceutical company policies showed that transparency commitments vary greatly between companies [182]. Since 2013, GlaxoSmithKline has published CSRs of all GSK drugs approved or discontinued from 2000 and onwards [183]. 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 [184] or the Yale University Open Data Access Project (YODA) [185]. However, such requests are sometimes rejected [186-188] or the studies listed are incomplete [189].

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 [20]. This should follow a standardized approach using template letters or forms.

For example, IQWiG currently applies the following approach for this purpose [190]: 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. In this context, to avoid bias by selective provision of data it is important for the company to agree a priori to the publication of all relevant data (not the publication of all full documents). A 2-step procedure then follows: Firstly, the company is asked to provide a complete list of studies on the drug or medical device to be assessed. Secondly, the authors identify potentially relevant studies from this list and request detailed information from the company on unpublished studies or additional information on published studies. English-language sample contracts between IQWiG and pharmaceutical companies or medical device manufacturers are available on the IQWiG website [191,192].

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 [193,194] although they now publish various documents from the approval process. Jefferson et al. [195] 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) [196]. 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 [197,198]. Regulatory documents, including CSRs on all drugs submitted for approval, have since been available on the Agency´s website “European Medicines Agency – Clinical data” [199].

Regulatory agencies in other countries such as Canada [200] 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 [201].

2. Documents from regulatory agencies

Until recently, regulatory agencies did not publish complete CSRs but only published related documents from the approval process (e.g. FDA Medical and Statistical Review documents). These documents can offer important insights into clinical studies [20,202] 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 [181].

In Europe, information on centrally authorized drugs (e.g. European public assessment reports) can be found on the EMA website [203]. In the United States, the Medical and Statistical Reviews of drugs approved by the FDA can be found via Drugs@FDA [204].

Regulatory agencies in other countries such as Canada [205] or Japan [206] 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) [207]. 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 [208]. In the United States, information on FDA-approved devices, including data used for approval, is available via Devices@FDA [209].

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 [210].

Turner [211] and Ladanie et al. [212] provided a detailed overview on how to access and process FDA documents. Also Le Cleach et al. [213] 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 [155,214]. The OpenTrialsFDA website makes it easier to search through FDA documents. [215].

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 [4,19,216].

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 [217]. 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

[217]. 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 [218].

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 [4,216].

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 [219].

3.4.3. Further search techniques

The conventional search approach of applying Boolean operators (see Section 1.1.8) 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 [220]. 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 1.1.4), hand searching and methods of automated retrieval implemented in databases are some examples.

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 [221] (i.e.the reference lists of articles citing key articles) and using the “similar articles” function would seem to be an efficient search approach [61].

Verifying the studies identified solely by additional search techniques (e.g. checking reference lists) can validate the effectiveness of searches in bibliographic databases [57]. If these searches miss relevant articles, revising the search strategy and rerunning the search should be considered [222].

Further information on this topic can be found in the chapter “Value of using different search approaches“ on SuRe Info in [61].

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 [223]. Conference abstracts often provide limited details of study methodology, and may contain limited reporting of outcome data [224]. There can be differences between data presented in an abstract and that included in the full publication [5,225,226]. In addition, McAuley et al. [227] 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 [5,224].

However, especially if systematic literature searches for published studies yield no or very few citations, searching conference abstracts and proceedings may be considered to identify additional studies [224]. 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 [224].

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 3.1.9. 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 [224].

3.4.5. Dissertation and reports

Searching for dissertations and other reports seems helpful only in exceptional cases (e.g. religion and mental health [228]). 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” [229] and there seems to be little impact on the results or the conclusion of a review [229,230].

3.5. Reporting the search process

With PRISMA-S [231,232], 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 [4,5,19] (see PRISMA for a template [22,233]). Furthermore, the references of the studies included and excluded (for articles read in full text) should be presented in separate reference lists [121,234]. In contrast to journal publications, HTA reports do not have space restrictions, and should therefore document the search process as precisely as necessary [19].

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 [235,236] 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 [236].

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 adaptions 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) [234]).

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 selected.

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.

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” [234]) 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.

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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

1713

1714 Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid
1715 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

1716
1717

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 [237]) was identified that precisely covers the research question (Figure 2).

Figure 2: Preliminary search in Cochrane Library (Wiley)

The background section of the Cochrane Review was read to learn more about the topic; more importantly, the primary studies in the review could be used. A search in PubMed and on websites of HTA agencies identified two further SRs [238,239].

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.

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

Table 2: Databases and interfaces

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

Objectively-derived approach

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

Free-text terms

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

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

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

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

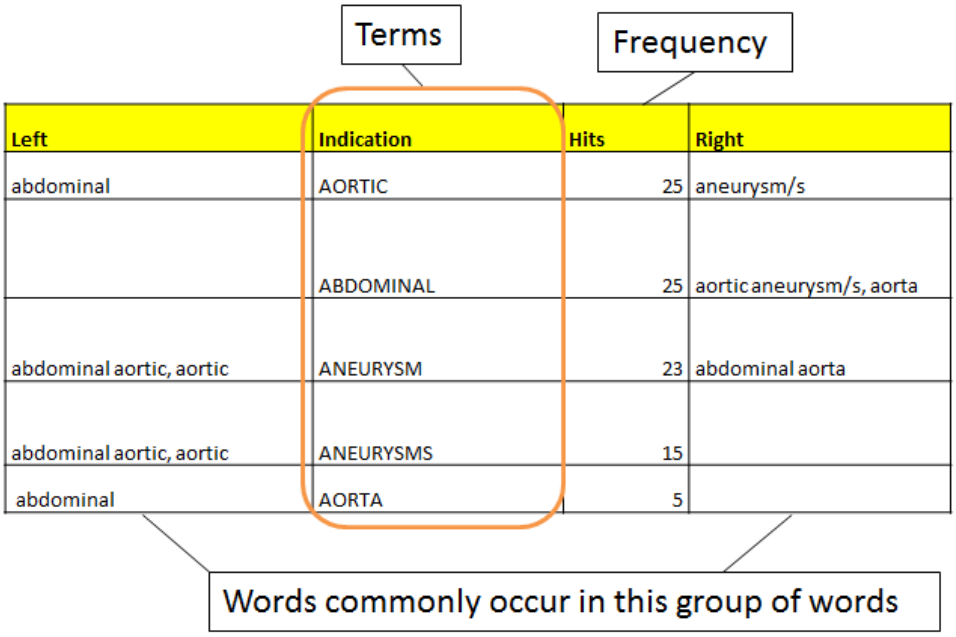


Figure 3: Common terms for concept 1

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

Phrases from Figure 3	Consequences	Example of the search syntax in Ovid

abdominal aortic aneurysm(s)	The words commonly occur in this group of word; the three terms are therefore linked with a proximity operator	abdominal adj1 aortic adj1 aneurysm (preliminary)
abdominal aortic / aorta aneurysm(s)	• "Aneurysm" is used both in the singular and plural form: this term is therefore truncated. • "Aorta" is also used in addition to "aortic"; the word stem "aort" is thus also truncated.	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* **adj3** aneurysm* (final)

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

Subject headings

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

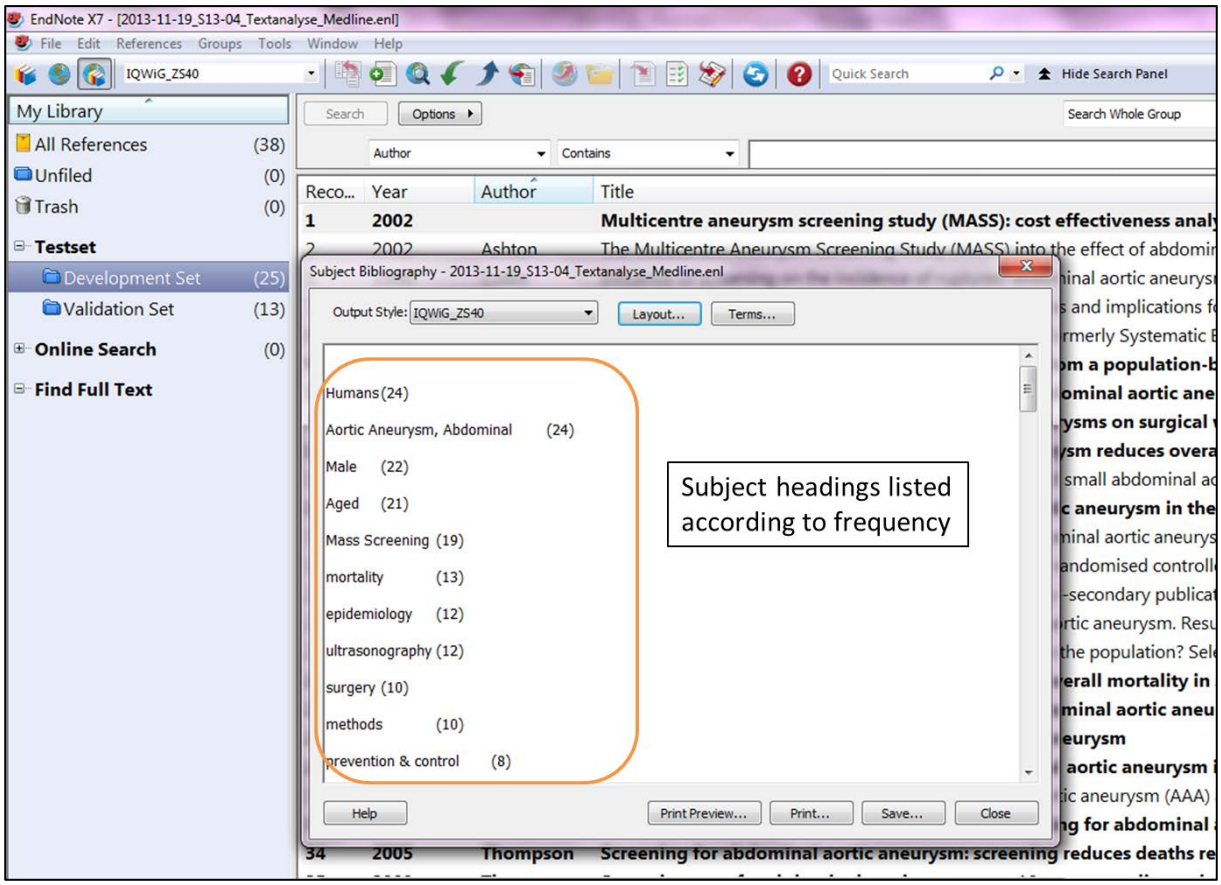


Figure 4: Analysis of subject headings in EndNote via the "Subject Bibliography" function

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

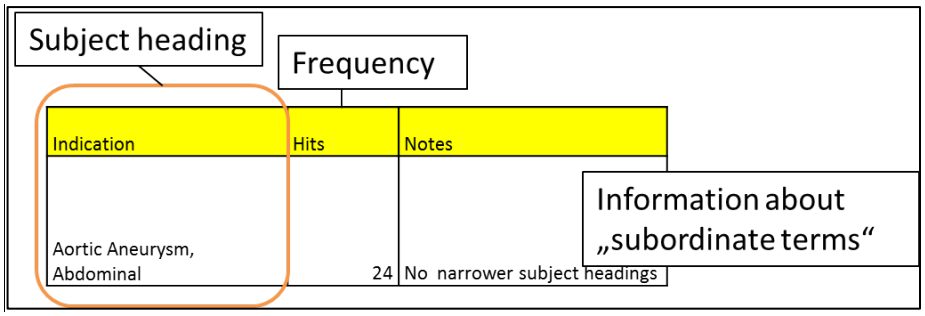


Figure 5: Common subject headings for concept 2 using the example of MEDLINE

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

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

Study filter

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

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

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

Our example shows the implementation for concept 1:

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

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

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

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

The search strategy was organized according to 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 6).

Our example shows the implementation for MEDLINE:

#	**Searches**	**Results**
1	Aortic Aneurysm, Abdominal/	13646
2	(abdominal* adj1 aort* adj3 aneurysm*).ti,ab.	14046
3	or/1-2 **[Concept 1]**	18402
4	Mass Screening/	83663
5	ultrasonography.fs.	198380
6	screening*.ti,ab.	341139
7	(ultraso* adj3 scan*).ti,ab.	14122
8	or/4-7 **[Concept 2]**	567366
9	randomized controlled trial.pt.	396032
10	controlled clinical trial.pt.	90636
…		
15	or/ 9-15 **[Study filter: RCT]**	391739
16	and/3,8,15 **[Concept 1 AND Concept 2 AND Study filter]**	520

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

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

Peer reviewing search strategies *(Back to top)*

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

Application of the PRESS checklist: The search strategy was checked for errors by a second person using the PRESS checklist (see [21]).

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 [99,240], Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision) [3]).

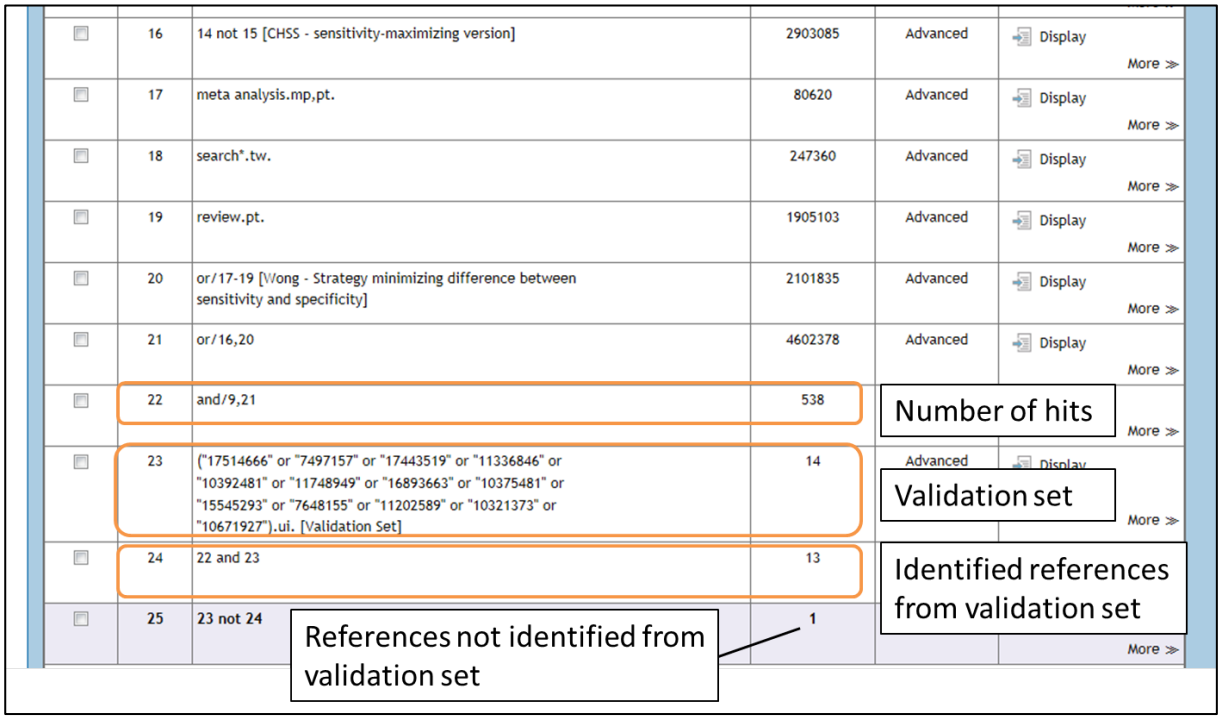


Figure 6: Validation set

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; [241]). 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 7).

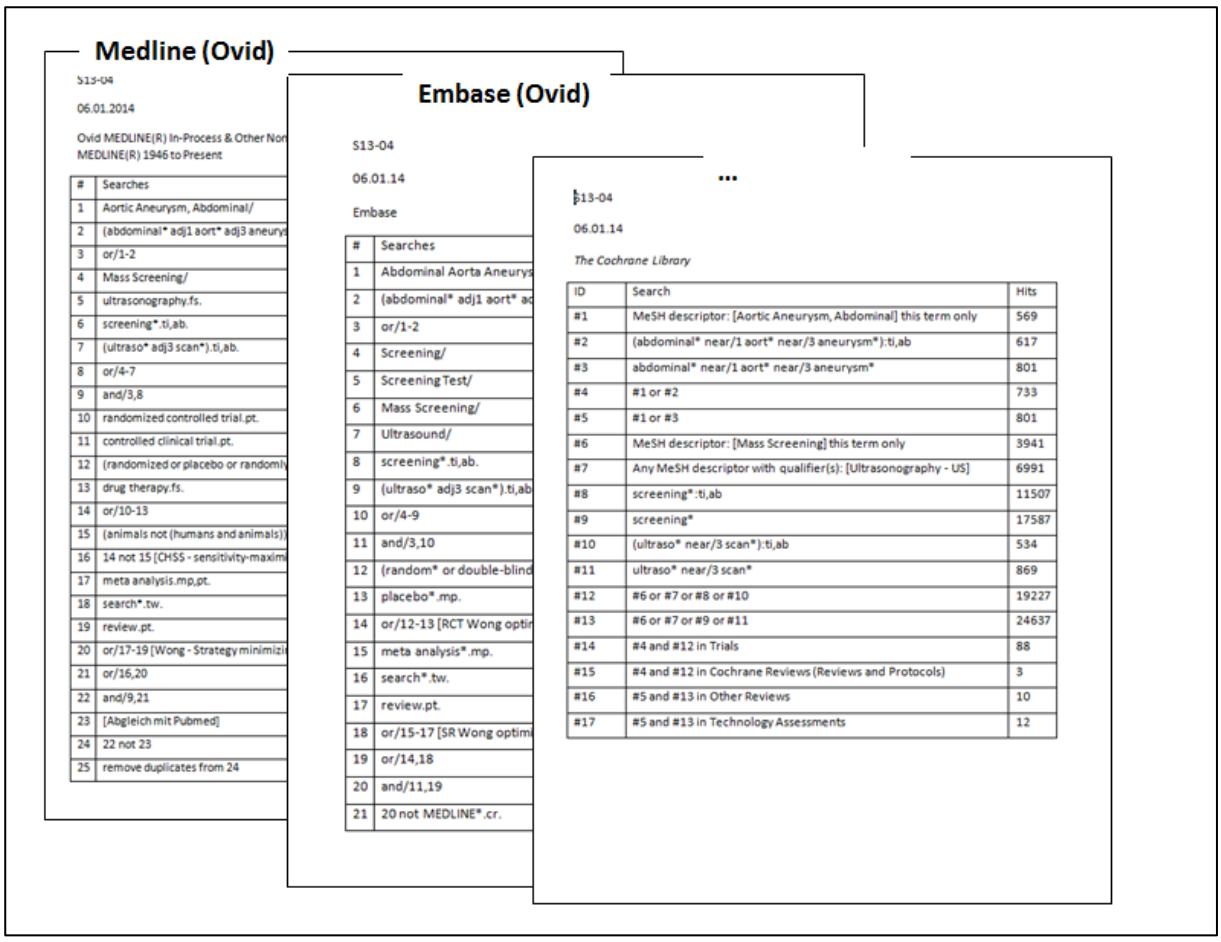


Figure 7: Documentation of the search strategies in the individual bibliographic databases

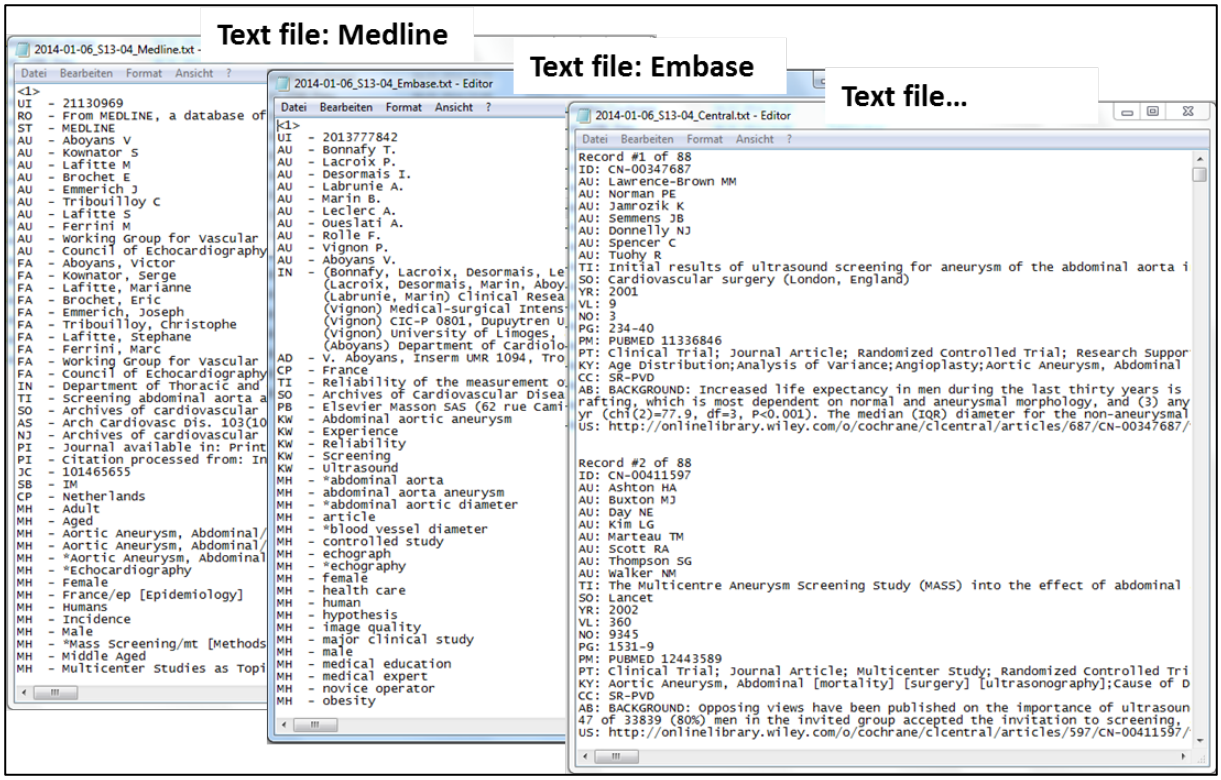


Figure 8: Documentation of the references in the individual bibliographic databases (as text files)

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

Table 7: Documentation of the search process in Excel

Reporting

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

MEDLINE
Search interface: Ovid

Database and interface

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

Database segment

Search filters used:
Systematic review: Wong – Strategy minimizing difference between sensitivity and specificity;
RCT: Lefebvre – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)

Search filter

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

Search Strategy

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

The results of the search, the check for duplicates, and the selection of studies following PRISMA [233] were presented in the results section of the report (see Figure 10).

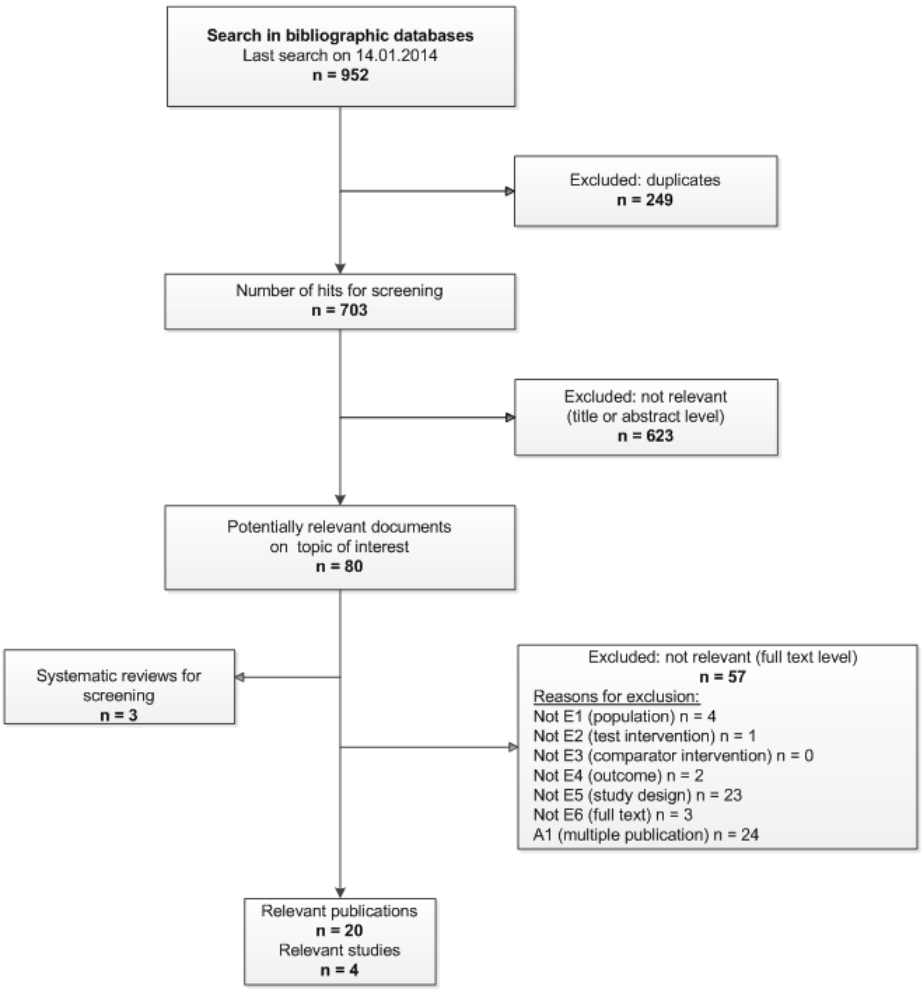


Figure 10: Flowchart for bibliographic database search in the results section of the report

In addition, the report contains the citations of all included studies and all excluded studies, together with the reasons for exclusion, (see Table 8 and Figure 11).

Study	**Available documents**	
	Full publication[a] (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.		

Table 8: Reporting of included studies in the HTA report

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.

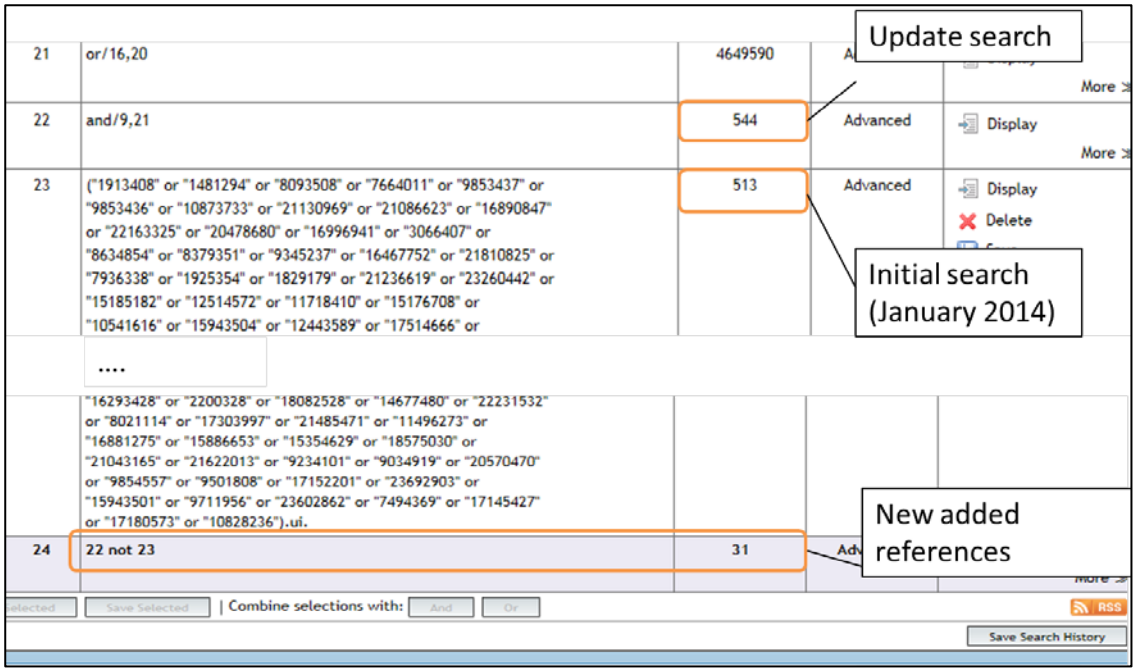


Figure 12: Result of the update search

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.

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

Table 9: Study registries

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

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

For concept 1 (“abdominal aortic aneurysm”) ClinicalTrials.gov synonyms corresponded with the identified terms in the text analysis (see Figure 13). No further adjustment was therefore necessary.

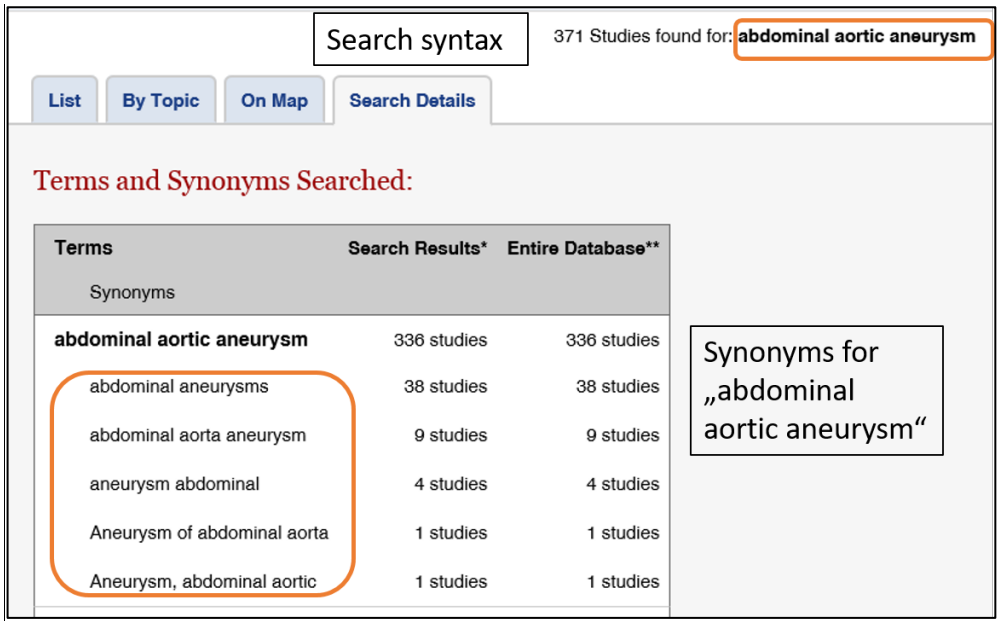


Figure 13: Synonyms for “abdominal aortic aneurysm” using the example of ClinicalTrials.gov

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).

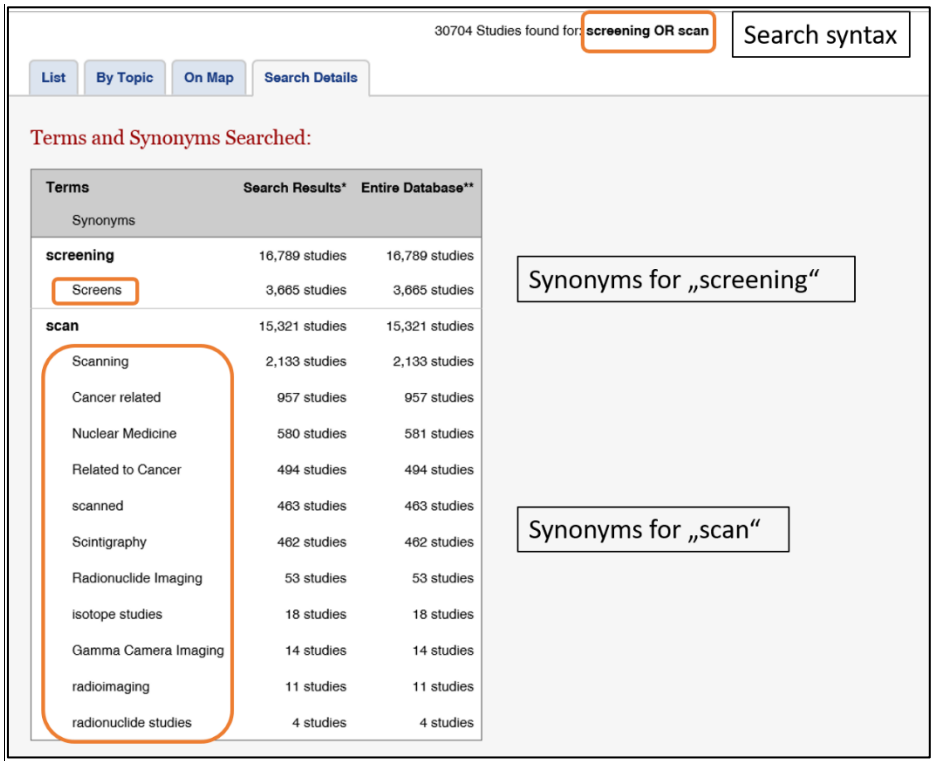


Figure 14: Synonyms for “screening OR scan” using the example of ClinicalTrials.gov

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).

Study registry	Search syntax	Comment
ClinicalTrials.gov	abdominal aortic aneurysm AND (screening OR scan)	• Brackets can be used in this registry
ICTRP Search Portal	abdominal aortic aneurysm AND screening OR abdominal aortic aneurysm AND scan[1]	• Use of brackets not possible
EU Clinical Trials Register	(abdominal aortic aneurysm) AND (screening OR scan)	• Brackets can be used in this registry

Table 10: Adapting the search syntax in each study registry

Peer reviewing search strategies[2] *(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).

[1] 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.

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

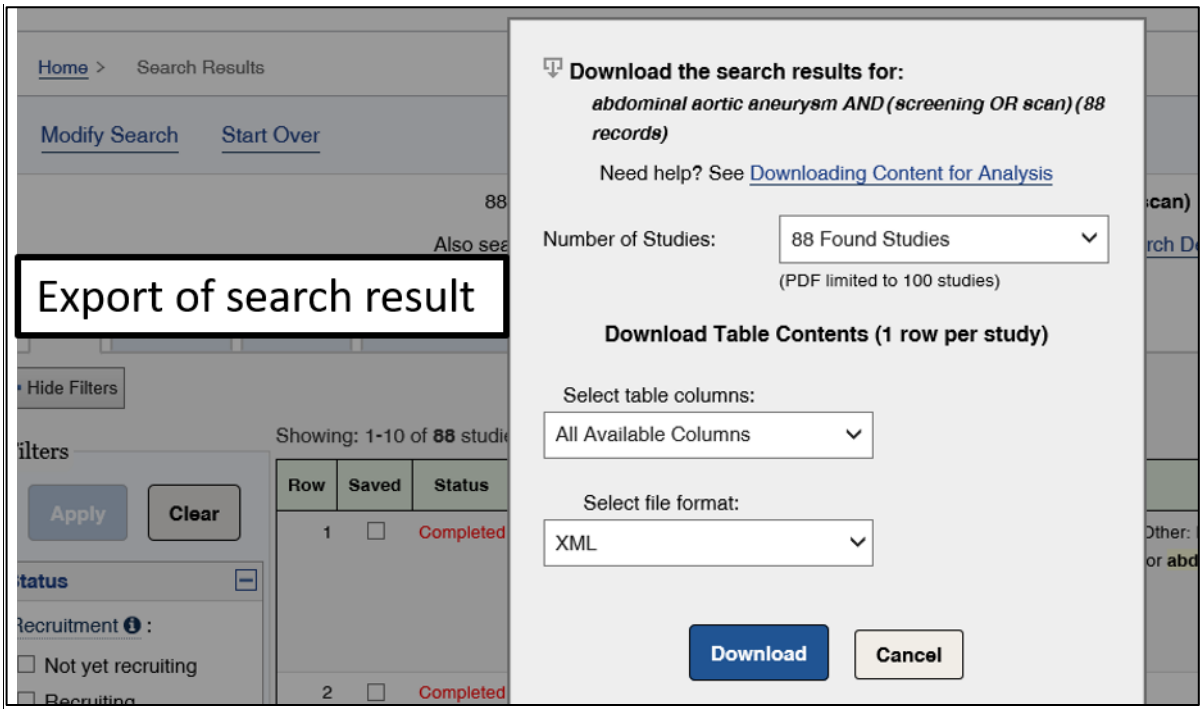


Figure 15: Export function using the example of ClinicalTrials.gov

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

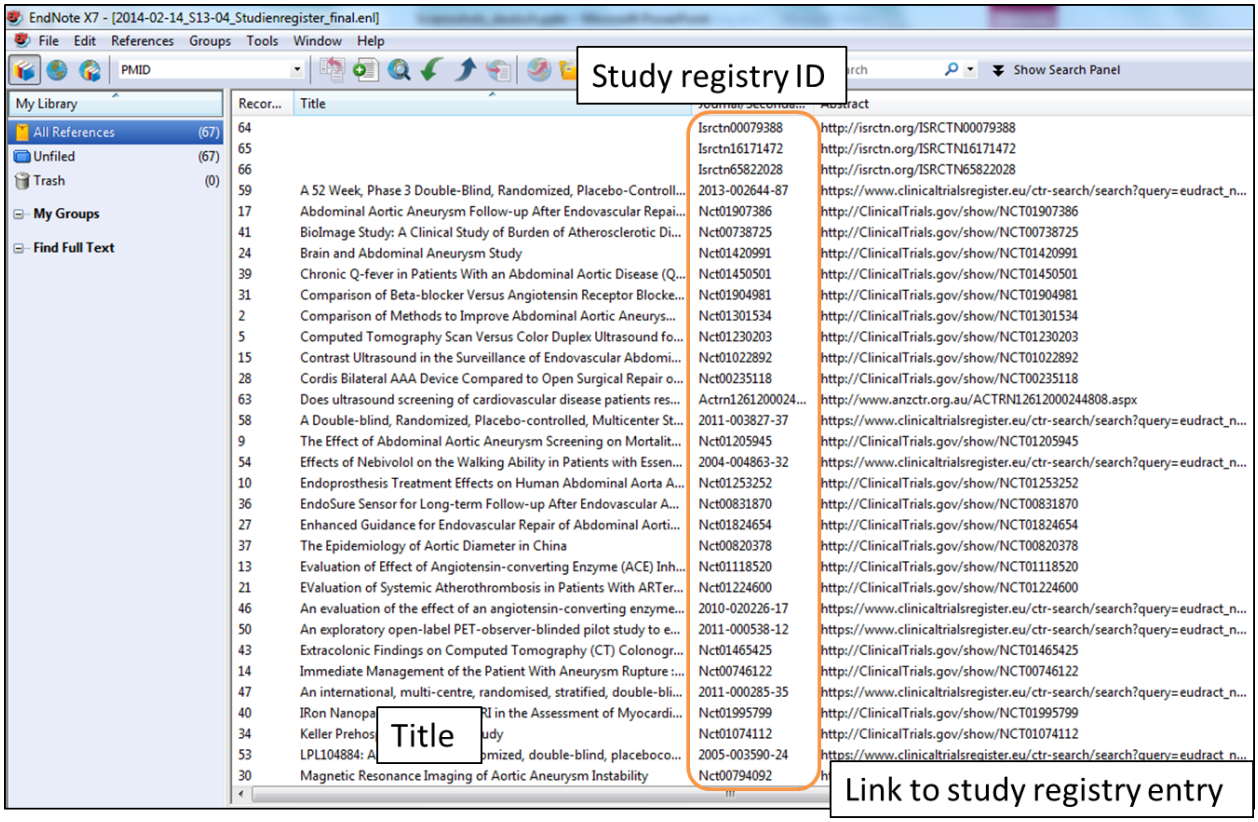


Figure 16: Result of the search in study registries after import into EndNote

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).

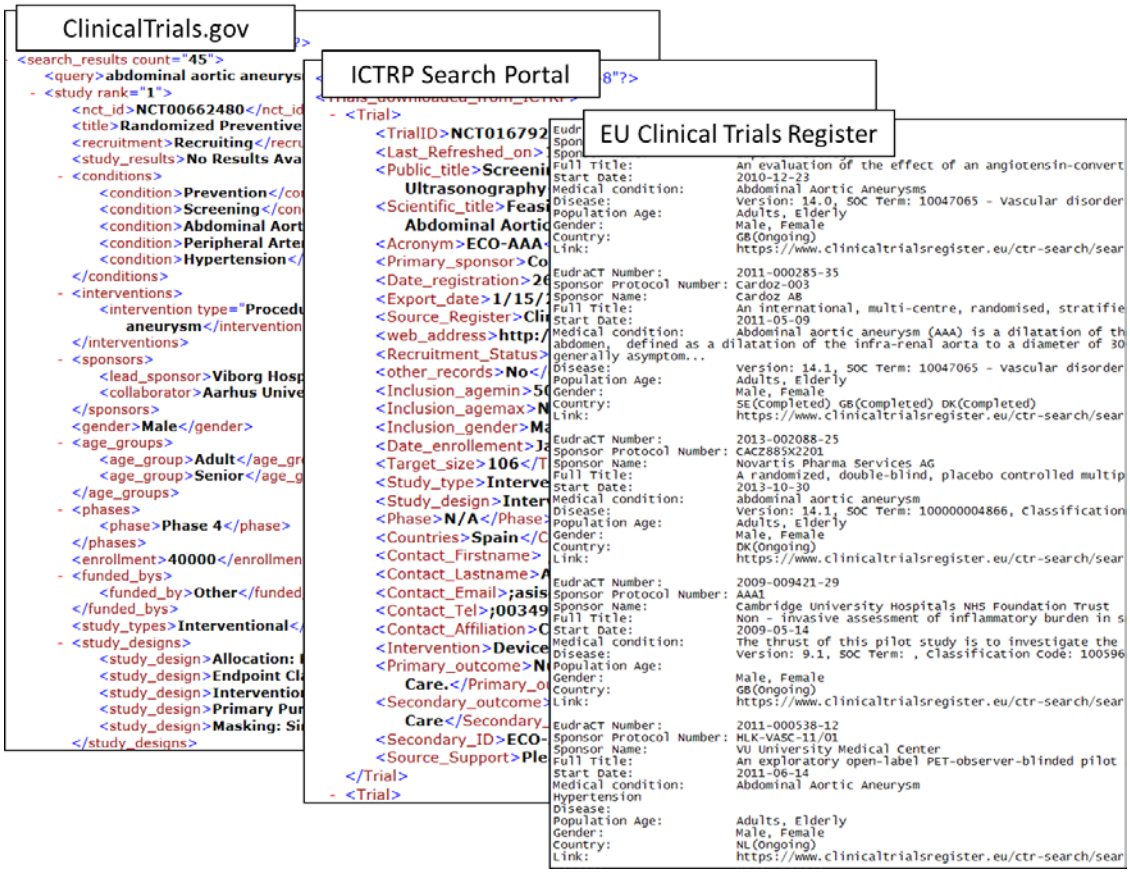


Figure 17: Screenshots of search results in study registries

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	Number of hits		Search syntax
Clinicaltrials.gov			
Search syntax	abdominal aortic aneurysm AND (screening OR scan)		
Nubmer 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-C	Date of search		
Searc	dominal aortic aneurysm AND (screening OR scan)		
Nubmer 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).

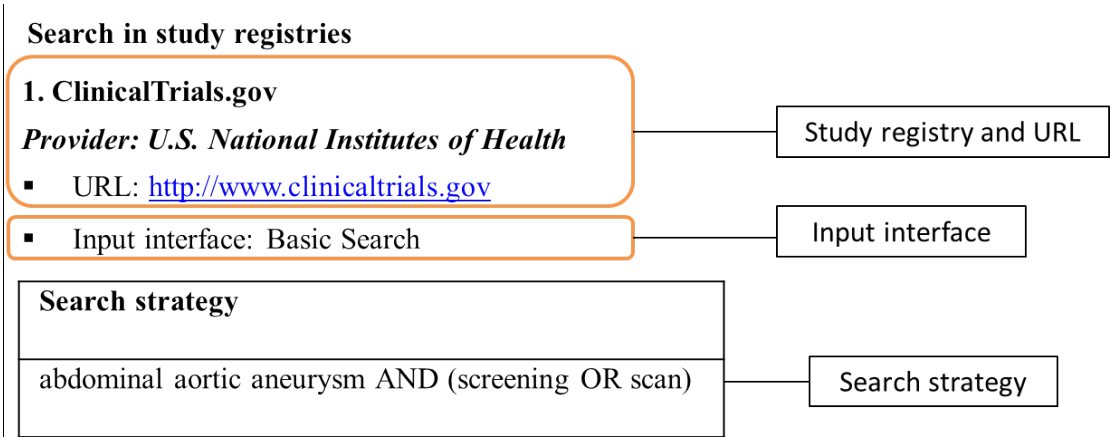
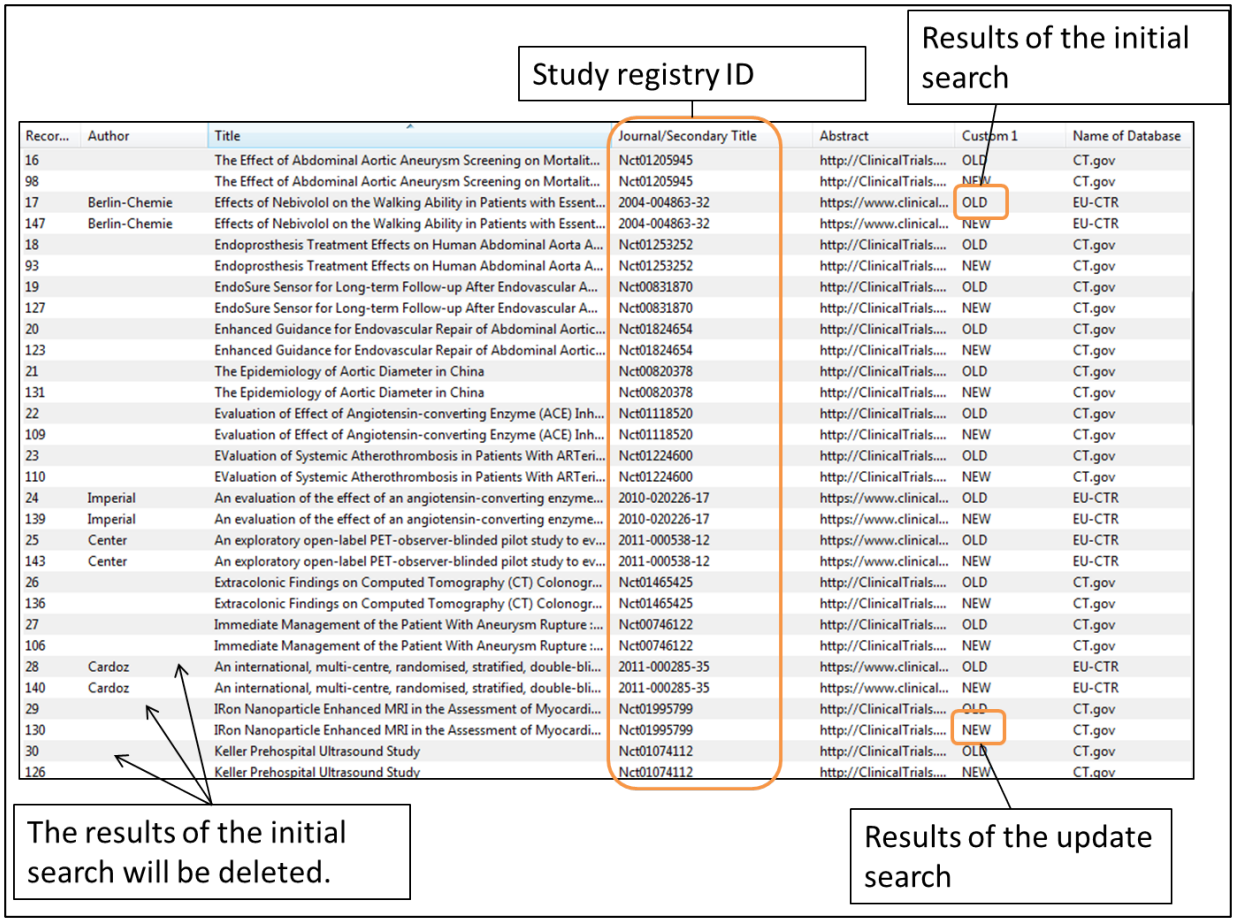


Figure 20: Reporting the search strategy of the report using the example of ClinicalTrials.gov

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

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.

Section in the Guideline	Example	EUnetHTA standards
General issues		
2.2.2Expertise in searching	n.a.	Information retrieval in bibliographic databases and study registries is conducted by an information specialist.
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).
		No language restriction is applied.
		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-ScoDevPPSubDos; 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).
3.4.3Further 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 file. 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.	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.
		An update search for primary studies is conducted for the period not covered by the SRs.
		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).