Search for Evidence & Critical Appraisal

Health Technology Assessment (HTA)

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KCE Process notes

Title: Search for Evidence & Critical Appraisal: Health Technology Assessment (HTA)

Authors: Irina Cleemput, Ann Van den Bruel, Laurence Kohn, Joan Vlayen, Imgard Vinck, Nancy Thiry, Dirk Ramaekers

Acknowledgments: Patrice Chalon, Mark Leys

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Figure 1 presents the procedure of a Health Technology Assessment and the contents of an HTA report. This scheme is further developed in this report. The preliminary phases (identification and scoping of the research topic) follow the general steps defined in the process docs of KCE (see appendix 1 for a brief schematic overview). The emphasis of this note is on the actual “Assessment report”, that describes the different aspects that need to be considered in a full HTA and which procedures need to be followed for an HTA. Procedures for short HTAs are highly similar. The structure of the report is the same, but the literature review may be less elaborate for some aspects.
of the assessment. Short HTAs generally take 3 to 4 months, whereas full HTAs take about 12 months to be completed.

The reference to a checklist for HTA reports, proposed and used by INAHTA (International Network of Health Technology Assessment Agencies) is presented in appendix 6. It is recommended to refer explicitly to this checklist in the HTA reports and if necessary replicate and comment on it in appendix. The items on the checklist do not have to be considered in all reports. Omission of items can be justified in appendix.

1.1 DEFINITION OF HTA

Health technology assessment is a multidisciplinary field of policy analysis. It studies the medical, social, ethical, and economic implications of development, diffusion, and use of health technology (INAHTA). Health technology is defined as prevention and rehabilitation, vaccines, pharmaceuticals and devices, medical and surgical procedures, and the systems within which health is protected and maintained.

The central idea of HTA is to involve all interested parties in the assessment of a health technology. Interested parties include manufacturers or sponsors of the technology, users of the technology (professionals, providers), patient groups and the commissioner of the assessment project.

1.2 GENERAL PROCEDURE HTA

HTA generally runs over two phases. In a first phase, topics for HTA are identified, priorities determined, research questions specified and the scope defined. Experts and stakeholders are identified, available literature scanned and preliminary analyses performed. (pre-assessment). This phase encompasses the first 4 frames in Figure 1 and is reflected in processes 1 to 3 of the Masterplan of KCE.

In the second phase, the assessment is being performed and a report developed. The HTA report is based on input from internal and external experts as well as from stakeholders. The process includes in principle different consultation rounds with experts during the assessment and one open consultation round after publication of the report. The number of rounds may vary from project to project. The final report, however, should take the comments of the different reviewers and stakeholders into account. This phase of the HTA encompasses processes 4 to 9 of the Masterplan of KCE.

This process note develops the second phase of the HTA process. For more information on the first phase and the relationship with other KCE processes, the reader is referred to Appendix 1.

An HTA always evaluates 4 elements:

- Clinical effectiveness: benefits and risks of the technology, expressed in for the patient relevant outcomes
- Cost-effectiveness: comparative analysis of the cost-effectiveness/cost-utility of alternative courses of action
- Patient issues: needs and preferences, patient information, compliance, obstacles and fears related to the use of the technology. These preferences could be discussed in a societal context, given prevailing social justice concerns (i.e. ethical-normative aspects of the technology)
- Organisational issues: optimal organisation of the health care infrastructure, diffusion of the technology, professional requirements, quality control, budget impact, legal recognition of the technology, legal aspects of organisation

To enhance our understanding of the impact of the use of a technology in Belgium, information should be gathered from scientific databases as well as from web-sites, interest groups (providers, patients, voluntary organisations and producers) and Belgian health care databases. Sufficient efforts must be put in collecting published and unpublished ("grey") literature.
International experience has shown that it may also be useful to consult informal documents, such as descriptions of training programmes, job descriptions, patient information leaflets, etc. This might improve the understanding of the current actual situation in Belgium and how this can be improved efficiently.

The different steps in the HTA process depend on the type of the technology and its phase in the technology life cycle.

A distinction is made between:
- emerging technologies
- establishing technologies
- mature technologies
- out-dated technologies

The process of an HTA and the major focus within the HTA will depend on the phase the technology. Depending on whether a technology is emerging, established, mature or outdated, the different elements of the HTA will get more or less emphasis and some sources of information will become more or less important. For example, in case of an emerging technology, the importance of grey literature will increase, due to a lack of published peer-reviewed evidence. In these cases interviews with stakeholders, surveys and focus groups might provide a useful input for the assessment.
2 METHODOLOGICAL APPROACH TO LITERATURE SEARCH FOR HTA: CLINICAL EFFECTIVENESS AND COST EFFECTIVENESS

Within the context of literature searching for health technology assessment (HTA), a search protocol is an explicit, structured procedure for tackling the task of locating information.

This note describes the required methodological approach to HTA literature searches performed for KCE. It provides guidance for reviewers on the various steps of the search, appraisal and presentation of the results. This approach should be followed for all HTAs.

The reader is also referred to the methodological note on evidence searches for GCP (specifically for the clinical effectiveness part). The major components of that note - where relevant for HTA - are also repeated in this note.

It is expected that researchers search in an “intelligent” manner. This means that appropriate use should be made of existing search filters and relevant MeSH terms. After one person has performed a literature search and selected relevant articles, a quality check should be performed by a second person. This quality control is an essential requirement and should be described in the report.

An evidence report consists of the following steps:
1. Formulating the problem and developing a protocol
2. Locating studies
3. Selecting studies
4. Quality assessment of studies
5. Collecting data, analysing and presenting results
6. Analysing and interpreting results

2.1 STEP 1 – FORMULATING THE QUESTION AND DEVELOPING A PROTOCOL

The first milestone of any review is the development of the protocol before proceeding with the literature review itself. The protocol specifies the plan to identify, appraise and collate evidence. A protocol for carrying out a review is equivalent to, and as important as, a protocol for a primary research study. A review is less likely to be biased if the questions are well developed beforehand, and the methods that will be used to answer them are decided on before gathering the necessary data and drawing inferences. In the absence of a protocol, it is possible that study selection and analysis will be unduly driven by (a presumption of) the findings.

2.1.1 Objectives

The review should begin with a precise statement of the primary aim of the review, including the intervention(s) or test(s) reviewed and the targeted problem. This may be followed by a series of specific objectives relating to different participant groups, different comparisons of interventions or different outcome measures.

The definition of a set of clear and focused clinical and economical questions is fundamental to the successful completion of a review. It is also important to be realistic about the number of questions that can be addressed in a single review if the final product is not to be too large to be useable. A large number of key questions also implies a very high workload for the reviewers, and care must be taken to ensure that this is kept within manageable limits.
2.1.2 Key components of a question

There are several key components to a well-formulated question (Richardson 1995, Counsell 1997). A clearly defined question should specify the population type (participants), types of interventions or exposures, and the types of outcomes that are of interest. A well known acronym used in this context is PICO (population, intervention, comparator, outcome). In addition, the types of studies that are relevant to answering the question should be specified.

In general the more precise one is in defining components, the more focused the review. Equal precision in addressing each component is not necessary. For example, one may want to concentrate on various treatments for a particular stage of breast cancer, or alternately to focus on a particular drug for any stage of breast cancer. In the former example, the stage and severity of the disease would have to be defined very precisely within the ‘Types of participants’. On the contrary, in the latter example, the treatment formulation would have to be defined very precisely within the ‘Types of intervention’.

2.1.3 Methods outlined for the review

In the protocol, details on the methods of the review should be outlined. Essential components are the databases that will be searched, the search terms that will be used, and the selection criteria by which studies will be in- or excluded from the review. Subsequently, the methods for quality assessments should be described, as well as the consequences of the appraisal, e.g. will low quality studies be excluded from the review, treated separately or included with the good quality studies.

Finally, a description of the data extraction and possible analyses should be included.

**Key points formulating the question and developing a protocol**

- Define the objective(s) of the review
- Define the PICO
- Specify the databases that will be searched, the search terms and the selection criteria for studies

2.2 STEP 2 – LOCATING STUDIES

A search strategy consists of several aspects. The research question should be used as a guide to direct the search strategy. For electronic searches, it is important to list the databases in which studies are sought, the terms used and filters applied and the dates on which the searches were performed to make it reproducible. Other sources can be consulted in order to identify all relevant studies. These include reference lists from relevant primary and review articles, journals, grey literature and conference proceedings, research registers, researchers and manufacturers and the internet.

In practice, it is rare for a single search to cover all the questions being addressed within a review. Different questions may be best answered by different databases, or may rely on different levels of evidence related to the research design and risk of bias. Authors are encouraged to take an iterative approach to the search, carrying out a search for high level evidence in first instance. After the results of this search have been evaluated, the questions may be redefined and subsequent searches focused on the most appropriate sources and study types.

In some cases good quality, directly relevant evidence synthesis (secondary sources) such as good quality systematic reviews or Health Technology Assessments (HTA) will have been produced on some of the issues that fall within the remit of the review. In these circumstances reference will be made to the existing evidence rather than repeating work that has already been done. All HTA reports or systematic reviews that are identified must be evaluated on their quality and be shown to have followed an acceptable methodology before they can be considered for use in this way.
In other cases existing evidence may not be directly relevant to the KCE, or may be found to have methodological weaknesses. In those cases, existing evidence can not be used in the review. But, excluded systematic reviews or HTA reports are a useful source of references that might be used later on in the review.

In summary, literature searches for the KCE should follow an iterative approach, searching for evidence synthesis first (HTAs and systematic reviews) and subsequently complementing this by searching for original studies.

The various bibliographic databases are listed in the following paragraph.

2.2.1 Electronic searches

Multiple electronic bibliographic databases exist. Some databases, such as MEDLINE and EMBASE, cover all areas of health care and index journals published from around the world. The Cochrane Collaboration has been developing an electronic database ("CENTRAL") that is now the best single source of information about records that relate to controlled trials (Dickersin 2002). For economic searches, NHSEED of CRD should be searched in addition to MEDLINE and EMBASE. ECONLIT can be a complement to these databases for economic studies, but in general the added value of this database for finding economic evaluations is limited, as most economic evaluations figuring in this database are also included in MEDLINE and/or EMBASE.

Authors of an HTA should always start by consulting the HTA-database via the CRD website: http://www.york.ac.uk/inst/crd/revs.htm and individual agencies’ sites (see www.inahta.org under members and HTAi vortal). In general, existing HTA’s on the same subjects will already be located and retrieved during the pre-assessment in the preparatory stage of the research project.

Systematic reviews can be found in the Cochrane Database for Systematic Reviews, in DARE or in Medline. The three electronic bibliographic databases generally considered as the richest sources of primary studies - MEDLINE, EMBASE, and CENTRAL - are essential in any literature review for the KCE. Details of other databases that might contain eligible records are listed at the website of NICE (http://www.nice.org.uk/page.aspx?o=516408). Specifically for drugs and technology reviews, data from the US Federal Drug Administration or EMEA can be helpful. Providing an exhaustive list of all possible sources is not possible.

2.2.1.1 Selected general medical databases

- Centre for Reviews and Dissemination (CRD) includes the Database of Abstract of Reviews of Effects (DARE), the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment Database (HTA): The 3 different CRD databases include structured abstracts, identified by regular searching of bibliographic databases, and hand searching of key journals.
- MEDLINE: Bibliographic records and abstracts of biomedical literature, from 1966 onwards.
- EMBASE: Records of biomedical literature, from 1974 onwards.

2.2.1.2 Specific medical databases

- CENTRAL (The Cochrane Controlled Trials Register): Records of randomised controlled trials and controlled clinical trials in healthcare identified through the work of the Cochrane Collaboration including large numbers of records from MEDLINE and EMBASE as well as much material not covered by these databases.
- CINAHL (Cumulative Index to Nursing and Allied Health Literature): Records of literature on all aspects of nursing and allied health disciplines.
- PEDro: PEDro is the Physiotherapy Evidence Database. It contains records of RCT’s, systematic reviews and evidence-based clinical practice guidelines in physiotherapy. Most trials on the database have been rated for quality to quickly discriminate between trials which are likely to be valid and interpretable and those which are not.
Clinical Trial Registries: several initiatives have been taken recently to register ongoing trials. The WHO Registry Platform is a project within the World Health Organization, to unite all possible trial register (http://www.who.int/ictrp/en/). Other examples are ClinicalTrials.gov (http://clinicaltrials.gov/), TrialsCentral (www.trialscentral.org), Current Controlled Trials (www.controlled-trials.com), or Eudract (http://eudract.emea.europa.eu/). Ongoing trials may have limited use as a means of identifying studies relevant to systematic reviews, but may be important so that when a review is later updated, these studies can be assessed for possible inclusion.

2.2.1.3 Search terms

Constructing an effective combination of search terms for searching electronic databases requires a structured approach. One such approach involves breaking down the review question into ‘facets’, such as population, interventions, outcomes and study designs.

The next stage is to identify the search terms in each ‘facet’ which best capture the subject. The group of search terms covering each facet of the review question should include a range of text words (free text) in the title and abstract of studies as well as any available subject indexing terms that are assigned by the database producer. Text words and their variants can be identified from reading relevant reviews and primary studies identified during earlier searches. Information on the subject indexing used by databases can be found by consulting the relevant indexing manuals and by noting the manner in which key retrieved articles have been indexed by a given database. The final search strategies will be developed by an iterative process in which groups of terms are used, perhaps in several permutations, to identify the combination of terms that seems most sensitive in identifying relevant studies. This requires skilled adaptation of search strategies based on knowledge of the subject area, the subject headings and the combination of ‘facets’ which best capture the topic.

An example:

The question: In patients undergoing hip replacement, to what extent is the risk of post-operative infection reduced by antimicrobial prophylaxis?

Break down of the question into ‘facets’

<table>
<thead>
<tr>
<th>Population</th>
<th>Interventions</th>
<th>Outcome</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients undergoing hip replacement</td>
<td>Antimicrobial prophylaxis</td>
<td>Post-operative infection</td>
<td>Randomised Controlled Trials</td>
</tr>
</tbody>
</table>
Subject headings, synonyms or spelling variants for post-operative infection:

<table>
<thead>
<tr>
<th>Text terms</th>
<th>MEDLINE subject headings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial infection</td>
<td>BACTERIAL INFECTIONS</td>
</tr>
<tr>
<td>Postoperative complication(s)</td>
<td>POSTOPERATIVE COMPLICATIONS</td>
</tr>
<tr>
<td>Wound infection</td>
<td>SURGICAL WOUND INFECTION</td>
</tr>
<tr>
<td>PROSTHESIS-RELATED INFECTIONS</td>
<td></td>
</tr>
<tr>
<td>Septicaemia</td>
<td>SEPSIS</td>
</tr>
<tr>
<td>Bacterial contamination</td>
<td>INFECTION CONTROL</td>
</tr>
</tbody>
</table>

2.2.1.4 Filters

In systematic reviews, if time and resources allow, specificity is often sacrificed in favour of sensitivity, to maximize the yield of relevant articles. Therefore, it is not unusual to retrieve large numbers (possibly thousands) of bibliographic references for consideration for inclusion in an extensive systematic review. This means that reviewers may have to spend a lot of time scanning references to identify perhaps a limited number of relevant studies.

Search filters are available to focus the search according to the type of study that is sought, for example to focus on randomized controlled trials, on diagnostic accuracy studies, on prognostic studies or on systematic reviews (see example in Appendix). Several filters are available in PubMed at the Clinical Queries screen. Other filters can be found at the SIGN website: [http://www.sign.ac.uk/methodology/filters.html#systematic](http://www.sign.ac.uk/methodology/filters.html#systematic). Within the KCE library, several filters are available, also for the EMBASE database. For an example of a filter for systematic reviews, see note on search strategies for GCP.

2.2.2 Hand searching: checking reference lists

Authors should check the reference lists of articles obtained (including those from previously published systematic reviews) to identify relevant reports. The process of following up references from one article to another is generally an efficient means of identifying studies for possible inclusion in a review. Because investigators may selectively cite studies with positive results (Gotzsche 1987; Ravnskov 1992), reference lists should never be used as a sole approach to identifying reports for a review, but rather as a complement to other approaches.

2.2.3 Finding unpublished data

For registration purposes related to marketing and reimbursement, producers provide data to regulatory agencies such as FDA (drugs, implants, medical devices) and EMEA (drugs only). Part of this data can be consulted, although the search can be quite cumbersome.

In the HTA process, the manufacturers are demanded to supply all clinical data, published and unpublished, possibly with a confidentiality clause if needed.

2.2.4 Finding evidence on adverse effects

The first sources to investigate for information on adverse effects are reports from trials or other studies included in a systematic review. Excluded reports might also provide some useful information. There are a number of specific sources of information on adverse effects of drugs, including Current Problems produced by the UK Medicines Control Agency (http://www.open.gov.uk/mca), MedWatch produced by the US Food and Drug Administration, and the Australian Adverse Drug Reactions Bulletin (http://www.health.gov.au/). In Belgium, there is currently no public database on adverse events. Other regulatory authorities (such as the websites of FDA and EMEA) and the
manufacturer may also be able to provide some information. Information on adverse effects might also be sought from other types of studies than those considered appropriate for the systematic review (e.g. cohort and case-control studies, uncontrolled trials, case series and case reports). However, all such studies and reports are subject to bias to a greater extent than randomized trials, and findings must be interpreted with caution. Sometimes, the authors of pivotal trials need to be contacted.

2.2.5 Documenting a search strategy

The search strategy has to be sufficiently detailed, so that by following the description, the search can be reproduced with the same result. That is to say, it should include information about not only how you intend to perform the literature search, but also how you in fact did search for it.

The bibliographic databases searched, the dates and periods searched and any constraints, such as language should be stated. The full search strategies for each database should be listed in an additional table in the appendix.

The following information should be included for each electronic bibliographic database each time it is searched, including CENTRAL and specialized registers:

- Title of database searched (e.g. MEDLINE)
- Name of the host (e.g. Ovid version xx)
- Date search was run (month, day, year)
- Years covered by the search
- Complete search strategy used, including all search terms (preferably cut and pasted rather than retyped)
- One or two sentence summary of the search strategy indicating which lines of the search strategy were used to identify records related to the health condition and intervention, and which lines were used to identify studies of the appropriate design
- Any language restrictions or the absence of it

Standard search strategy tables should be used to document your search strategy (appendix 2). These tables are included in the appendix of the HTA report:

**Key points**

<table>
<thead>
<tr>
<th>Steps for locating studies:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Search for HTA studies (published or ongoing)</strong></td>
</tr>
<tr>
<td><strong>Search for Systematic reviews</strong></td>
</tr>
<tr>
<td><strong>Search for Primary studies</strong></td>
</tr>
<tr>
<td><strong>Search for Evidence-based Guidelines</strong></td>
</tr>
<tr>
<td><strong>Search for (ongoing) trials</strong></td>
</tr>
<tr>
<td><strong>Search additional resources: grey literature, government publications, registration agencies, professional associations, hand searching, web-searching</strong></td>
</tr>
</tbody>
</table>
2.3  **STEP 3 – SELECTING STUDIES**

Study selection is a multi-stage process. The process by which studies will be selected for inclusion in a review should be described in the review protocol.

2.3.1  Evidence sifting

Before any papers are acquired for evaluation, sifting of the search output is carried out to eliminate irrelevant material. Papers that are clearly not relevant to the key questions are eliminated based on their title. Abstracts of remaining papers are then examined and any that are clearly not appropriate study designs, or that fail to meet specific methodological criteria, will be also eliminated at this stage. All reports of studies that are identified as potentially eligible must then be assessed in full text to see whether they meet the inclusion criteria for the review.

The reproducibility of this process should be tested in the initial stages of the review, and if reproducibility is shown to be poor more explicit criteria may have to be developed to improve it.

Authors must decide whether more than one author will assess the relevance of each report. Whatever the case, the number of people assessing the relevance of each report should be stated in the Methods section of the review. Some authors may decide that assessments of relevance should be made by people who are blind or masked to the journal from which the article comes, the authors, the institution, and the magnitude and direction of the results by editing copies of the articles (Berlin 1997a; Berlin 1997b). However, this takes much time, and may not be warranted given the resources required and the uncertain benefit in terms of protecting against bias (Berlin 1997b).

2.3.2  In- and exclusion

The final inclusion/exclusion decisions should be made after retrieving the full texts of all potentially relevant citations. Reviewers should assess the information contained in these reports to see whether the criteria have been met or not. Many of the citations initially included may be excluded at this stage.

The criteria used to select studies for inclusion in the review must be clearly stated:

**TYPES OF STUDIES**

Eligible study designs should be stated here, along with any thresholds for inclusion based on the conduct or quality of the studies. For example, ‘All randomised controlled comparisons’ or ‘All randomised controlled trials with blind assessment of outcome’ or ‘All full economic evaluations’. Exclusion of particular types of randomised studies (for example, cross-over trials) should be justified. It is generally for authors to decide which study design(s) to include in their review. Some reviews are more restrictive, and include only randomized trials, while others are less restrictive, and include other study designs as well, particularly when few randomized trials addressing the topic of the review are identified. For example, many of the reviews from the Cochrane Effective Practice and Organization of Care (EPOC) Collaborative Review Group include before-and-after studies and interrupted time series in addition to randomized and quasi-randomized trials.

**TYPES OF PARTICIPANTS**

The diseases or conditions of interest should be described here, including any restrictions on diagnoses, age groups and settings. Subgroup analyses should not be listed here.

**TYPES OF INTERVENTIONS**

Experimental and control interventions should be defined here, making it clear which comparisons are of interest. Restrictions on dose, frequency, intensity or duration should be stated. Subgroup analyses should not be listed here.
**Types of Outcome Measures**

Note that outcome measures do not always form part of the criteria for including studies in a review. If they do not, then this should be made clear. Outcome measures of interest should be listed in this section whether or not they form part of the inclusion criteria.

**Quality Control**

For most reviews it will be worthwhile to pilot test the inclusion criteria on a sample of articles (e.g. ten to twelve papers, including ones that are thought to be definitely eligible, definitely not eligible and questionable). The pilot test can be used to refine and clarify the inclusion criteria, train the people who will be applying them and ensure that the criteria can be applied consistently by more than one person.

Even when explicit inclusion criteria have been specified, decisions concerning the inclusion of individual studies remain relatively subjective. There is evidence that using at least two authors has an important effect on reducing the possibility that relevant reports will be discarded (Edwards 2002). Agreement between assessors may be formally assessed mathematically using Cohen’s Kappa (a measure of chance-corrected agreement). Many disagreements may be simple oversights, whilst others may be matters of interpretation. These disagreements should be discussed, and where possible resolved by consensus after referring to the protocol. If disagreement is due to lack of information, the authors may have to be contacted for clarification. Any disagreements and their resolution should be recorded. The influence of uncertainty about study selection may be investigated in a sensitivity analysis.

It is useful to construct a list of excluded studies at this point, detailing the reason for each exclusion. This list may be included in the report of the review as an appendix. The final report of the review should also include a flow chart or a table detailing the studies included and excluded from the review. A separate flow chart for the clinical review and the economic review is warranted.

In appendix 3 a tool for documenting evidence sifting and in- and exclusion of articles is presented. Appendix 4 presents a flow chart for documenting the study selection. If resources and time allow, the lists of included and excluded studies may be discussed with the expert panel. It may be useful to have a mixture of subject experts and methodological experts assessing inclusion.

**Key points about study selection**

- Studies should be selected based on selection criteria resulting from the review questions, and that have been piloted to check that they can be reliably applied.
- Study selection is a staged process involving sifting through the citations located by the search, retrieving full reports of potentially relevant citations and, from their assessment, identifying those studies that fulfil the inclusion criteria.
- Parallel independent assessments minimise the risk of errors of judgement. If disagreements occur between reviewers, they should be resolved according to a predefined strategy using consensus and arbitration as appropriate.
- The study selection process should be documented, detailing reasons for inclusion and exclusion.
2.4 **STEP 4 – CRITICAL APPRAISAL OF THE EVIDENCE**

Each report, article or guideline that is selected as a potential source of evidence is critically appraised based on the following questions:

1. Is the article relevant to the subject?
2. Are the article’s results valid?
3. Are the article’s results important for answering the question?

The methodological assessment is based on a number of key questions that focus on those aspects of the study design that have a significant influence on the validity of the results reported and conclusions drawn. These key questions differ between study types, and a range of checklists can be used to bring a degree of consistency to the assessment process (appendix 5):

- For **HTA reports**, the INAHTA checklist is recommended (see reference in appendix 6). Key questions are the adequacy of the literature search and quality appraisal of the selected studies.
- For the quality appraisal of **systematic reviews**, the checklist of the Dutch Cochrane Centre can be used (see appendix 6). These checklists were translated into a French version by experts of the KCE (available on demand). Key aspects are similar to those for HTA reports (adequacy of literature search and quality appraisal).
- Examples of checklists for **primary studies**, such as those from Dutch Cochrane (also translated in French by KCE experts) and SIGN, can be found in appendix. For randomised controlled trials, the randomisation process, blinding of the outcome assessors and an intention-to-treat-analysis are important quality criteria. For observational studies, blinded assessment of the outcomes and adequate dealing with confounders are essential.
- A quality assessment checklist for **economic evaluations** is presented in appendix 6. The checklist offers a qualitative assessment of the quality of an economic evaluation. No quality score is assigned. Final decision depends on the evaluation of the author of the review.

The critical appraisal process inevitably involves a degree of subjective judgement. To minimise any potential bias resulting from this, it is recommended that each study is evaluated independently by two members of the project group. Any differences in assessment should be discussed. Where differences cannot be resolved, an independent reviewer or an experienced member of the staff will arbitrate to reach an agreed quality assessment. Validation by a third researcher experienced in literature review is highly recommended as part of the quality control process.

2.5 **STEP 5 – DATA EXTRACTION, TABLES OF EVIDENCE, AND LEVEL OF EVIDENCE**

Data extraction implies the process of extracting the information from the selected studies that will be ultimately reported. In order to allow an efficient data extraction, the process should be detailed in the protocol before the literature search is started. Key components of the data extraction for clinical studies include:

- information about study reference(s) and author(s);
- verification of study eligibility;
- study characteristics:
  - study methods
  - participants
  - interventions
  - outcome measures and results
Key components of the data extraction for economic evaluations include:

- information about study reference(s) and author(s);
- verification of study eligibility;
- study characteristics:
  - study design (cost-effectiveness, cost-utility, cost-benefit analysis + observational, model)
  - perspective
  - Time window
  - population
  - interventions
  - cost and outcome measures + source
  - modelling assumptions
  - discount rates
  - sensitivity analysis
  - results

A template for the economic data extraction sheet is presented in appendix 6.

All validated studies identified from the systematic literature review relating to each key search question are summarized into evidence tables. The content of the evidence tables is determined by the entire project group. Completion for all retained articles is done by one member of the project group.

As a basis for the tables of clinical evidence, the Summary of Findings (SoF) tables of the Cochrane Collaboration are used. For an example, see KCE note on evidence searches for GCP. SoF tables have been suggested to help readers quickly focus on the key results and access information that is needed to inform a decision. The SoF table includes information on each of the main outcomes addressed in the review. The number of patients and trials, the control group risk, the effect size (relative and absolute), and the quality of the evidence are presented for each main outcome separately.

For the economic evidence, separate SoF tables may have to be developed for the different aspects of the economic evaluations to increase readability (e.g. perspective, time window and discount rate could be combined in one table; outcomes, costs and cost-effectiveness ratios in another). The project group should determine the contents of the SoF tables.

To allocate a level of evidence to clinical evidence, the GRADE system is used (http://www.chestjournal.org/cgi/reprint/129/1/174?ijkey=1eeff3fc9de62d407c46a389d2e968d93532eceb). The quality of the evidence ranges from high, over moderate and low, to very low. The study design is the major determinant for the level of evidence, but this level can be lowered or increased depending on the quality of the evidence.

**2.6 STEP 6 – ANALYSING AND INTERPRETING RESULTS**

Once the eligible studies are selected and quality appraised, the magnitude of the intervention effect should be estimated. The best way to do this is by performing a meta-analysis (i.e. the statistical combination of results from two or more separate studies), although this is not always feasible. An interesting tool for doing a limited meta-analysis is the free Review Manager software of the Cochrane Collaboration.

For economic evaluations meta-analyses are usually not feasible, given the large impact of contextual factors on estimates of costs. The analysis and interpretation of economic results from literature will therefore usually be qualitative. Exceptions are where Belgian data are available in literature. In that case, it is necessary to report (separately) the incremental costs, incremental effects and incremental cost-effectiveness ratio.

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*a* [http://www.cochrane.org/ccsg/SummaryofFindingstableandsplainlanguagesummaries.doc](http://www.cochrane.org/ccsg/SummaryofFindingstableandsplainlanguagesummaries.doc)

*b* [http://www.cc-ims.net/RevMan](http://www.cc-ims.net/RevMan)
3 METHODOLOGICAL APPROACH TO THE SEARCH FOR INFORMATION FOR HTA: ETHICAL AND PATIENT ISSUES

Two levels are relevant for the discussion of patient issues: the patient level and the societal level. For each of these levels, the following sources of information can be suggested; apart from the literature databases earlier described:

3.1 PATIENT LEVEL

- Patient associations / Self-help groups: by inviting them at experts meeting or by meeting their representatives separately, it is possible to be informed on the patients’ difficulties, expectations and initiatives. In case of absence of such groups, patients could be directly interviewed (separately or by focus groups)
- Implication on Quality of Life (QoL) and well-being: these aspects have to be studied to have an overview on the implications of the studied technology for the patient’s daily life. Psychosocial impact of the technology could be included here as well as a very pertinent theme. A literature (including grey literature) and Internet search (discussion forums) are recommended here, besides the meeting with patient associations if these exist.
- Economic implications for the patient: Besides the cost-effectiveness of the technology, implications for the patient have to be documented: does the social insurance cover all the expenses, what are the out-of-pocket expenses for the technology, at which frequency, for how long. These could be appraised by reviewing the literature, the Internet or interviewing patients (separately or by focus groups) …
- Ethical issues: Does the technology have to be proposed / imposed to everyone, what are the ethical questions that this technology raises? After having defined the ethical questions that the technology raises, answers could be addressed by means of a literature search but may have to be complemented with a roundtable with ethicists, using eventually theoretical cases to stimulate the discussion.

3.2 SOCIETAL LEVEL

Social justice has to be addressed by literature search and/or by roundtables with ethicists, sociologists and or economists.

Literature that clarifies questions on the patient/user perspective can be found in databases like Sociological Abstracts, PsycInfo, Embase and Medline, but often it will be necessary to supplement this information with literature and information from other sources. This might be found on the patient organisations’ websites or others.

To appraise the patient issues related to a technology, several qualitative methodologies could be used to retrieve the kind of information needed:

- Literature review
- Search on the Internet
- Interviews or focus groups
- Roundtables
METHODOLOGICAL APPROACH TO LITERATURE SEARCH FOR HTA: ORGANISATIONAL AND LEGAL ISSUES

To address organisational and legal issues, it is often useful to study the organisation and legislation with respect to the technology in other countries.

For legal issues, the following databases are useful:

- Jura (Belgian legislation, jurisdiction)
- http://www.legifrance.gouv.fr/ (French legislation)
- http://wetten.overheid.nl/ (Dutch legislation)
- http://bundesrecht.juris.de/ (German legislation)
- http://www.bundesanzeiger.de/ (German legislation)
- http://www.opsi.gov.uk/legislation/about_legislation.htm (British legislation)
- http://eur-lex.europa.eu/ (European legislation)

For organisational issues, the methodological approach is highly similar to the approach described in “Methodological approach to literature search for HTA: clinical effectiveness and cost effectiveness”, with an appropriate search strategy for this specific issue. Grey literature may be relatively more important for this component of HTA.
### APPENDICES

#### APPENDIX 1: DESCRIPTION OF ALL STEPS IN THE HTA PROCESS (FULL HTA)

<table>
<thead>
<tr>
<th>&lt; -3 months</th>
<th>Process 1</th>
<th>Board of KCE decides to review technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month -3</td>
<td>Process 2</td>
<td>Preparation of Pre-project fiche (PPF)</td>
</tr>
<tr>
<td>Month -2</td>
<td>Process 3</td>
<td>Preparation of Project fiche (PF)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Internal project: redaction final PF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Outsourcing: selection external partner</td>
</tr>
<tr>
<td>Month 0</td>
<td>Process 4 &amp; 5</td>
<td>Search for evidence and data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Collection of evidence and data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Consultation with stakeholders/ industry to submit evidence</td>
</tr>
<tr>
<td>Month 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>Process 4 &amp; 5</td>
<td>Quality assessment of evidence</td>
</tr>
<tr>
<td>Month 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 5</td>
<td>Process 6</td>
<td>Critical appraisal of evidence and data analysis</td>
</tr>
<tr>
<td>Month 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 8</td>
<td>Process 7</td>
<td>Synthesis of findings (pre-final HTA report)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- consultation with external experts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- (consultation with industry for feedback on analyses)</td>
</tr>
<tr>
<td>Month 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 10</td>
<td>Process 8</td>
<td>External validation of HTA report</td>
</tr>
<tr>
<td>Month 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 12</td>
<td>Process 9</td>
<td>Presentation of HTA report to the Board of KCE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Publication on the website of KCE</td>
</tr>
</tbody>
</table>
# APPENDIX 2: DOCUMENTING A SEARCH STRATEGY

<table>
<thead>
<tr>
<th>Author</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td></td>
</tr>
<tr>
<td>Project number</td>
<td></td>
</tr>
<tr>
<td>Project name</td>
<td></td>
</tr>
<tr>
<td>Keywords</td>
<td></td>
</tr>
</tbody>
</table>

| Date (day month year) |  |
| Database (name +provider; eg Medline OVID) |  |
| Search Strategy (attention, for PubMed, check « Details ») |  |
| Note |  |

The second table must be copied as many times as necessary.
# APPENDIX 3: LITERATURE SELECTION TOOL

## Sheet 1: selection criteria

<table>
<thead>
<tr>
<th>Selection criteria</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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</thead>
<tbody>
<tr>
<td>Population</td>
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<td></td>
</tr>
<tr>
<td>Intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Design</td>
<td></td>
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</tbody>
</table>

## Sheet 2: Database Searching

<table>
<thead>
<tr>
<th>Nbr</th>
<th>Citation</th>
<th>Title and abstract evaluation</th>
<th>Full text evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Citation selected</td>
<td>Citation excluded</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

## Sheet 3: Database search synthesis

### References excluded (abstract)

- Design: 0
- Intervention: 0
- Outcome: 0
- Population: 0

**Total:** 0

### References excluded (full text)

- Design: 0
- Intervention: 0
- Outcome: 0
- Population: 0
- Language: 0
- Same as already published: 0
- Reference not found: 0

**Total:** 0
APPENDIX 4: FLOW DIAGRAM OF STUDY SELECTION PROCESS QUORUM


Potentially relevant studies identified and screened for retrieval (n=…)

Studies excluded with reason x (n=…)

with reason y (n=0)

Studies retrieved for more detailed information (n=…)

Studies excluded with reason x (n=…)

with reason y (n=0)

Potentially appropriate studies to be included in the review (n=…)

Studies excluded with reason x (n=…)

with reason y (n=0)

Studies ultimately included in the review (n=…)
APPENDIX 5: QUALITY APPRAISAL CHECKLISTS

HTA REPORTS

INAHTA checklist for the appraisal of HTA reports:
http://www.dimdi.de/static/de/hta/methoden/sammlung/inahtachecklist.pdf

QUADAS CHECKLIST FOR DIAGNOSTIC ACCURACY STUDIES

http://www.biomedcentral.com/1471-2288/3/25

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was the spectrum of patients representative of the patients who will receive the test in practice?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Were selection criteria clearly described?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Is the reference standard likely to correctly classify the target condition?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Did patients receive the same reference standard regardless of the index test result?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Was the execution of the index test described in sufficient detail to permit replication of the test?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Was the execution of the reference standard described in sufficient detail to permit its replication?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Were the reference standard results interpreted without knowledge of the results of the index test?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Were uninterpretable/intermediate test results reported?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Were withdrawals from the study explained?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
DUTCH COCHRANE CHECKLISTS


HIERARCHY OF ECONOMIC STUDIES


<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Evaluation of important alternative interventions comparing all clinically relevant outcomes against appropriate cost measurement, and including a clinically sensible sensitivity analysis</td>
</tr>
<tr>
<td>2</td>
<td>Evaluation of important alternative interventions comparing a limited number of outcomes against appropriate cost measurement, but including a clinically sensible sensitivity analysis</td>
</tr>
<tr>
<td>3</td>
<td>Evaluation of important alternative interventions comparing all clinically relevant outcomes against inappropriate cost measurement, but including a clinically sensible sensitivity analysis</td>
</tr>
<tr>
<td>4</td>
<td>Evaluation without a clinically sensible sensitivity analysis</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion with no explicit critical appraisal, based on economic theory</td>
</tr>
</tbody>
</table>

CHECKLIST FOR ASSESSING ECONOMIC EVALUATIONS


- Is there a well defined question?
- Is there comprehensive description of alternatives?
- Are all important and relevant costs and outcomes for each alternative identified?
- Has clinical effectiveness been established?
- Are costs and outcomes measured accurately?
- Are costs and outcomes valued credibly?
- Are costs and outcomes adjusted for differential timing?
- Is there an incremental analysis of costs and consequences?
- Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?
- How far do study results include all issues of concern to users?
- Are the results generalisable to the setting of interest in the review?
## APPENDIX 6: ECONOMIC EVALUATIONS SUMMARY SHEET

<table>
<thead>
<tr>
<th>Author</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td></td>
</tr>
<tr>
<td>Design</td>
<td></td>
</tr>
<tr>
<td>Perspective</td>
<td></td>
</tr>
<tr>
<td>Time window</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td></td>
</tr>
<tr>
<td>Assumptions</td>
<td></td>
</tr>
<tr>
<td>Data source for costs</td>
<td></td>
</tr>
<tr>
<td>Cost items included</td>
<td></td>
</tr>
<tr>
<td>Data source for outcomes</td>
<td></td>
</tr>
<tr>
<td>Discounting</td>
<td></td>
</tr>
<tr>
<td>Costs</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td></td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td></td>
</tr>
<tr>
<td>Conclusions</td>
<td></td>
</tr>
<tr>
<td>Remarks</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX 7: USEFUL LINKS

- Cochrane: [www.cochrane.org](http://www.cochrane.org)
  - Dutch Cochrane Centre: [www.cochrane.nl](http://www.cochrane.nl)
  - CEBAM: [www.cebam.be](http://www.cebam.be)
- SIGN: [http://www.sign.ac.uk/](http://www.sign.ac.uk/)
- CRD: [http://www.york.ac.uk/inst/crd/index.htm](http://www.york.ac.uk/inst/crd/index.htm)
- EUNETHA: [http://www.eunetha.net/](http://www.eunetha.net/)
- GRADE working group: [http://www.gradeworkinggroup.org/](http://www.gradeworkinggroup.org/)
- PubMed: [http://www.pubmed.gov](http://www.pubmed.gov)
- FDA: [http://www.fda.gov](http://www.fda.gov)
KCE Process notes

Searching for Evidence and Critical Appraisal

- Good Clinical Practice (GCP)
- Health Technology Assessment (HTA)
- Health Services Research (HSR)