eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

GUIDELINE

COMPARATORS & COMPARISONS

Criteria for the choice of the most appropriate comparator(s)
Summary of current policies and best practice recommendations

Adapted version (2015)

based on

"Comparators & Comparisons: Criteria for the choice of the most appropriate comparator(s)" - February 2013

The primary objective of EUnetHTA JA1 WP5 methodology guidelines was to focus on methodological challenges that are encountered by HTA assessors while performing a rapid relative effectiveness assessment (REA) of pharmaceuticals.

The guideline “Comparators & comparisons: criteria for the choice of the most appropriate comparator(s)” has been elaborated during Joint Action 1 by experts from NICE, reviewed and validated by HAS and by all members of WP5 of the EUnetHTA network; the whole process was coordinated by HAS.

During Joint Action 2 the wording in this document has been revised by WP7 in order to extend the scope of the text and recommendations from pharmaceuticals only to the assessment of all health technologies. Content and recommendations remained unchanged.

This 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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Acronyms – Abbreviations

AHRQ	Agency for Healthcare Research and Quality (USA)
ATC	Anatomical Therapeutic Chemical Classification System
CADTH	Canadian Agency for Drugs and Technologies in Health (Canada)
CE mark	a mandatory conformance mark on many products placed on the single market in the EU (including medical devices)
CHMP	Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
EUnetHTA	European network for Health Technology Assessment
FDA	Food and Drug Administration (USA)
HIQA	Health Information and Quality Authority (Ireland)
HTA	Health technology assessment
JA	Joint Action
MSAC	Medical Services Advisory Committee (Australia)
NICE	National Institute for Health and Clinical Excellence (England and Wales)
PBAC	Pharmaceutical Benefits Advisory Committee (Australia)
PICO	Population, Intervention, Comparator, Outcome
PHARMAC	Pharmaceutical Management Agency (New Zealand)
REA	relative effectiveness assessment
SMC	Scottish Medicines Consortium (Scotland)
SPC	Summary of Product Characteristics

Summary and recommendations

Summary

A comparator in a relative effectiveness assessment (REA) is a health care intervention or other technology with which the intervention/technology to be assessed is compared in order to establish if it has an added therapeutic benefit (including clinical as well as quality of life benefits). Such comparator could be a pharmaceutical, but also a medical device, a procedure or psychological approach, radiotherapy, physiotherapy, surgery or, if appropriate, providing advice, for example advice on diet or smoking, a combination of health care interventions carried out simultaneously or in sequence, or “watchful waiting” (no intervention).

Based on the guideline development during JA1 this document summarises the available literature, the advice provided by existing national guidelines, and the information from current national practice on the choice of comparator for REA[1], established previously through a EUnetHTA background review on the use of REA across Europe. The analysis of this information demonstrates that there is broadly agreement across countries about the general definition of the comparator for a REA: in the context of making decisions about where a new health technology would be used in clinical practice, or about reimbursement, a comparator is commonly defined as current routine care in the individual health care system, the most used, or what would be replaced by the introduction of that new health technology..

Therefore, under ideal circumstances the comparator for a REA applicable across European countries would be the reference treatment according to up to date high-quality clinical practice guidelines at European or international level, with good quality evidence on the efficacy and safety profile from published medical literature, and with an EU marketing authorisation or another form of recognised regulatory approval for the appropriate indication and line of treatment.

However, in many circumstances there is no consensus across European countries on what constitutes routine clinical care, and real life patient populations are likely to be heterogeneous across countries. Furthermore, in some countries the choice of comparator is governed by legislation, and can also refer to cost. In other countries, it is governed by the purpose to gain as much insight as possible about the new health technology; for example to achieve this for pharmaceuticals, the comparator needs to be from a similar pharmaceutical class. Only for pharmaceuticals to treat rare diseases, the Orphan Medicinal Designation endorses a consensus position on standard of care in rare diseases.

Therefore, the detailed approaches vary across countries and the choice of the comparator for REA depends mainly on the specific assessment question in each country.

This document provides a summary of current national policies and best practice recommendations for HTA assessors for selecting the most appropriate comparator for relative effectiveness assessments.

[1] This document does not intend to provide advice on how to design clinical trials.

Recommendations

Recommendations on the choice of the most appropriate comparator depend on the specific assessment question in any REA. The recommendations below assume that the assessment question is to establish the relative effectiveness of a health technology compared with routine clinical care, the most used, or what would be replaced by the introduction of that new technology.

Recommendation 1

Under ideal circumstances the comparator for a REA applicable across European countries should be the reference treatment according to up to date high-quality clinical practice guidelines at European or international level with good quality evidence on the efficacy and safety profile from published scientific literature, and with an EU marketing authorisation or another form of recognised regulatory approval for the respective indication and line of treatment.

Recommendation 2

Where there is no European-wide agreed reference comparator

- evidence needs to be available that the chosen comparator intervention is routinely used in clinical practice (Recommendation 3)
- the comparator intervention is validated for the respective clinical indication/population and evidence is available (Recommendation 4)

Recommendation 3

Evidence that the intervention is used in routine clinical care could come, in order of preference, from:

- National reimbursement lists if available
- Prescription statistics (if appropriate)
- Market surveys
- Discussion with clinical specialists and patient organisations
- Registries
- Validated clinical protocols
- If the above are not available: Internet searches, in particular patient and professional websites

Recommendation 4

The choice of comparator should be supported by evidence on its efficacy and safety profile described in published medical literature, and based on randomised controlled trials, pragmatic trials or good quality observational studies.

Recommendation 5

Where the comparator is a pharmaceutical, it has to be optimally dosed or scheduled in line with its marketing authorization or high-quality clinical practice guidelines.

Where the comparator is not a pharmaceutical, it should be used according to evidence based methodology and its instructions for use.

Recommendation 6

Where patient subpopulations are considered, for example according to disease severity, lines of treatment, stages of disease or genetic characteristics, additional comparators may need to be included and should be clearly identified.

Recommendation 7

The most appropriate comparators for an assessment should be identified before the assessment begins or in the early phase of an assessment.

The following recommendations relate to specific national procedural rules, and are only relevant for specific countries

Recommendation 8

If required by national procedural rules, the comparator must have an EU or national marketing authorisation, or if not a pharmaceutical, another form of recognised regulatory approval, for the appropriate indication and line of treatment.

Recommendation 9

If required by national procedural rules, if there are several alternatives, the more economic therapy should be selected as comparator, preferably one for which there is a reference price within the health care system.

Recommendation 10

If required by national procedural rules, and depending on the assessment question, for pharmaceuticals the comparator may need to be from a similar pharmaceutical class.

1. Introduction

1.1. Definitions and general information

In the context of relative effectiveness assessment, a comparator is a health care intervention with which a given intervention/technology of interest is compared in order to establish if it has an added therapeutic benefit (including clinical as well as quality of life benefits). Such comparator could be a pharmaceutical, a medical device, a procedure or psychological approach, surgery or, if appropriate, providing advice, for example advice on diet or smoking, any combination of these, or “watchful waiting” (no intervention).

Because many aspects of selecting the appropriate comparator are governed by national policies, and are not a scientific matter, a full methodological guideline is not possible to establish. Therefore, this document provides a summary of current national policies and general best practice recommendations for HTA assessors for selecting the most appropriate comparator for relative effectiveness assessments.

1.2. Context

1.2.1. Problem statement

Comparing new health care interventions with existing treatments is carried out for different purposes. For the purposes of granting a marketing authorisation of a pharmaceutical, the EMA and FDA specify the comparator to be placebo and/or active comparator. The EMA has recently published a consultation paper on the regulatory position of the importance of an active control in the marketing authorisation application (EMA, 2010). In this paper, an adequate active comparator has been defined as the gold-standard, EU-licensed product for the appropriate indication and line of treatment, following relevant CHMP guidelines and international treatment guidelines as appropriate, or if there is no licensed product for the claimed indication, as investigator’s best choice of therapy, medicines licensed by other regulatory agencies but not in the EU, and/or medicines for which use is clearly supported by medical literature. However, the paper does not include advice on how this choice should have been made.
For HTA purpose, a relative effectiveness assessment (REA) compares the clinical outcomes resulting from use of a certain health care intervention with those resulting from alternative options for treatment, diagnosis or prevention of a disease, for example other available pharmaceuticals or other health care interventions or technologies.

The relative efficacy and relative effectiveness (or added therapeutic benefit) of any intervention depends on what this intervention is compared with, meaning ‘what it is relative to’. Therefore, it is important to establish, and provide advice on, what constitutes an appropriate comparator when conducting such assessment.

The High Level Pharmaceutical Forum (http://ec.europa.eu/pharmaforum/) has developed the following definitions (High Level Pharmaceutical Forum, 2010):

- The relative efficacy is the extent to which an intervention does more good than harm, under ideal circumstances, compared to one or more alternative interventions.

- The relative effectiveness is the extent to which an intervention does more good than harm compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of health care practice.

For a REA conducted at the time of market entry, only efficacy or relative efficacy data are available in most cases; evidence on the use of the technology when provided under the usual circumstances of health care practice are normally not available at this stage of market entry.

However, in some countries an extrapolation of outcomes from the relative efficacy trials is made through disease modelling that takes into consideration the natural history of the condition in the specific healthcare system and any empirical evidence on the translation of surrogate endpoints into long term clinical outcomes. Therefore relative effectiveness can be estimated based on the projected outcomes in real life (Massol et al, 2007), but only a reassessment of a health technology later in its life cycle can be based on empirical real-life data (Le Jeunne et al 2008).

1.2.2. Discussion on the problem statement

REA can be carried out with a variety of aims, such as demonstrating the therapeutic benefit, demonstrating cost-effectiveness (not addressed within EUnetHTA Joint Action 1 work package 5), defining the place of the new health care intervention in routine clinical practice and/or establishing if the new technology should be reimbursed in the health care system. Ideally, the mechanisms to select the comparator across those aims should be broadly identical. However, it is important to recognise that the most appropriate comparator depends on the explicit aim of the assessment, that is: the specific research question or decision problem asked.

It is therefore important to consider

- How a comparator should be established
    - Whether recently approved health technologies can be chosen as comparator, or if it is preferable to use comparators with well-known/well established efficacy and safety profile in the target population
    - Whether technologies not approved for the indication under assessment can be included as comparators
    - Whether a pharmaceutical could be a comparator for a non-drug-intervention, or vica versa, and
    - What to do in situations where it is not feasible to define one pharmaceutical /technology/ intervention as the most appropriate comparator, and instead several are used in clinical practice, possibly for specific subpopulations of patients.
- What sources should be used and who should be involved in establishing the most appropriate comparator used.
- At what stage of the assessment process the comparator should be best defined.

1.3. Scope/Objective(s) of this document

This document was originally developed in JA1 and is intended to summarise the available literature, the advice provided by existing national guidelines and the information from current national practice on the choice of comparator, and to outline some of the challenges arising when establishing what the comparator for a specific assessment should be. During Joint Action 2 the wording in this document has been revised by WP7 in order to extend the scope of text and recommendations to non-drug interventions. Finally, this document provides a set of internationally agreeable best practice recommendations for the selection of the most appropriate comparator when completing a REA.

This document is intended to be useful for organisations carrying out HTA, HTA assessors and for organisations that make decisions about the place of any new health technologies in a health care system.

1.4. Relevant EunetHTA documents

The choice of comparator is relevant in the application of the EUnetHTA Core HTA model, particularly for the effectiveness and safety domains.

2. Synthesis of the analysed literature, available national and international guidelines, and individual national practice

2.1. Definition of the comparator for REA[2]

The definitions of the comparator in the published individual national guidelines from HTA organisations (see Annex 3) vary, but the majority of HTA organisations responding to the EUnetHTA survey specify the comparator as the intervention most used in clinical practice. This is described in a variety of ways, for example:

- 'Usual care'
- 'Currently accepted standard therapy (therapies) that the new intervention is intended to replace'
- 'Routinely used standard therapy (therapies) in common practice'

The EUnetHTA survey of 26 European and Australia, Canada, New Zealand and the US has shown that some countries state that they use 'whatever was used in the registration trials' for REA, but these countries also indicated that this would not be the only option for the choice of comparator. One country's entry indicates 'the most inexpensive treatment', and other entries refer to 'treatments that have been shown to be cost-effective'. Four countries state that they would use 'best possible care' as comparator, but only in one country would this be the only option considered.

The majority of countries stated 'best standard care' or 'other' as the comparator, but further analysis indicated this to be similar to routine care as described above as it was defined were as follows:

- Usually the treatment(s) used in current clinical practice
- Most frequently used therapy
- Routine care, that is, the technology or technologies most widely used in clinical practice
- Currently accepted therapy which is defined as the single most prevalent clinical practice
- Most commonly used alternative pharmaceutical in case of assessments of pharmaceuticals in some countries
- Currently reimbursed treatments with the same or equivalent therapeutic indication
- The most relevant alternative treatment, usually the most cost effective alternative

In some countries, national legislation or other procedural requirements limit the choice of the comparator within certain rules, for example in line with criteria related to cost such as a reference price within the respective health care system, or the pharmacological class in case of pharmaceuticals. Consideration should be given to special areas where legislation creates a framework for identifying standard of care such as in rare diseases.

2.2. What is the most appropriate comparator

2.2.1. Drug assessments: Pharmaceuticals or other interventions

The published national guidelines do not always specify whether or not the comparator must be another pharmaceutical or can also be another healthcare intervention. The EUnetHTA survey indicates that, in the majority of countries (70%), health care interventions other than pharmaceuticals can also be considered as comparator in REA.

[2] This document does not explore how to select comparators for clinical trials.

However, there appears to be an ongoing debate if a comparison with another pharmaceutical is considered more important than a comparison with another healthcare intervention. However, this question depends very much on the assessment question asked and on the evidence available for the comparator intervention, bearing in mind that the evidence base for pharmaceuticals is often more extensive than for other interventions.

If the comparator is another pharmaceutical, some countries specify that it should have similar pharmacological properties or a similar pharmacological mechanism of action as the pharmaceutical to be assessed. However, this may not be possible in all cases, for example in oncology, where products from new pharmaceutical classes such as monoclonal antibodies are introduced where previously taxanes or platinum compounds were used.

2.2.2. Drug assessments: Dose

Consideration should also be given to the choice of the adequate dose of the active comparator. This should be a dose that has shown the best benefit/harm ratio and a clinically relevant effect in the population of interest, or scheduled in line with its marketing authorisation or high-quality clinical practice guidelines. Comparing inappropriate doses may lead to over-estimation of the effect of the new drug (if the chosen dose of the reference treatment is too low) or underestimation of its adverse effects (if the chosen dose of the reference drug is too high). A source of information for choosing the right dose of a comparator can often be found in the summary of product characteristics in the comparator’s marketing authorisation (SPC), and in some countries, national legislation or other procedural requirements limit the eligible comparator dose to the dose specified in the SPC. However, uncertainty can arise when the use of a comparator in clinical practice differs substantially from its marketing authorisation, when several doses of a comparator are available, and when there are variations of dosage between countries (for example where there are national marketing authorisations). Where there is uncertainty, discussion between the HTA assessor and the product sponsor could take place to define how to best address it. Also, clinical practice guidelines should be considered, but also prescription data from the real world clinical settings. Where the comparator is not a pharmaceutical, it should be used according to evidence based methodology and in line with its instructions for use.

2.2.3. Regulatory status of health care interventions

No explicit information is available in the majority of national guidelines published in English as to whether or not the comparator must have a marketing authorisation or other regulatory approval. This question was not explicitly asked in the EUnetHTA survey either. A small proportion of these guidelines are explicit that only pharmaceuticals which have a marketing authorisation for the indication under assessment can be used as comparator. On the other hand, guidelines from one country explicitly state that comparators can include those that do not have a marketing authorisation (or CE mark for medical devices) if it can be demonstrated that they are used routinely for the indication in the health care service. The rationale behind this is the need to compare the new technology with what is currently being done (what would be replaced), regardless of whether or not a product has a marketing authorisation, and recommendations are explicitly made for the technology under assessment, not the comparator.

2.2.4. Level of evidence

Another important consideration is the evidence available for the chosen comparator particularly if it has no marketing authorisation for the particular indication. If an intervention is used routinely in clinical practice, it is most likely that evidence of its effectiveness and safety profile is available for the target population. This however is not always the case for interventions that have been used historically for a long time and, in particular, for small target indications. It is highly desirable that only comparators be used in REA for which a reasonable amount of good quality evidence is available.

In addition, and under ideal circumstances, the evidence for the chosen comparator should allow for a, preferably blinded, randomised controlled comparison, even if done indirectly. Although not explicitly stated in the national guidelines, there seems to be in practice an implicit

preference for direct comparisons. It is acknowledged that this may sometimes be difficult considering the way of administration, or any difference in safety profile and adverse effects that can affect the blinding or favour different patient subpopulations. Evidence for the chosen comparator can also be taken from pragmatic trials, observational studies or registries, but these have to be of high quality. In addition, the decision whether or not specific studies are suitable for a(n) (indirect) comparison often needs rigorous assessment of the studies, which cannot be done for all possible comparators.

There are situations where no good evidence for the effectiveness of the routine care is available, and in these situations no clear advice is given in any national guidelines. A possibility in this situation is to find a proxy comparator and resolve this through a pragmatic and deliberative rather than a fully evidence based approach.

2.2.5. Recently introduced versus established health technologies

Pharmaceuticals

Comparators are often pharmaceuticals licensed a long time ago for which there is extensive efficacy and safety data available. However, comparators can also include pharmaceuticals which have only recently received a marketing authorisation and for which there is less data available and which may not have become routine practice. The general consensus seems to be that such newer pharmaceuticals should be included as comparators where appropriate to allow the REA to be as up to date as possible.

Challenges can also arise when it is identified that an alternative technology may be licensed within the timeframe of the REA or is subject to another proposed or ongoing REA. This means that at the point of decision making, routine clinical care may have changed, be at the point of changing, or be subject to consideration at the same point in time as the technology. Often the decision maker wishes to see comparisons with the new pharmaceuticals. However, this can pose a problem, particularly for those conducting or contributing to a REA because the data may not be available to support either direct or indirect comparison of effectiveness with the most recent/emerging comparator.

A related challenge is that a new pharmaceutical might have just received a positive reimbursement decision, could represent a clinical advancement and be therefore considered ‘best standard care’, but is actually not yet widely used in the health care service. This situation happens regularly in therapeutic areas with rapid development of new treatments, such as oncology, and it can be difficult to come to a unanimous approach about the comparator, and this is usually resolved through a case-by-case basis.

Non-drug interventions

It might also be challenging for the REA of non-drug interventions and technologies to choose the most appropriate comparator. Some clinical areas are characterised by dynamic scientific and clinical developments (e.g. genetic test methods/strategies used in personalised medicine approaches in oncology). Therefore the same problems may arise to identify a “best standard care” as it has been said for pharmaceuticals.

2.2.6. More than one possible comparator/ treatment sequences

Several of the published national guidelines recognise that more than one specific treatment may currently being used in clinical practice. One of the reasons for this could be that different treatments are relevant for different subpopulations of patients (see section 2.2.7). However, there may be other reasons. Some guidelines specify that in this situation, the main comparator should be an intervention that is used to treat the particular indication for the largest number of patients. However, it does not go as far as specifying how this should be established.

There is also no advice currently as to what approach should be taken in situations where there is no clear main comparator identifiable or where there is considerable uncertainty, or where there is an even split between several technologies used in clinical practice.

It is also important to distinguish between situations where the intervention is an additional element in a treatment pathway or treatment sequence (where the comparator would be the same treatment pathway or sequence without the new intervention); this is similar to situations where the new technology is an add-on to standard care. This is different from the situation where the new technology is a distinct alternative that could replace another element in the treatment strategy (where the comparator would be the treatment pathway or sequence including the potentially replaced intervention). This is outlined in some of the national guidelines.

There may also be legal requirements, stipulating that if there are several alternatives, the more economic therapy should be selected as comparator, preferably one for which there is a reference price within the health care system.

2.2.7. Subpopulations of patients

If a new health technology has a wide therapeutic indication, covering the treatment of patients at different lines of treatment (for example 1st line or 2nd line), different degrees of severity, different stages of a disease (for example early cancer or metastatic cancer), or genetic characteristics, it is important to consider that the comparator for such different subpopulations within an overall indication could be different. Other specific clinical characteristics of patient groups, such as co-morbidities can also be important. In this case it may be necessary to define comparator interventions separately for all subgroups and sub-indications, depending on the evidence available.

2.3. Sources used to specify the comparator

The published national guidelines do not usually specify which sources are used as input for choice of comparator, by which method the most appropriate comparator should be established and who should be involved in defining the comparator.

The responses received to the EUnetHTA survey showed that in the majority of countries the product sponsor, clinical and patient experts, clinical guidelines, and (international) methodological guidelines have an input into the choice of the comparator. In addition, others involved in the choice of comparator included experts and internal technical teams within the assessment organisation, as well as the decision making organisations.

However, in three countries the product sponsor does not play a role in the choice of the comparator; in one of these only the HTA agency is involved, in the other two countries experts are involved and clinical guidelines and international methodological guidelines are used. Only in one country it was indicated that the product sponsor only chooses the comparator.

It appears that the variations in the responses to the survey are linked to the individual national procedural requirements.

2.4. When should the choice of comparator be specified

National guidelines rarely specify whether or not the comparator is agreed before or during the assessment. Ideally the comparator for a REA should be agreed before the assessment starts. Such a process step is sometimes described as ‘scoping’, consistent with the PICO table approach to define a research question (Population, Intervention, Comparator, Outcome). This approach is in fact described in a number of the published national guidelines.

If a final agreement on the comparator needs to be reached before the assessment starts, the HTA organisation or the decision maker has to carry out validation work on the comparator beforehand. This is not possible in all national processes, particularly where the process has to follow tight timelines.

Additionally, it is possible that such scoping processes are carried out before the actual assessment. This is also considered important by Bekkering and Kleijnen (2008)[3]. If scoping is carried out a long time before the actual assessment, clinical practice may have changed by the time the assessment starts, as outlined above. In this case the scoping process can only define a maximum list of possible comparators, from which the actual comparator will have to be chosen in the analysis. Other approaches may be to see the PICO table in the scope as definite list of comparators to be included in the analysis, but this latter approach involves extensive validation work beforehand to establish the comparator with certainty.

[3] This publication does not describe the current status on methods for benefit assessments in Germany.

3. Discussion and conclusion

The choice of the comparator in a REA, and the mechanism by which this choice is made, widely depends on the aim of the respective health care system (whether explicitly stated or not), and the legal and cultural context within which each national health care system operates.

The JA1 analysis of the information available for this document demonstrates that there is broadly agreement across countries about what should be the comparator for a REA: in the context of making decisions about the place of a new pharmaceutical in clinical practice, or about reimbursement, the comparator mainly defined as current routine care in the individual health care system, the most used, or what would be replaced by the introduction of that new pharmaceutical.

Therefore, under ideal circumstances the comparator for a European-wide acceptable REA would be

- the reference treatment according to high-quality clinical practice guidelines at European or international level
- with good quality evidence on effect size and adverse effects from medical literature
- with an EU or national marketing authorisation for the appropriate indication and line of treatment.

However, in many circumstances there is no consensus across European countries of what constitutes standard/routine/ best clinical care, and real life patient populations are likely to be heterogeneous across countries because of the absence or multitude of validated therapeutic recommendations. For any REA that is applicable across European countries, the comparator would often be a difficult choice because of the absence of validated therapeutic recommendations, or if the recommendations and procedural and legal requirements vary across countries (Berdai et al 2010, Bekkering and Kleijnen 2008). For drug assessments it may be useful to take into account the best active comparator identified by the EMA, although ultimately this may not be an appropriate comparator for REA in all countries.

Furthermore, in some countries the choice of comparator is governed by legislation, and refers also to cost (such as reference prices, or cost effectiveness). For creating reference prices in the context of assessments of pharmaceuticals, similar pharmaceuticals are taken into consideration and these need to be included as comparators. In other countries, the choice is governed by the purpose to gain as much insight as possible about the new technology; in that situation – for pharmaceuticals - the comparator needs to be from a similar pharmaceutical class.

In addition, establishing a priori the most appropriate comparator for a given REA applicable across European countries would require additional time and resources. In some situations a universal comparator that allows answering all countries’ needs for a specific REA may not exist. However, there may be countries with similar health care patterns, and in this situation ‘clusters’ of countries with the same comparator could be established, and separate REA for these clusters be carried out. Alternatively, several comparisons could be provided in one large multi-comparator REA. However, in both cases it would need to be demonstrated that these approaches could genuinely inform national decision making and thereby generate efficiencies.

In summary, the detailed approaches vary across countries and the choice of the comparator for REA depends mainly on the specific assessment question. An exception exists with rare diseases where Orphan Medicinal Designation offers a framework for identification and endorsement of a European position on standard of care/comparator which can be used to assist in the establishment of REA.

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Annex 2. Methods and results of literature search

For the original version a literature review was undertaken during JA1 followed by a policy analysis of existing national guidelines.

Keywords

Decision making
Decision support techniques
Health care policy decisions
Policy
Cost benefit analysis
Clinical benefit
Outcome assessment
Pharmacoeconomic assessment
Pharmacoeconomic evaluation
Pharmacoeconomic research
Product evaluation
Treatment outcome
Comparator (free text search and truncated)
Active comparator
Best practice
Standard treatment
Gold standard
Reference therapy

Search engines and sources of information

Embase
Medline
Medline in Process
Health Technology Assessment
Cochrane Methodology Register
Google and Google Scholar

Other important sources were EMA, FDA, ISPOR, HTAi, PBAC, MSAC, CADTH/CEDAC, AHRQ, GIN, but also the websites of national HTA/reimbursement agencies.

Strategies of research

Free-text searching and where appropriate, subject heading searching. As the search is undertaken terms might need refinement.

Inclusion and non-inclusion criteria

Restricted to English language, although articles with an English abstract were considered for inclusion. The search was restricted to the years 2000 to 2010.

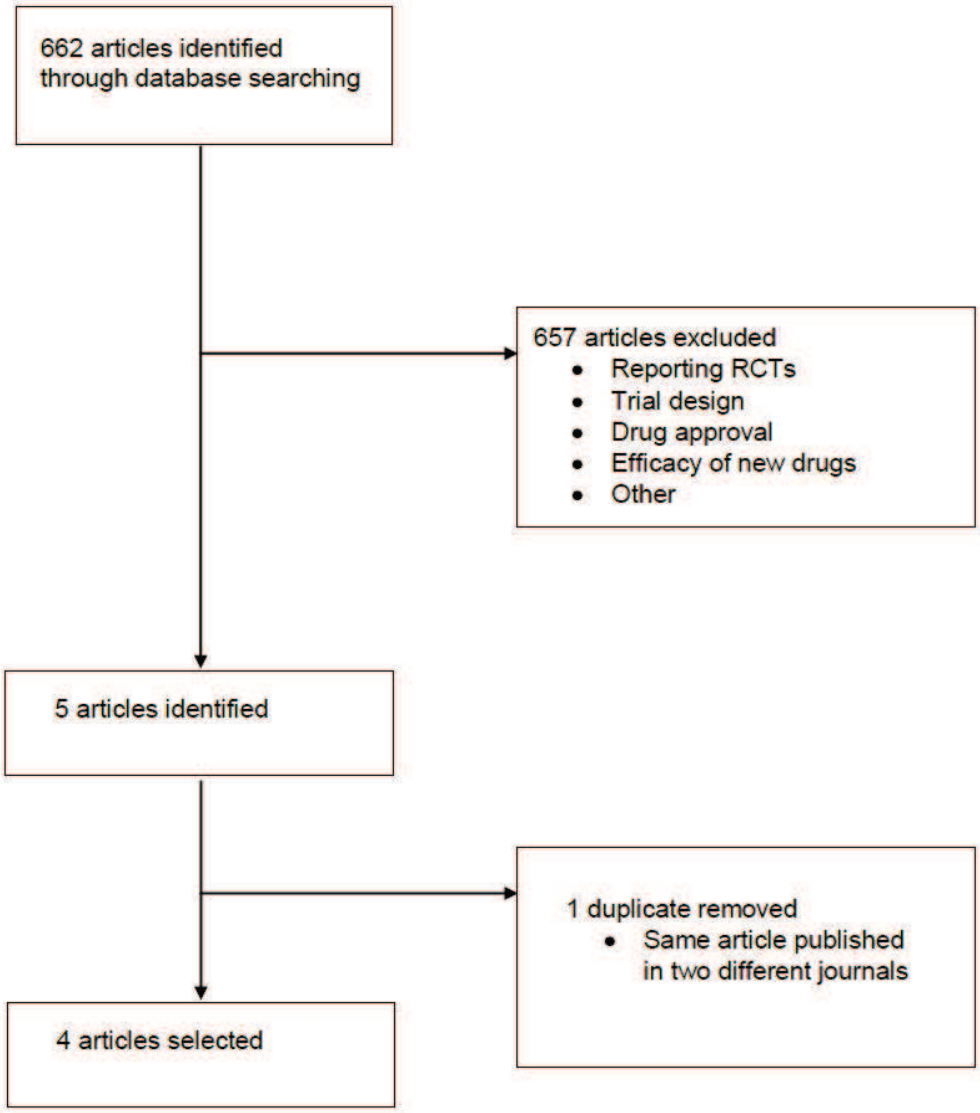
Results of the literature search

The literature search resulted in 662 articles being retrieved. These articles were initially screened by title and those that were not relevant were eliminated. Articles were considered to be not relevant if they discussed the choice of comparator in randomised controlled trials, the design of randomised controlled trials (ie should they be placebo-controlled or have an active comparator) and the pharmaceutical approval process, because these were not considered relevant for the current purpose. In addition, articles describing the results of RCTs or the efficacy of new treatments were eliminated. In total 657 articles were eliminated at this stage.

The next stage of the selection process involved screening the abstracts of the remaining 5 articles and eliminating any that were duplicates. Two articles were identified as being

duplicates - the same articles which had been published in two different journals. Therefore four articles were identified as being relevant to the search topic.

Summary of literature search



Reference	Main data/information
Berdai D, Hotton JM, Lechat P (July 2010) Comparators (Medicinal and non Medicinal) for Marketing Authorization, for Public Health, for Payers and at the European Level. *Therapie* 65 (4): 329-334.	The authors outline that the choice of the comparator for any new treatment is a key issue especially when there are differences in medical practice and when the use of the comparators depends on the geographical zones and their evolution with time. The choice of the comparators must satisfy sometimes different expectations from the regulatory authorities and for reimbursement decisions. The authors suggest that a universal comparator that allows answering all assessment questions does not exist, and that the quantification of the clinical added value can only be carried out in comparison with the current reference drug treatment/ current therapeutic strategy. The reference treatment is sometimes a difficult choice due to the absence of validated therapeutic recommendations or if the recommendations vary across countries. The expansion and international clinical practice guidelines would reinforce the robustness and efficiency of clinical research efforts with respect to the relevance of the comparison to reference treatments, including non-drug treatments. The authors also emphasise the importance of a consensus on clinically significant thresholds for the size of evaluated effects.
Bekkering GE, Kleijnen J (Nov. 2008) Procedures and methods of benefit assessments for medicines in Germany. *Eur.J Health Econ.* 9 Suppl 1: 5-29.[4] Bekkering GE, Kleijnen J (Dec. 2008) [Procedures and methods of benefit assessments for medicines in Germany]. *Dtsch.Med Wochenschr.* 133 Suppl 7: S225-S246.	[Same article published in two journals] In the article it says that the comparator is either the best possible treatment or the currently used routine treatment. Although the best treatment would be the comparator of choice, treatments representing routine German care should also be included in the evaluation. There may be several comparator treatments, depending on regional differences. The comparator needs to be defined as precisely as possible, especially if the circumstances of its use differ from the circumstances of use for the intervention being assessed. The choice of one (or more) comparator(s) needs to be discussed in the scoping process and justified in the protocol. As part of the licensing procedure, medicines are typically compared with placebo. Such trials answer the question whether the medicine is more effective than placebo. For benefit assessments, from the perspective of the health-care system, head-to-head trials comparing one medicine with another are to be preferred if the comparison therapy is the current standard therapy. Head-to-head trials should be evaluated in the same way as placebo-controlled trials. If the assignment to both treatments has been done randomly, such trials are level-1 evidence. If only placebo controlled trials are available, the additional benefit of medicines can be estimated using adjusted indirect comparisons
Massol J, Puech A, Boissel JP (Sept. 2007) How to anticipate the assessment of the public health benefit of new medicines? *Therapie* 62 (5): 427-435.	Summary derived from abstract only; main publication in French The authors describe the assessments and criteria required for defining the added therapeutic benefit (Public Health Benefit, PHB) within the French context. Issues discussed include that data are exclusively from randomised clinical trials which is not necessarily sufficient for assessing PHB. The authors offer ideas as to how the assessment of PHB differs from the marketing authorization process, particularly in terms of extrapolating the results from trial populations to the real world clinical practice, the predictive value of the surrogate criteria used in the trials, the lack of concurrent

[4] These two papers were published before new methods for benefit assessments in Germany were developed. New regulation in Germany starting from January 2011 can be found at AM-NutzenV § 6: http://www.bmg.bund.de/fileadmin/redaktion/pdf_gesetze/verordnungen/AM-NutzenV.pdf]

	and relevant epidemiological data related to indication. The authors suggest to adapt the clinical development plans for a better assessment of PHB, and to start early enough collecting reliable and relevant epidemiological data and the necessary elements for the assessment of the generalisability of the results. The authors also outline the need for effectiveness modelling due to the absence of all relevant trial or real life data. The authors' general recommendations to update the development plans seem especially appropriate as any such amendments would not only be beneficial to France but to all health authorities who would wish to assess the PHB of a new medicine on their territories.
Le Jeunne C, Woronoff-Lemsi MC, David N et al. (Mar. 2008) Relative added value: what are the tools to evaluate it? *Therapie* 63 (2): 113-11.	English abstract reproduced below; main publication in French The relative added value of a drug is currently evaluated in France by the Transparency Commission (TC) of the National Health Authority (HAS), by assigning a level of Improvement in Actual Benefit (IAB). IAB is based on two parameters, efficacy and safety of the product, in a defined target population, either as compared to one or more other drugs with similar indications, or within therapeutic strategy. The items used for evaluation, including the level of clinical effect, the relevance of the comparator, the choice of comparison criteria and the methodology used (indirect comparison, non-inferiority studies, etc.), have been reviewed by the working group in Giens with regard to an analysis of the opinion on TC issued between 2004 and 2007 in several therapeutic areas. First of all, this attempt at rationalisation based on the criteria used to assess the relative added value demonstrated the rareness of direct comparative data, and was followed by a discussion on the possible broadening of the evaluation criteria. The group discussed taking into account the Public Health Impact (PHI), which has now been incorporated into the assessment of Actual Benefit (AB). The group believes that PHI seems to be more related to the notion of IAB than to that of AB. Indeed, it is frequently the relative added value of a new drug that produces an impact in public health. Conversely, considering the comparative evaluation criteria of PHI, which are not systematically taken into account in AMSR (such as improvement in the health of the population, meeting a public health need or impact on the healthcare system), PHI could legitimately be included in the assessment of the relative added value of a drug. Other parameters such as compliance or impact on professional practice have been considered. Thus, the notion of relative added value, evaluated at initial registration, could be based on an expected improvement in medical service. The notion of expected medical service leads to the requirement of producing additional data in real life (post-registration studies), which would support the definitive notion of improvement in actual benefit at the time of renewed registration, while taking into account the place occupied by the drug in the therapeutic strategy.

The EUnetHTA survey gave the following options for the identification of the comparator:

- Product sponsor
- Experts
- Clinical guidelines
- (international) methodological guidelines
- other (these included experts within the assessment body and internal technical teams in the assessment body).

Annex 3. Other sources of information

Published guidelines

Published national guidelines or other information, available in English, from 2 regulatory authorities, the European Medicines Agency (EMA) and the Food and Drug Administration (FDA), and from HTA organisations, as listed below, were analysed during the original guideline development in JA1 for information related to the choice of comparator:

- Agency for Healthcare Research and Quality (AHRQ)
- Agency for Health Technology Assessment (AHTAPOL) Poland
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Danish Centre for Health Technology Assessment, National Board of Health (DACE HTA) Denmark
- Dental and Pharmaceutical Benefits Authority (TLV) Sweden
- Health Information and Quality Authority (HIQA)
- Hungarian proposal for methodology standards (Szende et al, 2002)
- Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) Germany,
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
- Medical Services Advisory Committee (MSAC)
- National Institute for Health and Clinical Excellence (NICE)
- Norwegian Medicines Agency
- Pharmaceutical Benefits Advisory Committee (PBAC)
- Pharmaceutical Management Agency (PHARMAC)
- Scottish Medicines Consortium (SMC)

EUnetHTA survey

As part of EUnetHTA JA1 work package 5, a survey was carried out amongst European and other English speaking countries on REA. In total, 34 countries were included in the analysis including 30 European countries, Australia, Canada, New Zealand and the US (with data of 27 countries available at time of writing). The responses to the questions relating to the choice of comparator have been used as source for this guideline, and were supplemented with information from contacts in the individual HTA organisations. The full survey results can be seen at http://www.eunethta.eu/outputs/final-version-background-review-relative-effectiveness-assessment.

The questions asked were:

With what is the pharmaceutical compared with?

- Whatever is used in registration trials
- Best possible care
- Best standard care
- Other

Is comparison limited to pharmaceuticals?

How is the comparator identified by the assessment body?

- Indicated by the product sponsor
- Experts
- Clinical guidelines
- (International) methodological guidelines
- Other