



**eunethta**

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

**WORK PACKAGE 5 JOINT ACTION:  
RELATIVE EFFECTIVENESS ASSESSMENT OF PHARMACEUTICALS**

**HTA Core Model® for  
Rapid Relative Effectiveness Assessment of  
Pharmaceuticals**

**version 3.0  
1 March 2013**

This draft model was developed by experts from the institutions listed below, and was reviewed and validated by members of Work Package 5 (WP5) of the EUnetHTA network; the whole process was coordinated by the Dutch Health Care Insurance Board (CVZ). The model represents a consolidated view of the non-binding recommendations of the EUnetHTA network members and is in no case the official opinion of the participating institutions or individuals.

### Participating institutions:

Full name	Abbreviation
Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (Andalusian Agency for Health Technology Assessment)	AETSA
University Hospital 'A.Gemelli'	A.Gemelli
L'Agencia Italiana del Farmaco (Italian Medicines Agency)	AIFA
Agència d'Informació, Avaluació i Qualitat en Salut (Catalan Agency for Health Information, Assessment and Quality)	CAHIAQ
Nacionālais veselības dienests (Centre of Health Economics)	CHE
College voor zorgverzekering (Health Care Insurance Board)	CVZ
Directorate for Pharmaceutical Affairs (DPA) at the Ministry of Health, the Elderly and Community Care	MHEC-DPA
Säkerhets- och utvecklingscentret för läkemedelsområdet (Finnish Medicines Agency)	FIMEA
Institutet för hälsa och välfärd (Finnish Office for Health Technology Assessment at the National Institute for Health and Welfare)	FINOHTA/THL
Gesundheit Österreich GmbH	GÖG
Haute Autorité de Santé (French National Authority for Health)	HAS
Hauptverband der Österreichischen Sozialversicherungsträger (Association of Austrian Social Insurance Institutions)	HBV
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)	IQWiG
Inštitut za varovanje zdravja Republike Slovenije (Institute of Public Health of the Republic of Slovenia)	IPH-RS
Federaal Kenniscentrum (Belgian Health Care Knowledge Centre)	KCE
Rijksinstituut voor ziekte- en invaliditeitsverzekering/ Institut national d'assurance maladie-invalidité (Belgian National Institute for Health and Disability Insurance)	RIZIV-INAMI
Swiss Network for Health Technology Assessment	SNHTA
HTA Unit, Agencia Laín Entralgo	UETS

**Authorship in collaborative writing of a living document**

This document represents collaborative writing by multiple authors at multiple time points. The authors worked on the previous versions of the Core Model updating and editing text written by others. Strong editorial input is present. This may challenge long-held concepts of property, credit and authority, but is the only way to engage a large number of experts in preparing high quality content and timely updates of continuously evolving documents. The authors of this document agreed on limitations to their individual authorship which means, for instance, that plans to publish an article about the content of this document should be carefully communicated to all previous contributors, and new authors are free to modifying subsequent versions.

## TABLE OF CONTENTS

<b>LIST OF ABBREVIATIONS.....</b>	<b>6</b>
<b>1 INTRODUCTION .....</b>	<b>7</b>
1.1 A NEW APPLICATION OF THE HTA CORE MODEL: THE HTA CORE MODEL FOR RAPID RELATIVE EFFECTIVENESS ASSESSMENT OF PHARMACEUTICALS .....	7
1.2 WHAT IS RELATIVE EFFECTIVENESS? .....	8
1.3 WHAT ARE THE DOMAINS?.....	8
1.3.1 Health problem and current use of the technology .....	9
1.3.2 Description and technical characteristics of technology .....	9
1.3.3 Safety.....	10
1.3.4 Clinical Effectiveness .....	10
<b>2 METHODS.....</b>	<b>12</b>
2.1 GUIDELINES FOR CONDUCTING A RAPID RELATIVE EFFECTIVENESS ASSESSMENT .....	12
2.2 SCOPING .....	12
2.2.1 General scope of the assessment .....	13
2.2.2 Checklist for potential ethical, organisational, social and legal aspects .....	14
2.3 SOURCES OF INFORMATION FOR THE ASSESSMENT.....	15
2.3.1 Basic documents .....	15
2.3.2 Search.....	15
2.4 HOW TO WORK WITH THE ASSESSMENT ELEMENT TABLES .....	17
2.4.1 Selecting relevant issues from the model.....	19
2.4.2 Formulating research questions.....	19
2.5 COLLECTING AND ANALYSING DATA .....	19
2.5.1 Appropriate study types.....	19
2.5.2 Quality appraisal .....	20
2.5.3 Effect measures and confidence intervals .....	21
2.5.4 Extrapolation of efficacy to give relative effectiveness data .....	21
2.6 EVIDENCE TABLES .....	22
2.7 INTERPRETING EVIDENCE.....	22
2.8 REPORTING .....	23
2.9 SUMMARISING THE RESULTS FOR A RAPID RELATIVE EFFECTIVENESS ASSESSMENT .....	23
<b>3 DOMAINS – ASSESSMENT ELEMENT TABLES .....</b>	<b>24</b>
3.1 HEALTH PROBLEM AND CURRENT USE OF TECHNOLOGY .....	24
3.2 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY.....	30
3.3 SAFETY .....	34
3.4 CLINICAL EFFECTIVENESS.....	38
<b>REFERENCES.....</b>	<b>42</b>
<b>APPENDIX 1. INFORMATION SOURCES.....</b>	<b>45</b>
REGISTRIES .....	45
REGULATORY INSTITUTIONS AND LEGAL FRAMEWORK.....	46
NATIONAL OR INTERNATIONAL SAFETY MONITORING SYSTEMS (DATABASES).....	47
A0024&A0025 LIST OF WEBSITES WHERE YOU CAN FIND GUIDELINES.....	48
A0021 LIST OF WEBSITES OF NATIONAL AGENCIES WITH INFORMATION ON REIMBURSEMENT.....	48
<b>APPENDIX 2. TEMPLATES .....</b>	<b>50</b>
TEMPLATE 1. FORMAT FOR SCOPING THE ASSESSMENT .....	50
TEMPLATE 2. CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, SOCIAL AND LEGAL ASPECTS .....	51
TEMPLATE 3. SELECTING RELEVANT ASSESSMENT ELEMENTS AND TRANSLATING THE GENERIC ISSUES INTO ACTUAL RESEARCH QUESTIONS .....	53
TEMPLATE 4. RESULT CARD .....	54
TEMPLATE 5. TABLE FOR REPORTING RESULTS FROM CLINICAL TRIALS .....	55
TEMPLATE 6. DOMAIN REPORT .....	58
TEMPLATE 7. SUMMARY .....	60

TEMPLATE 8. REIMBURSEMENT STATUS.....	62
<b>APPENDIX 3. SYSTEMATIC REVIEW OF THE LITERATURE .....</b>	<b>63</b>
HOW TO PLAN AND CONDUCT A SYSTEMATIC REVIEW OF EFFECTIVENESS .....	63
SELECTION OF STUDIES .....	65
CRITICAL APPRAISAL .....	67
SEARCH STRATEGY FOR SAFETY DATA .....	67
<b>APPENDIX 4. DEVELOPMENT OF THE MODEL FOR RAPID RELATIVE EFFECTIVENESS ASSESSMENT .....</b>	<b>69</b>
BACKGROUND INFORMATION ON EUNETHTA JOINT ACTION WORK PACKAGE 5.....	69
COURSE OF DEVELOPMENT .....	69
MOST RELEVANT DEVIATIONS FROM THE HTA CORE MODEL .....	70
<i>Definitions specific to the Rapid and Full models for relative effectiveness assessment of pharmaceuticals .....</i>	<i>71</i>
WORKING PROCESS FOR DEVELOPING THE MODEL FOR RAPID RELATIVE EFFECTIVENESS ASSESSMENT ..	71
<i>First version of the Model for Rapid Relative Effectiveness Assessment.....</i>	<i>71</i>
<i>Second version of the Model for Rapid Relative Effectiveness Assessment.....</i>	<i>73</i>
<b>APPENDIX 5. RECOMMENDATIONS OF GUIDELINES ON METHODOLOGICAL ISSUES ....</b>	<b>74</b>
ENDPOINTS USED IN REA OF PHARMACEUTICALS: .....	74
<i>Clinical endpoints.....</i>	<i>74</i>
<i>Composite endpoints .....</i>	<i>75</i>
<i>Surrogate endpoints.....</i>	<i>76</i>
<i>Safety .....</i>	<i>77</i>
<i>Health-related quality of life and utility measures .....</i>	<i>79</i>
COMPARATORS AND COMPARISONS .....	81
<i>Criteria for the choice of the most appropriate comparator(s).....</i>	<i>81</i>
<i>Direct and indirect comparisons .....</i>	<i>83</i>
LEVELS OF EVIDENCE.....	84
<i>Internal validity of randomised controlled trials.....</i>	<i>84</i>
<i>Applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals.....</i>	<i>85</i>

## LIST OF ABBREVIATIONS

ATC	Anatomical therapeutic chemical
DTC	Description and technical characteristics of the technology
EMA	European Medicines Agency
EPAR	European public assessment report
EUnetHTA	European Network for Health Technology Assessment
FDA	Food and Drug Administration
HPCU	Health problem and current use domain
HTA	Health technology assessment
ICD	International Classification of Diseases
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical subject headings
NNH	Number needed to harm
NNT	Number needed to treat
PICO	Patient, intervention, comparison, outcome
POP	Planned and ongoing projects
PSUR	Periodic safety update report
RCT	Randomised controlled trial
REA	Relative effectiveness assessment
RMP	Risk management plan
SPC	Summary of Product Characteristics
WHO	World Health Organisation
WP	Work package

# 1 INTRODUCTION

## 1.1 A new application of the HTA Core Model: the HTA Core Model for Rapid Relative Effectiveness Assessment of pharmaceuticals

The HTA Core Model defines the content elements to be considered in a health technology assessment (HTA) and facilitates standardised reporting. The aim is to share information, to avoid duplication of work, and to facilitate the adaptation of information in national HTA reports and the co-production of HTA reports (by multiple HTA agencies). Detailed information about the principles of the HTA Core Model can be found in [The HTA Core Model® Online Handbook](#).

Because different types of technology – such as pharmaceuticals, devices or procedures – may require different kinds of assessment, it was decided that different Core Model applications should be developed for their assessment. This document describes the model application for the rapid relative effectiveness assessment (REA) of pharmaceuticals, entitled the ‘HTA Core Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals’ abbreviated as ‘Model for Rapid REA of Pharmaceuticals’.

A rapid assessment is an assessment of a specific technology within a limited timeframe in comparison with one or more relevant alternative interventions. It may assess a new pharmaceutical launched onto the market, or (re)assess a pharmaceutical for a new indication or when new relevant data are available (Kleijnen et al. 2012).

This application of the HTA Core Model is developed with a different collaboration model in mind than the collaboration model that is generally used for other HTA Core Model applications (involving tens of individuals as authors from several HTA agencies each working on specific domain(s)). It is intended that for rapid assessments authoring of all four domains is limited to a few authors from one or two organisations. To ensure broad participation and quality assurance several organisations are involved in in-depth review.

In addition, the following issues have been considered relevant and specific to the Model for Rapid REA of Pharmaceuticals:

- Following the European Transparency Directive (Directive 89/105/EEC relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion within the scope of national health insurance systems), some countries are legally obliged to assess pharmaceuticals within a specified time period (90/180 days). The Model for Rapid REA of Pharmaceuticals has been developed with these strict timelines in mind.
- Instead of the nine domains included in the other applications of the Core Model, only the first four domains are included in the Model for Rapid REA of Pharmaceuticals (see Figure 1). The ‘Cost and Economic Considerations Domain’ was explicitly excluded based on the recommendations of the High Level Pharmaceuticals Forum (HLPF, 2008a). In addition, the ethical, organisational, social and legal domains are replaced by a short checklist for quickly assessing the relevance of the ethical, organisational, social and legal issues for the project.
- There is more focus on the relative nature (in comparison to comparators) of the assessment.
- The methods, normally presented separately for each domain, are merged into one methods section in the Model for Rapid REA of Pharmaceuticals.
- The assessment elements in the four domains represent a subset of the elements in the HTA Core Model selected for their relevance and feasibility for inclusion in a rapid assessment.
- A REA submission file provided by the marketing authorisation holder and the European Public Assessment Report (EPAR) are the primary sources of information for the assessment. The REA submission file and the EPAR are checked for the completeness of the

scientific literature listed; a systematic literature search in reference databases is only performed if the REA submission file appears to be incomplete or relevant new information is likely to be available.

- Guidance is added on how to produce a summary of relative effectiveness of the pharmaceutical based on evidence from the four domains..

For more details about the background of Joint Action Work Package 5 and the development process and methods of the Model for Rapid REA see [Appendix 4](#).

## 1.2 What is relative effectiveness?

Two definitions are commonly used in the context of a relative effectiveness assessment (HLPF, 2008b):

- **Relative efficacy** can be defined as the extent to which an intervention does more good than harm, under ideal circumstances, compared with one or more alternative interventions.
- **Relative effectiveness** can be defined as the extent to which an intervention does more good than harm compared with one or more alternative interventions for achieving the desired results when provided under the usual circumstances of health care practice.

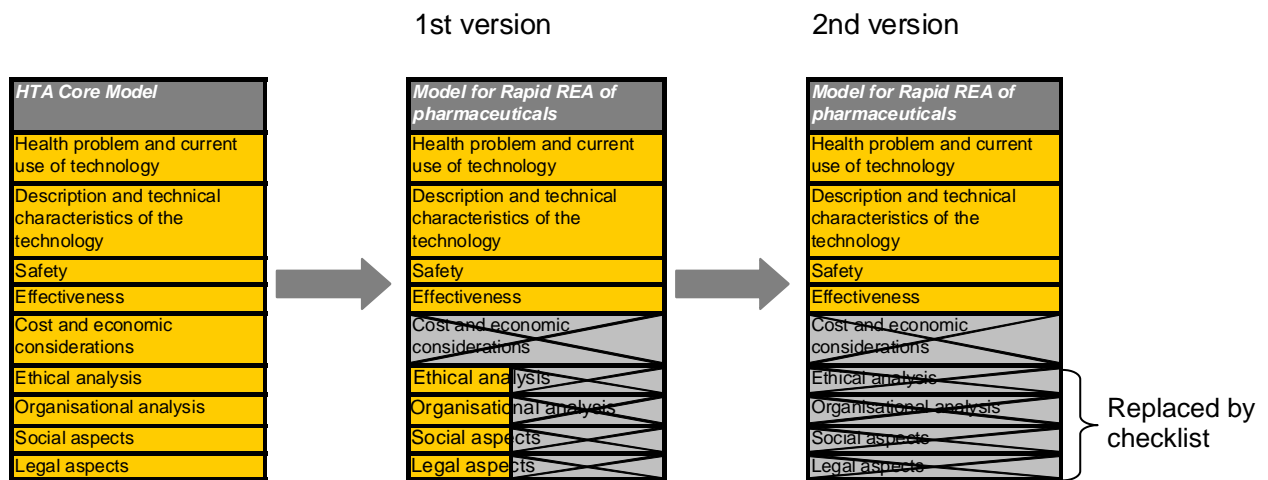
When assessing the relative effectiveness of pharmaceuticals the focus is on determining the magnitude of the health benefits and harms of a (new) pharmaceutical compared with existing pharmaceuticals or some other technology. As stated in the principles on relative effectiveness (HLPF 2008b), a REA should include a comparison with the most appropriate healthcare intervention(s). The assessment should primarily focus on data derived from usual circumstances of health care practice, although these are usually not available right after marketing authorisation. Additionally, the assessment should present the uncertainties affecting interpretation of reliability and clinical relevance of the results.

## 1.3 What are the domains?

The original HTA Core Model is based on nine domains (see [Figure 1](#)). The purpose of dividing the assessment into specific domain is to facilitate systematic presentation of information. Because of the specific focus of a rapid REA this model includes only the first four domains (for more information see Introduction and [Appendix 4](#)). This section introduces these four domains.



Figure 1. Development of the Model for Rapid REA of pharmaceuticals



### 1.3.1 Health problem and current use of the technology

The health problem and current use of the technology (HPCU) domain describes the target conditions and target group, and the availability and patterns of use of the technology. Some of the topics considered relevant for this domain have been considered as ‘Background Information’ in previous European projects or recommendations for conducting assessments (Burls et al. 2000; Velasco et al. 2002; Liberati et al.1997).

The qualitative description of the **target condition**, including its underlying mechanism (pathophysiology), natural history (i.e. course of disease), diagnosis and prognosis, and epidemiology (incidence, prevalence), as well as the underlying risk factors for acquiring the condition are covered in this domain. A description of subgroups or special indications should be included especially when the technology does not target the whole population.

**Current management** patterns of the condition should be described, including the technology as such and its alternatives, and recommended policies for determining the target population. It should be specified whether the technology is intended to replace or supplement another technology in the management chain. Potential problems with the use of a technology within a health system should be identified: examples include risk of use beyond the authorised marketing label, compliance challenges, and the misuse or diversion of the product.

*The issues in this domain should be considered at an early stage in a rapid assessment,* because they may help in refining the research questions and formulating the methodological approach in, for example, the effectiveness and safety domains.

### 1.3.2 Description and technical characteristics of technology

This domain describes the technology’s mode of action and target condition/stage of disease, when it was developed and for what purposes, who will be using it, in what manner, and at which level of health care (e.g. primary care, secondary care). The material requirements for premises, equipment and staff are described (e.g. fume cupboards, reconstitution chambers for chemotherapy) and information needs associated with the new technology.

The description of the characteristics of the technology under review should be detailed enough to distinguish it from related technologies. The terms and concepts used should allow those

unfamiliar with the technology to get an overall understanding of its use. Important terms should be defined and a glossary or list of product names may be useful to facilitate understanding.

***As with the HPCU domain, the issues in this domain should be considered at an early stage in a rapid assessment.*** Nevertheless some issues should be rechecked after finalising the safety and effectiveness domains because the information presented in these domains may be needed to fully describe the technology.

### **1.3.3 Safety**

The harmful effects of a technology are essential in quantifying the net benefit (benefit minus harms) of an intervention. The harms are identified, quantified in terms of frequency, incidence, severity and seriousness, and finally compared to those of the comparator(s). The authors of REA should use consistent and precise terminology described in the Medical Dictionary for Regulatory Activities (MedDRA) .

The following safety issues specific to pharmaceutical technologies should be considered while working on the safety domain (CADTH, 2008; European commission, 2009; INAHTA 2006; Ioannidis & Lau, 2001).

- |   |
|---|
| 1. Drug safety relates to safety during drug intake and, if applicable, to drug withdrawal reactions after stopping the drug.   |
| 2. Patient safety can be related to errors in the route of administration, storage conditions, posology and dosage, or schedule plan.   |
| 3. Adverse drug reactions, which are by definition well described and causally linked to drug use, as well as interactions with other drugs, foods or diagnostic tests should be included.  |
| 4. Patient susceptibility or specific patient conditions, such as age, comorbidities, pregnancy, hypersensitivity or intolerance to the drug or its excipients, may alter the application of the pharmaceutical. This can result in warnings for users or even formulation of contraindications.  |
| 5. Pharmaceutical safety is rigorously evaluated before market entry; nevertheless, once on the market the pharmaceutical product is administered to heterogeneous patient groups (elderly persons, patients affected by multiple diseases and co-medication) and to a substantially larger patient population. This is one reason why adverse drug reactions may occur later in the life cycle without having been discovered during clinical trials. Thus all health personnel, regulatory authorities and pharmaceutical companies are involved in continuing pharmacovigilance and safety assessment after marketing authorisation. |

For further details see the guideline [\*Endpoints used in REA of pharmaceuticals – Safety.\*](#)

### **1.3.4 Clinical Effectiveness**

The relative benefits of the new pharmaceutical are discussed in the clinical effectiveness domain and can be determined under experimental conditions (e.g. within the protocol of a randomised controlled trial [RCT]) or under routine conditions (e.g. by a physician in a community hospital treating outpatients) (adapted from the International Network of Agencies for Health Technology Assessment [INAHTA] glossary). Key elements of a benefit assessed under routine conditions are that (a) effective interventions should be directly compared and (b) studies should include patients who are typical of day-to-day health care settings (Sox et al. 2009)..Although data about the

relative benefits under routine conditions are preferred for a relative effectiveness assessment, they are rarely available at the usual timing of a rapid assessment (soon after marketing authorisation). Where sufficient good quality head-to-head studies are available, direct comparisons are preferred as the level of evidence is high. Should substantial indirect evidence be available, then it can act to validate the direct evidence. When there is limited head-to-head evidence or more than two treatments are being considered simultaneously, the use of indirect methods may be helpful (See [guideline Comparator and comparisons - Direct and indirect comparisons](#)).

The assessment of health benefits should primarily consider clinically meaningful endpoints such as mortality, morbidity, and quality of life (See guideline [Endpoints used in REA of pharmaceuticals- clinical endpoints](#)). Surrogate endpoints act as substitutes for clinically meaningful endpoints and are expected to predict the effect of therapy (benefit and/or harm). Surrogate endpoints should only be used if they are adequately validated. The level of evidence, the uncertainties associated and the limits of their use should be explicitly explained (See guideline [Endpoints used in REA of pharmaceuticals- surrogate endpoints](#)).

## 2 Methods

### 2.1 Guidelines for conducting a rapid relative effectiveness assessment

WP5 has developed guidelines on nine specific methodological issues. The recommendations provided in these guidelines should be considered when conducting a rapid REA with the Model for Rapid REA. Throughout the model text, specific guidelines are referred to when appropriate.

#### Box 1. WP5 guidelines on methodological issues

##### Endpoints used for REA of pharmaceuticals:

- Clinical endpoints ([link to recommendations](#), [link to full text guideline](#))
- Composite endpoints ([link to recommendations](#), [link to full text guideline](#))
- Surrogate endpoints ([link to recommendations](#), [link to full text guideline](#))
- Safety ([link to recommendations](#), [link to full text guideline](#))
- Health-related quality of life and utility measures ([link to recommendations](#), [link to full text guideline](#))

##### Comparators and comparisons

- Criteria for the choice of the most appropriate comparator(s) ([link to recommendations](#), [link to full text guideline](#))
- Direct and indirect comparison ([link to recommendations](#), [link to full text guideline](#))

##### Levels of evidence

- Internal validity of randomised controlled trials ([link to recommendations](#), [link to full text guideline](#))
- Applicability of evidence in the context of a relative effectiveness assessment ([link to recommendations](#), [link to full text guideline](#))

### 2.2 Scoping

#### *Key messages for scoping*

- Scoping should be done following the PICO structure ([Template 1. Format for scoping the assessment](#))
- The REA submission file supplied by marketing authorisation holder and, if available, the European Public Assessment Report (EPAR) should be used as the basic documents for scoping.
- The guidelines [Comparator and comparison](#) and [Endpoints used for REA of pharmaceuticals](#) should be consulted for choosing the comparator and the endpoints.
- The choice of comparator/outcomes should be justified explicitly in the report.
- Preferably, the marketing authorisation holder should be consulted regarding the scope.
- The project scope should be **re-evaluated** after completing the first two domains ('HPCU' and 'Description and technical characteristics [DTC]').
- During the scoping phase the [Checklist for potential ethical, organisational, social and legal aspects](#) should be completed.

### *2.2.1 General scope of the assessment*

The **first step** in a rapid REA is to specify what exactly should be assessed (e.g. the scope) following the so-called PICO structure. The letters stand for

- Population / patients with the disease of interest
- Intervention(s), i.e. the technology under assessment
- Comparison(s), that should serve as reference
- Outcomes, which encompass the endpoints for assessing effectiveness and safety

The REA submission file supplied by marketing authorisation holder and, if available, the EPAR should be used as the basic documents for scoping.

The PICO structure will drive the evaluation in all four domains. The population, intervention and comparison will generally be the same for all domains. However, it may sometimes be necessary to deviate from the scope due to, for example, a subpopulation of special interest or the absence of data for the population defined in the scope.

The marketing authorisation holder should, preferably, be consulted about the scope.

The scope of the assessment should be determined at the beginning of the assessment; however it should also be **re-evaluated after completing the first two domains** (Health problem and current use of the technology and Description and technical characteristics of the technology).

The following considerations are relevant regarding the PICO elements in the context REA.

- **Marketing authorisation status.** Assessments of pharmaceuticals should take their marketing authorisation status (e.g. <http://www.ema.europa.eu/>) into account, that is, they should be within the marketing authorisation status of the pharmaceutical. **Assessments should usually not evaluate and thus support decisions about off-label use.**
- **Population / patients with the disease of interest.** The basic definition of the patients who will receive the intervention is in general given by the marketing authorisation, which in turn is based on the evidence provided by the marketing authorisation holder. The purpose of use of the pharmaceutical should be specified. It is relevant to specify whether it is for example first- or second- line treatment and whether the intended purpose is treatment or prevention (for example a cholesterol-lowering pharmaceutical can be used either to treat or to prevent coronary artery disease).
- **Intervention(s).** For the REA of pharmaceuticals, the dose(s) of the comparator(s) is a crucial issue. This is true for direct as well as indirect comparisons. For example, comparing a low dose of one pharmaceutical with a medium or high dose of another pharmaceutical will lead to over-estimation of the tolerability of the first pharmaceutical and/or under-estimation of its efficacy or effectiveness. Familiarity with the recommended therapeutic doses of each comparator and knowledge of their dose-response relationships are a prerequisite for interpreting the results of the comparisons. For dose comparisons to be useful, the doses, the dosing schedules as well as the route of administration should be consistent with those recommended in the marketing authorisation.
- **Comparison(s).** The comparator(s) should be chosen carefully, preferably based on input on the current treatment pathway from various countries. In the context of a rapid relative assessment, the number of comparators should be limited and thus the most meaningful comparator will be routine clinical care because this will be most informative and relevant.

**The choice of comparator should be justified explicitly in the report.** For detailed information regarding the choice of comparator, please see the guideline [Comparators and comparisons – Criteria for the choice of the most appropriate comparator\(s\)](#).

- **Outcomes.** For the assessment of relative effectiveness, consideration must be given to the appropriateness of the outcome variables on which information on the intervention effect is available. A set of recommendations for the selection of clinical outcomes when completing a REA are presented in the guideline [Endpoints used for REA of pharmaceuticals – clinical endpoints](#).

When surrogate variables (e.g. Low-density lipoprotein cholesterol concentration) are used as outcome measures, the clinical validity of these measures needs to be considered (For more details see guidelines [Endpoints used for REA of pharmaceuticals – surrogate endpoints](#)). Composite endpoints should generally not be used if a suitable single primary endpoint is available. If a single primary endpoint is not available or if a composite endpoint can be justified to be more suitable (e.g. rare disease/event), it may be chosen instead.. (For more details see guidelines [Endpoints used for REA of pharmaceuticals – composite endpoints](#)).

When possible, adverse events relevant for the assessment should be identified in advance and should be listed in the scope (For more details see guidelines [Endpoints used for REA of pharmaceuticals – safety](#)).

**The choice of outcomes should be justified explicitly in the report.**

A template for reporting the scope is included in Appendix 2 ([Template 1. Format for scoping the assessment](#)).

### ***2.2.2 Checklist for potential ethical, organisational, social and legal aspects***

The Model for Rapid REA of pharmaceuticals is based on the EUnetHTA Core Model, which contains nine domains. However, due to the nature of the technology (pharmaceuticals) and the purpose of the assessment (usually the assessment is done in the context of a reimbursement decision on newly authorised pharmaceuticals) with its inherent time limits, the assessment focuses on the first four domains of the Core Model. In addition, based on the discussion in the Pharmaceutical Forum (HLPF, 2008a), cost-effectiveness was excluded and therefore the economic domain is currently not included in the model for rapid assessment.

The four other domains are replaced by a short list of questions in order to determine whether there are specific ethical, organisational, social and legal aspects that also need to be addressed ([Appendix 2, Template 2](#)). Since the assessment is comparative in nature, only those issues for which there is a difference between the pharmaceutical to be assessed and its major comparator(s) should be described. Pre-established problems/issues, with regard to ethical, organisational, social and legal aspects, that are common to the technology to be assessed and its comparator(s) will, as a rule, not be addressed, as it is not to be expected that the addition of a new pharmaceutical will lead to changes.

If a question is answered 'yes', further analysis may be warranted, otherwise the domain need not be further considered.

## 2.3 Sources of information for the assessment

### *Key messages for sources*

- Basic sources for information for a rapid REA are the REA submission file supplied by the (future) marketing authorisation holder (which should include a literature review), the European Public Assessment Report of the pharmaceutical of interest as well as the comparator(s), original studies that were performed for the registration of the indication, and existing available health technology assessment reports on the pharmaceutical of interest and its comparative treatments, if available.
- The search performed by the marketing authorisation holder should be checked for completeness, for whether it is up to date, and for potential bias. The search should be updated if/as necessary.
- Additional sources may be useful to find domain-specific information ([see Table 1](#)).
- If no REA submission file is available a detailed search by the assessment agency is required (see [Appendix 3](#)).

### *2.3.1 Basic documents*

The following sources should preferably be available at the beginning of each rapid REA:

- A REA submission file (including a literature review).
- EPAR including Summary of Product Characteristics (SPC), of the pharmaceutical of interest. The availability of the EPAR and SPC very much depends on the timing of the assessment. In case of an early assessment (before marketing authorisation) they may not yet be available.
- EPARs, including SPCs, of comparators (only applicable if the comparators are pharmaceuticals).
- Original studies (if not published and if not included in the submission file) that are relevant for the REA. This may be published results on relevant comparators but also unpublished studies in the format of Clinical Study Reports (CSRs). Most probably, the latter information will be included in the submission file from the (future) marketing authorisation holder,
- Already available health technology assessment reports of the pharmaceutical of interest and its comparative treatments.

### *2.3.2 Search*

The search performed by the marketing authorisation holder (included in the REA submission file) should be checked for completeness, for whether it is up to date, and for potential bias. The search should be updated only if necessary.

If no REA submission file is available a detailed search by the HTA organisation is required. Guidance for how to do such a systematic search is described in Appendix 3.

The Planned and Ongoing Projects database ([POP database](#)) can be searched to identify other organisations that recently have been, are or will be working on the same topic (please note that only EUnetHTA members who provide data have access to this database).

Additional sources may be useful to find information for other domains. These are listed in the table below.

**Table 1. Domain specific sources**

Domain	Databases/websites
HPCU	<p>HTAs, systematic reviews and original research can be found in reference databases: Cochrane Database of Systematic Reviews and Cochrane CENTRAL, Centre for Reviews and Dissemination (CRD), Medline, Embase, Cinahl, PsycINFO</p> <p>Evidence-based guidelines can be found in reference databases, guidelines producers' websites and in Guidelines International Network's (GIN) website. A list of helpful websites is included in <a href="#">Appendix 1, A0024&amp;A0025</a>.</p> <ul style="list-style-type: none"> <li>• Websites of health technology assessment agencies (list with URLs is provided in Appendix 1, A0021)</li> <li>• Registers and statistics:                         <ul style="list-style-type: none"> <li>- Disease registers (e.g. <a href="http://www.socialstyrelsen.se/statistics">http://www.socialstyrelsen.se/statistics</a>*, <a href="http://www.kvalitetsregister.se/web/Quality_Registries.aspx?pageID=8d07dd0a-4079-4ad7-b47b-58759d7055cb">http://www.kvalitetsregister.se/web/Quality_Registries.aspx?pageID=8d07dd0a-4079-4ad7-b47b-58759d7055cb</a>** , <a href="http://www.bhf.org.uk/research/statistics.aspx">http://www.bhf.org.uk/research/statistics.aspx</a>***)</li> <li>- Utilisation registers (e.g. <a href="http://www.norpd.no/#">http://www.norpd.no/#</a>, <a href="http://www.gjpdatabank.nl/#">http://www.gjpdatabank.nl/#</a>)</li> <li>- Birth defect registries</li> <li>- Routine collected statistics and administrative data (e.g. diagnosis related groups, discharge databases, reimbursement claims databases)</li> </ul> </li> <li>• Horizon scanning databases and websites: e.g. EuroScan <a href="http://www.euroscan.org.uk">http://www.euroscan.org.uk</a></li> <li>• Ongoing research databases</li> <li>• Scientific specialist associations' websites</li> <li>• Patient organisations' and associations' websites</li> <li>• Marketing authorisation and other regulatory institutions' websites e.g. (<a href="http://www.ema.europa.eu">http://www.ema.europa.eu</a>, <a href="http://www.fda.gov/default.htm">http://www.fda.gov/default.htm</a>). For more details see <a href="#">Appendix 1. Regulatory institutions and legal framework</a>.</li> <li>• National health services' websites</li> <li>• Regional/local governments' health departments' websites</li> <li>• Benefits and sickness funds' websites</li> <li>• Technology developers and manufacturers websites</li> </ul>
DTC	<p>Medline, CINAHL, the Cochrane Library, NHS Economic Evaluation Database, EBSCO Psychology and Behavioural Sciences Collection and Health Business on the Pubmed and EBSCO systems.</p> <p>Grey literature may be identified by searching the websites of health technology assessment and related agencies, professional associations, and other sources, including: System for Information on Grey Literature in Europe (SIGLE); World Health Organization (WHO); National Health System (NHS) Evidence; TRIP database and the European Directorate for the Quality of Medicines (EDQM). This literature may include technical reports from regulatory and government agencies [e.g. European Medicines Agency (EMA), Food and Drug Administration (FDA), Agency for Healthcare Research and Quality (AHRQ)], working papers from research groups or committees, white papers, or preprints, as well as conference proceedings. Google, Google Scholar and other internet search engines may be used to search for additional information.</p>
Safety	<p>Published research:</p> <p>Medical reference databases: CLIB, Medline; EMBASE</p> <p>Primary sources of information or data:</p> <ul style="list-style-type: none"> <li>• Manufacturers' product data sheets or applications for a product license if available. European Public Assessment Reports of pharmaceuticals. Risk Management Plans for pharmaceuticals.</li> <li>• National or international safety monitoring systems (see <a href="#">Appendix 1</a>) of adverse events which may be managed by a national statutory body or by a supra-national body. Risk Management Programs and systematic safety research e.g. European Commission's 7th Framework Programme. Particular attention is needed for label warnings and for open questions in pharmacovigilance (Eichler 2008).</li> <li>• Disease or technology monitoring registries (see <a href="#">Appendix 1</a>) of patients receiving treatment, which may be organised at an international, national or regional level and managed by a government agency, professional body or the manufacturer.</li> <li>• Pharmacovigilance data analysis and pharmacovigilance systems or spontaneous adverse event</li> </ul>



Domain	Databases/websites
	<p>databases (see <a href="#">Appendix 1</a>): e.g. WHO Uppsala Monitoring Centre spontaneous reporting database (<a href="http://www.who-umc.org">http://www.who-umc.org</a>); and the Vigibase Services, maintained by Uppsala Monitoring Centre, responsible for the management of the WHO Programme for International Drug Monitoring. The EMA collects adverse reactions reports on medicines licensed across the EU through the EudraVigilance database. Reports are received from EU regulatory agencies and pharmaceuticals companies. Adverse Event Reporting System (AERS), the database supported by the FDA's post marketing safety surveillance program for approved drugs. The MedWatch website, on which the FDA collects information about adverse reactions.</p> <ul style="list-style-type: none"> <li>• Specific enquiries to manufacturers, regulators, professional bodies or patient group perspectives may help identify additional sources of information.</li> <li>• The periodic safety update reports (PSUR), as a pharmacovigilance tool; collecting information from a variety of different sources (spontaneous reports from different countries, clinical trials, registries).</li> </ul> <p>Details on a dedicated search strategy for safety data (in general not applicable to a rapid assessment) are included in <a href="#">Appendix 3</a>.</p>

\* The Swedish National Board of Health and Welfare maintain a number of registers including the pharmaceutical register, the cause of mortality register and the registers containing the diagnoses of all hospitalised patients in Sweden.

\*\* A system of 70 national quality registries has been established in the Swedish health and medical services. It contains individualised data concerning patient problems, medical interventions, and outcomes after treatment.

\*\*\* British Heart Foundation's statistics website is an up-to-date source of statistics on the burden, prevention, treatment and causes of heart disease in the UK

# Norwegian pharmaceutical prescription database.

## Dutch database on pharmaceuticals and medical aids.

Alerts: databases such as Pubmed and EBSCO provide an alert service (regular emails with new published literature on your search terms), which will facilitate easy updating.

## 2.4 How to work with the assessment element tables

### ***Key messages for the assessment element tables***

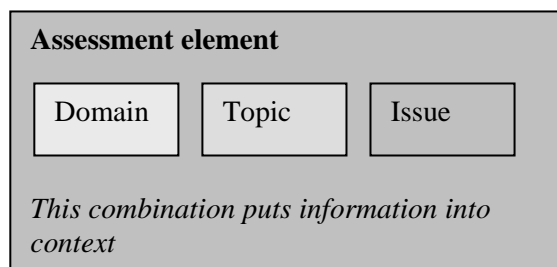
- Assessment elements are the standardised pieces of HTA information.
- Each domain has its specific assessment elements that represent the research questions that can be answered for this domain.
- For each assessment only those assessment elements should be selected that are considered relevant for the assessment.
- The selected issues (generic questions) should be translated into actual research questions (answerable questions).

The HTA Core Model structures the information of an HTA first by dividing it into *domains* (see [Figure 1](#)). Each domain is divided into three or more *topics*, and each topic is further subdivided into several *issues*. The issues are the generic questions that should be considered when doing a rapid assessment. The combination of domain, topic and issue defines an assessment element (see [Figure 2](#)).

Assessment elements are the standardised parts of a Core HTA. Each assessment element is connected to information about its importance and transferability, about how to answer it, and about how it relates to other elements. The answers to questions defined by the assessment elements are recorded as structured pieces of information on the relevant 'result cards'. These are

associated with relevant metadata to enable their effective use in the database of HTA information that is being built within EUnetHTA.

**Figure 2. An assessment element**



that are included in the assessment element table.

The following table explains the columns

**Table 2. Explanation of assessment element table**

Information (column)	Explanation	Format
Element ID (a)	An individual code for each element.	Code
Domain (b)	The domain to which the element belongs.	Standard list
Topic (c)	The topic to which the element belongs. A subset of a domain.	Standard list
Issue (d)	A generic question, the answer of which provides information that may be useful for the decision on the use or non-use of any given technology. A subset of a topic.	Standard list
Clarification (e)	A brief explanation of the issue. Clarification is not necessarily needed if the issue is self-explanatory.	Free text
Importance (f)	Defines the importance of considering the particular issue when conducting the HTA <sup>1</sup> .  This importance relates to significance from the viewpoint of HTA. This is not always the same as 'relevance' in a particular policy context.	3 categories: <i>Critical=3</i> <i>Important=2</i> <i>Optional=1</i>
Transferability (g)	An estimate of the transferability of data or other findings from one context to another <sup>1</sup> .	3 categories: <i>Complete =3</i> <i>Partially =2</i> <i>Not =1</i>
Information sources(s) (h)	A brief explanation of where to find and how to analyse answers to	Free text

<sup>1</sup> In the current version of this document the importance and transferability of each element has not always been considered enough. Therefore any judgements should be regarded as tentative. Further piloting will provide more accurate values. Importance is included in the consideration to ensure that the core of the assessment is robust enough, i.e. that it contains information that is really significant from the viewpoint of HTA. The importance considered here is not equal to relevance of information for a particular policy question. It is assumed, however, that issues perceived important from the viewpoint of HTA are often useful when making decisions on health care policy. If the information is fully or partly transferable, it may provide valuable input beyond its original production location. Transferability is low for information that is very specific to a particular context (e.g. region, country, health care system) and is most likely not useful as such in other settings. On the other hand even non-transferable information may be useful; e.g. Italian incidence data on cardiovascular mortality is applicable to all Italian HTAs assessing cardiovascular technologies or, Swedish data on current use of the technology may suggest over- or underuse of the technology in one's own country.

Information (column)	Explanation	Format
	this particular issue.	
Reference (i)	Indicates the reference(s) for the issue. Serves (among other things) the following purposes: - Credit to earlier work - Sources for more information on the topic  Particular attention to earlier European HTA projects, as well as to international standards, such as the ICF (International Classification of Functioning, Disability and Health).	Free text.
Relations (j)	There may be similar issues in different domains that need to be assessed from both angles. This related content should be taken into account in the scoping phase in order to avoid overlap. There may also be time relationships because certain elements require the results from another element, and can thus be assessed only after completion of another element.	Element IDs of the related issues

After the general scope of the assessment has been determined the following actions should be undertaken:

- Selecting relevant issues from the assessment elements table of the model for rapid assessment.
- Translating the selected issues (generic questions) into actual research questions (answerable questions).

### ***2.4.1 Selecting relevant issues from the model***

The authors go through the generic questions, i.e. issues in the assessment table of the domains in the model for rapid REA, one by one, defining whether the question is relevant for this topic. The decisions are based on the authors' own expertise and on the literature retrieved from the basic documentation.

Classifying a question as relevant means that it should be assessed. Therefore, the word 'relevance' should be interpreted here as 'relevant in general, and relevant enough to be answered in this rapid assessment'. A brief justification should be provided for those elements that are regarded as not relevant. This information may be useful for readers of the report.

### ***2.4.2 Formulating research questions***

In this phase the authors should translate the issues, i.e. the generic questions in the relevant assessment element table, into actual research questions. One issue usually translates into one research question, but it is sometimes necessary to translate a single issue into two or more research questions. It is important that this phase results in a set of pragmatic and answerable questions for the authors to continue with.

A template for the authors for reporting the selection of relevant issues and formulation of actual research questions is included in Appendix 2 ([Template 3. Selecting relevant assessment elements and translating the generic issues into actual research questions](#)).

## **2.5 Collecting and analysing data**

### ***2.5.1 Appropriate study types***

#### ***Safety data***

A broad range of study types may be considered to identify harms relevant for the assessment, as they bring different and complementary information. Although safety data from RCTs is considered most reliable, reasons for including data from sources with higher risk of bias may be necessary when harms are unknown, rare, or occurring only in long follow-up. These may include observational studies, country registers and published case reports. Suggestions for building an optimal search strategy for safety information are presented in Appendix 3. For more details see section 2.4 of the guideline [Endpoints used in REA of pharmaceuticals – Safety](#).

### ***Effectiveness data***

The generally accepted standard for demonstrating a causal relationship between intervention and health outcomes is an appropriately designed and conducted RCT. In the assessment of pharmaceuticals, RCTs are usually possible and practically feasible. Therefore, as a general rule RCTs should be considered for assessing the health benefits of pharmaceuticals. A (well conducted) meta-analysis of the results of more than one RCT would provide the highest level of evidence. Non-randomised intervention studies or observational studies can be considered where an RCT is not feasible or complementary data is presented to RCTs.

If all of the studies concerning a technology have been performed under strict clinical trial conditions, no information on the benefit of the technology under routine conditions is available. This is often the case just after marketing authorisation. Generally, information on benefit under routine conditions may be collected in trials with a pragmatic approach (a trial setting that corresponds to usual circumstances of healthcare instead of a strict protocol-driven setting that is used in trials of an explanatory nature) or by observational studies. The results of pragmatic trials and country-specific observational studies are usually affected by local clinical practices. Consequently, the transferability and generalisability of the results may suffer and should be considered carefully. For more details see section 2.1 of the guideline [Applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals](#).

## **2.5.2 Quality appraisal**

### ***Safety data***

Methods used to assess bias should be clearly described and the risk of bias reported regarding both the information sources and how the data were collected. The way risk of bias information was used in the REA should be clearly explained. Detailed recommendations on how to assess the risk of bias and the quality of data on harms are included in section 2.4 of the guideline [Endpoints used in REA of pharmaceuticals – Safety](#).

Timeliness of literature and registration data should be evaluated, as well as their applicability in vulnerable patient groups such as elderly people with polypharmacy, people with comorbidities, neonates and children, pregnant women and immunosuppressed patients

### ***Clinical effectiveness data***

Internal validity describes the extent to which the (treatment) difference observed in a trial (or a meta-analysis) is likely to reflect the 'true' effect within the trial (or in the trial population) by considering methodological quality criteria. Because the 'truth' can never be assessed, it is more appropriate to speak of the potential for or risk of bias. The risk of bias concept should be used to assess the internal validity of clinical studies within an REA. The risk of bias should be assessed on two levels, i.e. firstly, on a (general) study level, and secondly, on an outcome level. For example, selection and performance bias threaten the validity of the entire study, while the other types of bias may be outcome specific.

Within an REA, how to deal with studies with a high or unclear risk of bias should be specified in advance. There are three main options: (i) rely only on studies with a low risk of bias; (ii) perform sensitivity analyses according to the different risk of bias categories; (iii) describe the uncertainty with regard to the different levels of risk of bias, so that subsequent decisions can be made considering this uncertainty.

For more details see the guideline [Levels of evidence – Internal validity of randomised controlled trials](#).

### **2.5.3 Effect measures and confidence intervals**

A number of measures of the intervention effect are in use. For dichotomous outcome data, relative effect measures, such as risk ratio (= relative risk), odds ratio, and relative risk reduction, or absolute effect measures, such as risk difference (= absolute risk reduction), are commonly used. The latter is often converted into number needed to treat (NNT) or events per thousand patients to allow comparison across studies and to facilitate interpretation. Both relative and absolute effect measures convey important complementary information and therefore presentation of both measures is encouraged by recent approaches such as the GRADE profiler ([www.gradeworkinggroup.org](http://www.gradeworkinggroup.org)).

Continuous data should be reported according the appropriate statistics. Commonly used effect measures that allow the summarising of the treatment effects are '*standardised mean difference*' or '*weighted mean difference*'.

A more recent statistic, the ratio of means, reports the proportional difference within the comparison (intervention of interest vs. comparator) in continuous data such as proteinuria. (Friedrich et al. 2005). In time-to-event analysis the most important measures of effect are hazard ratio (HR) and ratio of medians.

For more details about the assessment and presentation of effect measures we refer to the guidelines [Endpoints used in REA of pharmaceuticals- Clinical endpoints/Surrogate endpoints/Composite endpoints/Safety](#). Information about health-related quality of life is provided in the guideline [Health-related quality of life and utility measures and utility measures](#). In addition, effect measures and their calculation are comprehensively described in the [Cochrane Handbook](#).

A measure of the precision of the effect estimate (standard error or confidence interval) is required for the interpretation of the data. The absence of this essential information should be reported.

For safety data it is recommended that, whenever possible, the frequency of adverse events should be quantified, and information on the frequency of occurrence, relative risk or number needed to harm (NNH) should be obtained (Velasco et al. 2002). In case where adverse events are incorporated in utility values of quality of life, the source of the quantification should be accessible.

### **2.5.4 Extrapolation of efficacy to give relative effectiveness data**

For a rapid assessment most of the data are retrieved from RCTs. As these trials were conducted in a specific setting it is relevant to consider the **applicability** of the results to the intended population for treatment (AGDH, 2008). For further details see the guideline [Levels of evidence – Applicability of evidence in the context of a relative effectiveness assessment](#).

In the case of surrogate outcomes **transformation** into patient-relevant final outcomes of treatment should be considered (AGDH, 2008). For details about when and how surrogate endpoints can be used see the guideline [Endpoints used in REA of pharmaceuticals – surrogate endpoints](#).

It may be relevant for a REA to include data from **indirect comparisons**. Where sufficient good quality head-to-head studies are available, direct comparisons are preferred as the level of evidence is high. If substantial indirect evidence is available, then it can act to validate the direct

evidence. However, when there is limited head-to-head evidence, or more than two treatments are being considered simultaneously, the use of indirect methods may be helpful. For more details see the guideline [Comparator and comparisons – Direct and indirect comparisons](#).

At this stage, authors of a rapid assessment should check, that the data extracted is relevant to the research questions formulated in the beginning, and that analysing and synthesising the data is still answering the question. Often the evidence available is not quite as useful as hoped, and in that case it should be made explicit how well it answers the original research question.

## 2.6 Evidence tables

Comprehensive and informative *evidence tables* about the methodology and the content of the individual studies:

- foster transparency and reliability, which are prerequisites for the transfer of rapid REA reports from one setting to another;
- allow a judgment of the similarities and differences of the studies included; and
- provide the basis for the conclusions of the review.

Therefore, they should be a compulsory part of each REA.

The majority of HTA organisations produce tabulated evidence summaries that follow the PICO structure (ideally with an additional cell for comments on issues that are not captured by the PICO cells but could have an impact on the results). Although the items reported in each cell will be driven by the questions of the review, they follow some core considerations (Malmivaara et al. 2006). A description of the data extraction process, including the number of reviewers involved, assures objectivity and reliability of the results.

A table that was specifically designed in cooperation with the European Medicines Agency (EMA), for reporting results from clinical trials with pharmaceuticals should be used (Appendix 2, [Template 5. Table for reporting results from clinical trials](#)).

## 2.7 Interpreting evidence

The reader should be given an idea of the nature and magnitude or frequency of the event, and the overall robustness of the evidence behind this statement. There are several ways to provide this information. In many cases plain text is sufficient; in others an evidence table would be helpful.

For interpretation of the evidence the following aspects should be discussed in the report.

- The strength/uncertainties of the evidence available. This should include the internal validity of the body of evidence as well as the applicability of the evidence.
- The clinical relevance of the findings:
  - Statistical significance is not a sufficient precondition because numerically small differences can be statistically significant but clinically meaningless. Consider the magnitude (i.e. relevance) of the treatment effect (independent of its statistical significance) and compare this with the minimal clinically important effect size. One approach is to compare the lower limit of the 95% confidence interval of an estimated treatment effect with a 'maximal clinically unimportant effect size'.
  - Consider the relevance of the outcomes for clinical decision making (distinguishing between a critical and an important outcome as done when formulating the question).
  - Identify knowledge gaps by comparing the research questions (including the predefined outcome) with the available evidence.

To allow transfer of data across countries, REAs have to be sufficiently transparent and distinguish between evidence ('facts') and judgements (including values and preferences). Value judgements and preferences (of individuals or of health care systems) have to be labelled as such.

## 2.8 Reporting

Reporting is performed in three phases: the result cards, the domain reports and the full report. In the result cards the authors report the detailed methods and results for each research question separately. The cards are compiled in a domain report amended with chapters for domain specific methods, summary of main results, and discussion. Finally, all domain reports are taken together, and amended with the benefit-harm analysis and overall summary and discussion.

A template for result card is included in Appendix 2 (Template 4 Result card)

A template for writing the domain report is included in Appendix 2 ([Template 6. Domain report](#)).

## 2.9 Summarising the results for a rapid relative effectiveness assessment

In order to assess relative effectiveness according to the definition of the Pharmaceutical Forum, a synthesis of both effectiveness (benefits) and safety (harms) data is needed. The benefits and harms of the intervention(s) should be presented in comparison with the comparator(s). These data are presented in the relative effectiveness section (the summary) of the report. The following, at least, should be included in this summary. A detailed template for writing the summary is included in Appendix 2 ([Template 7. Summary](#)).

- Scope
- Introduction: description of health problem; description of current treatment; description of technology; description of comparators
- Results: description of available evidence and ongoing trials; description of relative effectiveness results; description of relative safety results; description of reimbursement status of pharmaceutical in various countries
- Summary table of relative effectiveness
- Discussion: discussion of potential limitations, including internal validity and applicability, of available evidence and identification of evidence gaps
- Conclusion: conclusion for each comparator as to whether the pharmaceutical is less, similarly, or more effective and safe; conclusion on further research required.

### 3 Domains – assessment element tables

#### 3.1 Health problem and current use of technology

a	b	c	d	e	f	g	h	i	j
Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Sources and methods	References	Relations
A0002	Health Problem and Current Use of the Technology	Target Condition	What is the disease or health condition in the scope of this assessment?	Relevant for all assessments. Especially when effectiveness depends on the subtype, stage or severity of the disease. Use the target condition and ICD codes defined in the scope of the project and consider adding details such as: description of anatomical site, disease aetiology and pathophysiology, types of disease or classification according to origin, severity, stages, or risk level, and different manifestations of the condition. The following properties of the target condition are defined in separate assessment elements: risk factors (A0003), natural course (A0004), symptoms (A0005), and burden of disease including prevalence and incidence (A0006).	3	3	<b>Sources:</b> REA submission file, text books, HTAs, guidelines, epidemiological reviews or studies, WHO documents, disease registers. <b>Method:</b> A descriptive summary.	Burls 2000, Velasco 2002, Liberati 1997, Imaz-Iglesia 1999, Kristensen 2007	
A0003	Health Problem and Current Use of the Technology	Target Condition	What are the known risk factors for the condition?	Describing risk factors is especially important when they suggest possibilities for primary and secondary prevention. This information may affect the choice of comparator or the appraisal of the overall value of the technology under assessment. The risk factors for acquiring the condition, and the risk factors for relapses or worsening of the condition should be reported here, separately. The prevalences of the various risk factors might differ in different geographic areas and among different sub-populations.	2	2	<b>Sources:</b> REA submission file, text books, HTAs, guidelines, epidemiological reviews or studies. <b>Method:</b> Systematic review is generally not required. A descriptive summary is sufficient.	Burls 2000, Velasco 2002, Liberati 1973, Imaz-Iglesia 1999, Kristensen 2007	
A0004	Health Problem and Current	Target Condition	What is the natural course of the	This assessment element should provide information on the prognosis and course of the condition when untreated. This information is relevant for appraising the overall value of the	3	3	<b>Sources:</b> REA submission file, text books, HTAs,	Burls 2000, Velasco 2002, Liberati 1973, Imaz-Iglesia 1999,	



a	b	c	d	e	f	g	h	i	j
Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Sources and methods	References	Relations
	Use of the Technology		condition?	technology. A technology targeted to cure a life-threatening condition has a different significance from a technology intended to alleviate the symptoms of self-limiting conditions. It may also guide the assessment of the predicted value or effectiveness of the technology, as technologies may work differently at different stages or severity grades of the disease, and there may be a relationship between earlier intervention and better prognosis.			guidelines, epidemiological reviews or studies. <b>Method:</b> A descriptive summary.	Kristensen 2007	
A0005	Health Problem and Current Use of the Technology	Target Condition	What is the burden of disease for the patient?	This issue is especially relevant when the patient or individual is expected to undergo a substantial change in pain, disability, psychosocial issues, or other determinants of quality of life. This element should describe the patient's relevant symptoms before intervention with the technology, their severity and whether they are persistent, intermittent, or undulating. Patients' perceptions of the burden of the disease are not always in line with the clinical seriousness of the disease or its societal burden.	3	3	<b>Sources:</b> REA submission file, text books, HTAs, quality of life studies, qualitative patient perception studies. <b>Method:</b> A descriptive summary.	Burls 2000, Velasco 2002, Liberati 1973 Imaz-Iglesia 1999, Kristensen 2007	
A0006	Health Problem and Current Use of the Technology	Target Condition	What is the burden of the disease for society?	Prevalence or incidence of the disease that is prevented or treated by using the technology; disease-specific mortality and disability, life years lost., and/or disability-adjusted life years	3	2	<b>Sources:</b> REA submission file, HTAs, registries and national statistics, WHO incidence, mortality and survival databases. <a href="http://www.who.int/cancer/resources/incidence/en/">http://www.who.int/cancer/resources/incidence/en/</a> <b>Method:</b> A descriptive summary.	Burls 2000, Velasco 2002, Liberati 1973 Imaz-Iglesia 1999, Kristensen 2007, WHO 2009	

a	b	c	d	e	f	g	h	i	j
Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Sources and methods	References	Relations
A0007	Health Problem and Current Use of the Technology	Target Population	What is the target population in this assessment?	Relevant for all assessments: both safety and effectiveness depend largely on the subpopulation towards which the intervention is targeted. The technology may be used for all patients with the condition, or only those in the early stages, or at a specific severity level, or for those at moderate risk of having the condition. Personalised medicine divides the target population into even smaller units when targeting the intervention to specific subgroups based on e.g. genetic profile. Use the target population defined in the scope of the project, and consider adding further details and description of who defined the selected subgroups and why.	3	2	<b>Sources:</b> SPC, HTAs, guidelines, reviews. <b>Method:</b> A descriptive summary.		
A0023	Health Problem and Current Use of the Technology	Target Population	How many people belong to the target population?	This information can also be used to give an idea of the resource requirements in general for implementing the pharmaceutical.. Estimates of likely relevant increases or decreases in the size of the target population in the future should also be included.	3	2	<b>Sources:</b> REA submission file, national registries, statistics, systematic reviews. <b>Method:</b> A descriptive summary.	Burls 2000, Velasco 2002, Liberati 1973 Imaz-Iglesia 1999, Kristensen 2007	
A0001	Health Problem and Current Use of the Technology	Utilisation	For which health conditions and populations, and for what purposes is the technology used?	'All relevant conditions, populations and populations should be included. This question is especially relevant when there are multiple potential target conditions and populations for which the technology is used, and multiple intended uses, both indicated and other. There may also be differing views about the appropriate use of the technology that it is essential to highlight. Describe the differences in the use of the technology for the various indications and how it might act differently in different patient groups. Point out e.g. if certain populations should be excluded from using the technology, or if they require a different dosage. Certain pharmaceuticals may be primarily indicated for second-line use but also used for first-line treatment.	3	3	<b>Sources:</b> HTAs, guidelines, reviews, clinician consultation. <b>Method:</b> A descriptive summary.	Burls 2000, Velasco 2002, Liberati 1973 Imaz-Iglesia 1999, Kristensen et al. 2007	B0002, B0004, B0005, C0005
A0011	Health Problem and Current Use of the	Utilisation	How much are the technologies utilised?	Provide national estimates for current and future utilisation rates, for both the technology under assessment and its comparators. Variations in utilisation reflect market access, sales figures, actual usage in hospital level and adherence to the use of the	3	2	<b>Sources:</b> REA submission file, echnology and procedure registers,	Burls 2000, Velasco. 2002, Liberati 1973 Imaz-Iglesia 1999, Kristensen 2007	B0003

a	b	c	d	e	f	g	h	i	j
Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Sources and methods	References	Relations
	Technology			technology by both professionals and patients. Data on current and previous utilisation reflect the phase of the technology (experimental, emerging, established or obsolete). This also has implications for the availability of evidence and the level of uncertainties.			guidelines, utilisation studies, REA submission files and sales data. <b>Method:</b> A descriptive summary narrative.		
A0024	Health Problem and Current Use of the Technology	Current Management of the Condition	How is the health condition currently diagnosed according to published guidelines and in practice?	The effectiveness of an intervention may vary in differently diagnosed populations. A sensitive test tends to have low specificity such that there are several people who do not have the condition among the test-positive population. The effectiveness of an intervention in that population may be lower than in a population examined with a less sensitive test (but with more true positive cases). It is important to point out possible discrepancies between guidelines and actual practice.	2	2	<b>Sources:</b> Clinical guidelines and published utilisation reviews; in the absence of these, clinical experts survey. <a href="#">See Appendix 1.</a> <b>Method:</b> Systematic review of clinical guidelines. Quality appraisal of guidelines can be done using e.g. AGREE II Instrument. For practice mapping, a pragmatic review or listing of available information is sufficient. Flowcharts are illustrative in reporting diagnostic pathways.	Burts 2000, Velasco 2002, Liberati 1973 Imaz-Iglesia 1999, Kristensen 2007	

a	b	c	d	e	f	g	h	i	j
Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Sources and methods	References	Relations
A0025	Health Problem and Current Use of the Technology	Current Management of the Condition	How is the health condition currently managed according to published guidelines and in practice?	It is important to describe whether the technology is an add-on or a replacement for the existing management options, and what the other evidence-based alternatives are. Are there differences in the treatment of diseases at their different stages? Identification of practice variations may imply differences in the quality of health care. Deviation from evidence-based guidelines may suggest over/under use of the technology.	3	2	<b>Sources:</b> Clinical guidelines and published utilisation reviews; in the absence of these clinical experts survey. <a href="#">See Appendix 1.</a> <b>Method:</b> Systematic review of clinical guidelines. Quality appraisal of guidelines can be done using e.g. AGREE II Instrument. For practice mapping, a pragmatic review or listing of available information is sufficient. Flowcharts are illustrative in reporting management pathways.		
A0020	Health Problem and Current Use of the Technology	Regulatory Status	What is the marketing authorisation status of the technology?	There are both international and national market authorisation systems. For pharmaceuticals the systems are established but for devices and procedures less so.	3	3	<b>Sources:</b> (Inter)national authorities (Europe: EMA; US: FDA; Canada: Health Canada; New Zealand: MedSafe; Australia: TGA) or manufacturer.	Burls 2000, Velasco 2002, Liberati 1973 Imaz-Iglesia 1999, Kristensen 2007	

a	b	c	d	e	f	g	h	i	j
Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Sources and methods	References	Relations
							Method: Descriptive summary.		
A0021	Health Problem and Current Use of the Technology	Regulatory Status	What is the reimbursement status of the technology?	Information on national reimbursement status from different countries for the technology as well as the comparators, including key dates and anticipated licensing timeframe should be listed here. Notice that reimbursement status may differ for different purposes: e.g. treatment vs prevention. Information on full coverage, co-payments, coverage under special circumstances/conditional coverage is useful.	2	3	<p>Sources: Websites of national medicines agencies, HTA agencies and insurance institutions (<a href="#">Appendix 1, List of websites of national agencies with information on reimbursement.</a>), manufacturers, policy studies dealing with benefit baskets.</p> <p>Method: Descriptive summary.</p>	Burils 2000, Velasco 2002, Liberati 1973 Imaz-Iglesia 1999, Kristensen 2007	

### 3.2 Description and technical characteristics of technology

a	b	c	d	e	f	g	h	i	j
Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Sources and methods	References	Relations
B0001	Description and technical characteristics of technology	Features of the technology	What is the technology and the comparator(s)?	This is relevant in all assessments. Use the descriptions of the technology and comparator(s) defined in the scope and elaborate them here in more detail. Describe separately for the technology and the comparator the type of device, technique, procedure or therapy; its biological rationale and mechanism of action; qualitative and quantitative composition of the pharmaceutical; pharmacodynamics and pharmacokinetics; method of administration, and dosage. Be clear about the difference between assessing the technology alone versus the whole process including the technology. Describe how the technology differs from its predecessors, and the various current modifications or different manufacturers' products, especially if the dissimilarities affect performance.	3	3	<b>Sources:</b> SPC, EPAR; HTAs, reviews, introduction sections of research articles. <b>Method:</b> Descriptive summary.		
B0002	Description and technical characteristics of technology	Features of the technology	What is the approved indication and claimed benefit of the technology and the comparator(s)?	This issue is especially relevant in new technologies with uncertain expectations and claims of benefit. Describe the expressed objectives for the implementation of the technology in health care; what are the claimed objectives e.g. increased safety, health benefit, accuracy or patient compliance, and whether it is intended to replace or to supplement existing technologies. Is the technology licensed as a monotherapy, or in addition to current	3	2	<b>Sources:</b> Market access authorities' websites; manufacturers' sites and REA submission files, HTAs, reviews, introduction sections of research articles, conference proceedings, consulting clinical professionals, lay journals and websites.		A0001, C0008

a	b	c	d	e	f	g	h	i	j
Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Sources and methods	References	Relations
				treatment (which should be specified) Are there stopping rules for use of the technology? Is there evidence that the technology works (or is used) outside its current indication area, or produces incidental findings that can have consequences relevant to effectiveness, safety, organisational, social and ethical domains? This information may explain the choice of comparator(s) and outcomes for the assessment and helps in appraising the overall results.			<b>Method:</b> Descriptive summary.		
B0003	Description and technical characteristics of technology	Features of the technology	What is the phase of development and implementation of the technology and the comparator(s)?	When was it developed and introduced in health care? Is the technology fully developed or in its early developmental phases (technological maturity)? Is the technology field changing rapidly? Is it a novel (or innovative) technology, or is it a modification of an existing technology or has it been used earlier for some other purpose? Is it experimental, emerging, established in use or obsolete (implementation level)? This information is relevant for the assessment while the evidence base may change rapidly for technologies that are at an earlier stage in their development. It is also important to establish whether new versions of the technology with substantial improvements are expected in the near future.	3	2	<b>Sources:</b> Manufacturers' information and efficacy/effectiveness studies for new technologies. HTAs, guidelines and reviews. <b>Method:</b> Descriptive summary.		A0020
B0004	Description and technical characteristics of technology	Features of the technology	Who performs or administers the technology and the comparator(s)?	Which professionals (nurses, doctors, and other professionals) apply and make decisions about starting or stopping the use of the technology? Do the patients themselves, or their carers, administer the technology? Who can select the patients, make referrals, decide to initiate the use of	3	2	<b>Sources:</b> Clinical guidelines, professionals' consensus statements, HTAs, manufacturers' websites, introduction sections of research articles, interviews with		A0012, A0025

a	b	c	d	e	f	g	h	i	j
Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Sources and methods	References	Relations
				the technology, or interpret the outcome? Are there certain criteria (skills, function, training requirements) for the patients or professionals who will administer the technology?			clinical professionals or patients. <b>Method:</b> Descriptive summary.		
B0005	Description and technical characteristics of technology	Features of the technology	In what context and level of care are the technology and the comparator used?	Describe the level of care in which the technology is used: self care, primary care, secondary and tertiary care. If secondary or tertiary care, describe whether it is intended to be used in the outpatient or inpatient setting.	3	1	<b>Sources:</b> Manufacturers' information, clinical guidelines, efficacy/effectiveness studies, consulting clinical professionals, national consensus or legislation. <b>Method:</b> Descriptive summary.		A0012, A0025
B0008	Description and technical characteristics of technology	Investments and tools required to use the technology	What kind of special premises are needed to use the technology and the comparator(s)?	Many technologies require purpose-built premises, such as radiation-secured areas, Faraday cages, dressing rooms for the patient, or specific premises for storage and reconstitution of chemotherapy pharmaceuticals equipped with fume cupboards. There may be different requirements for premises in primary or secondary care and marked differences from country to country.	3	2	<b>Sources:</b> User information from manufacturer, and market approval authority. HTAs, applicability studies, interviews with clinical experts and hospital managers. <b>Method:</b> Descriptive summary.		A0012, A0025
B0009	Description and technical characteristics of technology	Investments and tools required to use the technology	What supplies are needed to use the technology and the comparator?	Describe all required disposable items necessary for using the technology, such as syringes, needles, pharmaceuticals and contrast agents, fluids, bandages and tests to identify patients eligible for treatment.	3	3	<b>Sources:</b> Information from manufacturer, HTAs, applicability studies, interviews with clinical professionals and hospital managers. <b>Method:</b> Descriptive summary.		
B0010	Description and technical characteristics of technology	Investments and tools required to use the	What kind of data and records are needed to monitor the use	Describe the data that needs to be collected about the care process, professionals involved, patients and their health outcomes. These include: e.g. clinical indications,	3	2	<b>Sources:</b> Local authorities and legislation, administrative staff, clinical professionals.		



a	b	c	d	e	f	g	h	i	j
Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Sources and methods	References	Relations
		technology	of the technology and the comparator?	specified populations, prescriber information, inpatient or outpatient use, test results, review period, and health outcomes. In case of new technologies, consult EVIDENT database. Refer to SPC and EPAR.			<b>Method:</b> Descriptive summary.		
B0011	Description and technical characteristics of technology	Investments and tools required to use the technology	What kind of registry is needed to monitor the use of the technology and comparator?	Describe the general importance of having a registry to monitor the use of this particular technology and the comparator. Are there existing registries that should be used, or should a registry be established, to collect the necessary data to monitor safety or true life effectiveness? Provide national examples. Sometimes registries are connected with the risk sharing scheme that innovative pharmaceuticals require in some countries. Notice also the requirements of pharmacovigilance monitoring.	2	2	<b>Sources:</b> Local authorities and legislation, administrative staff, clinical professionals <b>Method:</b> Descriptive summary.		

### 3.3 Safety

a	b	c	d	e	f	g	h	i	j
Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Sources and methods	References	Relations
C0001	Safety	Patient safety	What kind of harms can use of the technology cause to the patient?	<p>Here one should identify and describe the direct harms of the use and the administration of the technology. User dependent harms are described in C0007, and comparative harms in C0008. The harms are identified in placebo-controlled trials, observational studies, and in registries. It is important to refer to the source and report separately harms identified in spontaneous reporting databases. The identified harms should be categorised according to their severity and frequency. Harm severity (intensity) is typically graded into 'serious' (deadly or permanently disabling), 'severe', 'intermediate' or 'mild'. Frequency of occurrence of each harm is usually presented in comparison with placebo or no treatment, as percentages or risk ratios. Finally, the harms should be grouped by their severity and frequency and ordered so that the severe and/or frequent harms are presented first. If there are many different harms reported in the literature, concentrate on reporting the most severe and the most frequent harms only. Additional information, which can be reported for each harm, includes: timing (immediate, early or late); duration; continuous vs intermittent; discontinuation rate due to harms; authors view on causality (Did the use of the technology cause the harm?). For further information see guideline <a href="#">Endpoints used in REA of pharmaceuticals – Safety</a></p>	3	3	<p><b>Sources:</b> Placebo controlled trials, observational research, FDA database, safety monitoring databases, registers, statistics.  <b>Method:</b> Systematic review. Results should be presented by risk level (i.e. the product of severity and frequency of harm).</p>	Derry 2001, Ioannidis 2001, MacMahon 2001, Velasco 2002, Wald 2003, McIntosh 2004, Papanikolaou 2006, Loke 2006, 2007, Golder 2006, 2008, Higgins 2011	C0007

a	b	c	d	e	f	g	h	i	j
Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Sources and methods	References	Relations
C0002	Safety	Patient safety	What is the dose relationship of the harms?	This is usually relevant with pharmaceuticals but may also be relevant with devices and procedures. Before marketing authorisation it is relevant to report harms at any dose. After market access the harms at doses normally used in practice are most relevant for HTA. Information should be included if safe use of the technology is sensitive to even small changes of the dose because this may have implications for the training and organisation of care. The potential for accumulated harm due to repeated dosage or testing should also be considered. For further information see <a href="#">Endpoints used in REA of pharmaceuticals – Safety</a>	3	3	<b>Sources:</b> Phase 1 studies for pharmaceuticals, other research articles, HTAs, manufacturers' product data sheets, safety monitoring databases. <b>Method:</b> Systematic review.	Edwards 2000; Aronson 2003, Loke 2007	A0020
C0004	Safety	Patient safety	How does the frequency or severity of harms change over time or in different settings?	This issue is especially relevant for new or evolving technologies where there are considerable uncertainties in the safety evidence, and in technologies with steep learning curves. How does the safety profile of the technology vary between different generations, approved versions or products? Is there evidence that harms increase or decrease in different organisational settings?	3	2	<b>Sources:</b> HTAs, efficacy and safety research articles, articles on learning curve, manufacturers' information. <b>Method:</b> Descriptive summary.		B0001, B0003
C0005	Safety	Patient safety	What are the susceptible patient groups that are more likely to be harmed?	Typically, people with comorbidities and co-medication, pregnancy, intolerances, or specific genetic profiles, elderly people, children.	3	3	<b>Sources:</b> HTAs, guidelines, market access authorities, manufacturers' product information, label warnings, safety monitoring databases. <b>Method:</b> Descriptive summary.	Aronson 2003, Eichler 2008	A0007

a	b	c	d	e	f	g	h	i	j
Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Sources and methods	References	Relations
C0007	Safety	Patient safety	What are the user-dependent harms?	Describe here what is known of the harms caused by the properties or behaviour of professionals, patients or other individuals who apply or maintain the technology. Is there e.g. a noteworthy risk of malfunction of a device, due to deficient user training or personal attitude; or a risk of errors related to reconstitution, dosage, administration, or storage of medicines, that may have serious consequences; or, is there a risk of addiction? Describe what is known of the learning curve, intra- or inter-observer variation in interpretation of outcomes, errors or other user-dependent concerns in the quality of care. For further information see <a href="#">Endpoints used in REA of pharmaceuticals – Safety</a> .	3	2	<b>Sources:</b> Studies on effectiveness, safety and health services research; manufacturers' product data sheets, safety monitoring databases, label warnings. <b>Method:</b> Systematic review .	Eichler 2008, Loke 2007;	B0004, C0001
C0008	Safety	Patient safety	How safe is the technology in relation to the comparator?	Highlight the differences in the most important risks (i.e. the most severe and frequent harms) of the technology and its comparator. For harms that are common to both the technology and the comparator, provide information on which has the higher risk of the particular harm. For further information see <a href="#">Endpoints used in REA of pharmaceuticals – Safety</a> .	3	2	<b>Sources:</b> Preferably head to head trials. In their absence, studies with other comparisons and reports with indirect comparison between the technologies <b>Method:</b> Systematic review.		
C0040	Safety	Environmental safety	What kind of harms are there for public and environment?	Several chemical substances or their toxic metabolites are potentially harmful in ecological environments; some of the most recent concerns are endocrine modulators and disruptors and nanoparticles. The statistical risk of radiation at the public level should also be described here.	1	2	<b>Sources:</b> OSH guidelines, chemical safety cards, research in occupational and environmental health and safety, safety authorities' websites, manufacturers' product data sheets, safety monitoring databases. <b>Method:</b> Systematic		

a	b	c	d	e	f	g	h	i	j
Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Sources and methods	References	Relations
							review.		

### 3.4 Clinical effectiveness

a	b	c	d	e	f	g	h	i	j
Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Sources and methods	Reference	Relations
D0001	Clinical effectiveness	Mortality	What is the expected beneficial effect of the intervention on overall mortality?	Mortality is the preferred, objective endpoint for assessments of life-threatening conditions. Overall mortality refers to all-cause mortality. It is expressed either as mortality rates (incidence in given population, at given time point and usually risk standardised), or survival (number of people alive for a given period after an intervention). Several methods are used to adjust mortality rates and survival curves, e.g. relative survival (observed versus expected survival), which can be quite misleading; and hazard ratio (derived from a statistical method comparing the median survivals in the two groups). Note that progression-free survival is not a mortality endpoint; it describes the time from the beginning of an intervention until a patient shows signs of disease progression. Consider separately absolute mortality (compared to placebo or waiting list) and mortality relative to the comparator. See also guideline <a href="#">Endpoints used in REA of pharmaceuticals</a> .	3	3	<b>Sources:</b> REA submission file, SPC, EPARs, HTAs, systematic reviews of RCTs, RCTs (both placebo-controlled and head-to-head trials). In the absence of head to head trials indirect comparison is required (for more details on indirect comparisons see guideline <a href="#">Comparator and comparisons – Direct and indirect comparisons</a> ). Health care register data. Modelling studies. <b>Method:</b> Systematic review included in REA submission file.	Hochman 2011, Black 2002	
D0002	Clinical effectiveness	Mortality	What is the expected beneficial effect on the disease-specific	Disease-specific mortality is a proportion of the all-cause mortality. It should be noted that even if a given treatment reduces one type of death, it could increase the risk of dying from another	3	3	<b>Sources:</b> SPC and EPAR, HTAs, systematic reviews of RCTs, RCTs, both placebo-controlled and head-to-head trials. In the absence of	Hochman 2011, Black 2002	

a	b	c	d	e	f	g	h	i	j
Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Sources and methods	Reference	Relations
			mortality?	cause, to an equal or greater extent. Disease-specific mortality is typically presented as rates and as age- and risk-adjusted measures such as hazard ratio. It is a frequently used endpoint in screening trials, where it is considered to be subject to bias. Consider separately absolute mortality (compared with placebo or waiting list) and mortality relative to the comparator. See also guideline <a href="#">Endpoints used in REA of pharmaceuticals</a> .			head-to-head trials indirect comparison is required (for more details on indirect comparisons see guideline <a href="#">Comparator and comparisons – Direct and indirect comparisons</a> ). Health care register data. Modelling studies. <b>Method:</b> Systematic review included in REA submission file.		
D0003	Clinical effectiveness	Mortality	What is the effect of the intervention on the mortality due to causes other than the target disease?	This issue includes all unintended, either positive or negative effects of the technology on mortality. There may be e.g. decrease of mortality of another disease observed or suspected; or increased mortality due to accidents or hazardous medical interventions after false positive or incidental test results.	2	2	<b>Sources:</b> HTAs, systematic reviews of RCTs, RCTs, both placebo-controlled and head-to-head trials. In the absence of head-to-head trials, indirect comparison is required (for more details on indirect comparisons see guideline <a href="#">Comparator and comparisons – Direct and indirect comparisons</a> ). Health care register data. Observational studies. SPC and EPAR. <b>Method:</b> Systematic review included in REA submission file.		C0001, C0005

a	b	c	d	e	f	g	h	i	j
Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Sources and methods	Reference	Relations
D0005	Clinical effectiveness	Morbidity	How does the technology affect symptoms and findings?	Describe the efficacy and effectiveness of the technology on relevant disease outcomes (symptoms and findings). Outcomes such as function, quality of life and patient satisfaction are reported in other assessment elements of this domain. Report changes in severity, frequency and recurrence of symptoms and findings, both in absolute terms and relative to the comparator. See also guideline <a href="#">Endpoints used in REA of pharmaceutical</a> .	3	2	<b>Sources:</b> HTAs, systematic reviews, trials, observational studies, SPC and EPAR. <b>Method:</b> Systematic review included in REA submission file.		
D0006	Clinical effectiveness	Morbidity	How does the technology affect progression of disease?	Report here efficacy and effectiveness outcomes such as complete cure, progression-free survival, time-to-event (next stage of disease, relapse). Report the results both in absolute terms and relative to the comparator. See also guideline <a href="#">Endpoints used in REA of pharmaceuticals</a> .	3	2	<b>Sources:</b> HTAs, systematic reviews, trials, observational studies prognostic studies, SPC and EPAR. <b>Method:</b> Systematic review included in REA submission file.		
D0011	Clinical effectiveness	Function	What is the effect of the technology on patients' body functions?	International classification of function proposes the following categories for body functions: mental, sensory and pain, voice and speech, cardiac, respiratory and immune functions, genitourinary and reproductive functions, movement-related, and skin functions. Report the results both in absolute terms and relative to the comparator. See also guideline <a href="#">Endpoints used in REA of pharmaceuticals</a> .	3	2	<b>Sources:</b> Trials and observational studies with functioning as an outcome. The instruments for outcome reporting should be validated. SPC and EPAR. <b>Method:</b> Systematic review included in REA submission file.	ICF <a href="http://apps.who.int/classifications/icfbrowser">http://apps.who.int/classifications/icfbrowser</a>	



a	b	c	d	e	f	g	h	i	j
Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Sources and methods	Reference	Relations
D0016	Clinical effectiveness	Function	How does the use of technology affect activities of daily living?	Report the results both in absolute terms and relative to the comparator. See also guideline <a href="#">Endpoints used in REA of pharmaceuticals</a> .	3	2	<b>Sources:</b> Trials, observational and qualitative studies, SPC and EPAR. <b>Method:</b> Systematic review included in REA submission file.		
D0012	Clinical effectiveness	Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	Report the results both in absolute terms and relative to the comparator. For further information see guideline <a href="#">Health-related quality of life and utility measures</a> .	3	3	<b>Sources:</b> Trials, observational and qualitative studies, SPC and EPAR. <b>Method:</b> Systematic review included in REA submission file.	EMA 2005, FDA 2009, Chassany 2002, Terwee 2007, Revicki 2008, Puhan 2006	
D0013	Clinical effectiveness	Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	Report the results both in absolute terms and relative to the comparator. For further information see guideline <a href="#">Health-related quality of life and utility measures</a> .	3	2	<b>Sources:</b> Trials, observational and qualitative studies, SPC and EPAR. <b>Method:</b> Systematic review included in REA submission file.	EMA 2005, FDA 2009, Chassany 2002, Terwee 2007, Revicki 2008, Puhan 2006	
D0017	Clinical effectiveness	Patient satisfaction	Was the use of the technology worthwhile?	Describe patients' overall perception of the value of the intervention and their satisfaction with the treatment. For further information see <a href="#">Endpoints used in REA of pharmaceuticals</a> .	1	1	<b>Sources:</b> Qualitative research, observational studies, trials. Survey of patients' opinions. <b>Method:</b> Systematic review included in REA submission file.		

## References

- Australian Government Department of Health and Ageing (AGDH). 2008. Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee. Version 4.3. Available at URL: [http://www.pbs.gov.au/html/industry/static/how\\_to\\_list\\_on\\_the\\_pbs/elements\\_of\\_the\\_listing\\_process/pbac\\_guidelines](http://www.pbs.gov.au/html/industry/static/how_to_list_on_the_pbs/elements_of_the_listing_process/pbac_guidelines) [accessed 16 December 2010].
- Aronson JK. Anecdotes as evidence. *BMJ* 2003; 326:1346.
- Black WC, Haggstrom DA, Welch HG. All-cause mortality in randomized trials of cancer screening. *J Natl Cancer Inst* 2002;94(3):167–73.
- Burls A, Cummins C, Fry-Smith A, et al. West Midlands Development and Evaluation Service Handbook. West Midlands DES 2000.
- Velasco M, Perleth M, Drummond M, Gürtner F, Jørgensen T, Jovell A, Malone J, Rüter A, Wild C. Best practice in undertaking and reporting health technology assessments. Working group 4 report. *Int J Technol Assess Health Care* 2002;18(2):361–422.
- Buyse M, Sargent DJ, Grothey A, Matheson A, de Gramont A. Biomarkers and surrogate end points—the challenge of statistical validation. *Nat Rev Clin Oncol* 2010;7(6):309–17.
- Burzykowski T, Buyse M. Surrogate threshold effect: an alternative measure for meta-analytic surrogate endpoint validation. *Pharm Stat* 2006;5(3):173–86.
- Chassany O, Sagnier P, Marquis P, et al. The ERIQA group. Patient reported outcomes: the example of health-related quality of life – a European guidance document for the improved integration of health related quality of life assessment in the drug regulatory process. *Drug Inf J* 2002; 36: 209 – 238.
- Canadian Agency for Drugs and Technologies in Health (CADTH). Common drug review: annotated clinical Review Report. February 2008. Available at URL: [http://cadth.ca/media/cdr/process/CDR\\_Clinical\\_Review\\_Template\\_Feb\\_2008.pdf](http://cadth.ca/media/cdr/process/CDR_Clinical_Review_Template_Feb_2008.pdf) [accessed September 2011].
- Derry S, Kong Loke Y, Aronson JK. Incomplete evidence: the inadequacy of databases in tracing published adverse drug reactions in clinical trials. *BMC Med Res Methodol* 2001; 1:7.
- Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis and management. *Lancet* 2000;356:1255–1259.
- Eichler HG, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. *Nat Rev Drug Discov* 2008;7:818–826.
- European Commission. A guideline on Summary of Product Characteristics. September 2009. Available at URL: [http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc\\_guideline\\_rev2\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf) [accessed September 2010].
- European Medicines Agency. Reflection paper on the regulatory guidance for the use of health related quality of life (HRQL) measures in the evaluation of medicinal products. London: EMEA; 2005.
- FDA. U. S. Department of Health and Human Services FDA, Center for Drug and Evaluation Research, Center for Biologics Evaluation and Research, Center for Devices and Radiological Health. Guidance for industry: Patient-reported outcome measures: use in medical product development to support labeling claims. Rockville: 2009. Available at URL: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>.

Friedrich JO, Adhikari N, Herridge MS, Beyene J. Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. *Ann Intern Med* 2005;142:510-24.

Golder S, McIntosh HM, Duffy S, Glanville J. Centre for Reviews and Dissemination and UK Cochrane Centre Search Filters Design Group. Developing efficient search strategies to identify reports of adverse effects in Medline and EMBASE. *Health Info Libr J* 2006;23(1):3-12.

Golder S, Loke Y, McIntosh HM. Poor reporting and inadequate searches were apparent in systematic reviews of adverse effects. *J Clin Epidemiol* 2008;61(5):440-8. Epub 2007 Oct 22. Review.

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org). Chapter 14: Adverse effects. Authors: Yoon K Loke, Deirdre Price and Andrew Herxheimer on behalf of the Cochrane Adverse Effects Methods Group.

HLPF 2008a; High Level Pharmaceutical Forum (2005–2008). Final Conclusions and Recommendations of the High Level Pharmaceutical Forum. Available at URL:

[http://ec.europa.eu/pharmaforum/docs/final\\_conclusions\\_en.pdf](http://ec.europa.eu/pharmaforum/docs/final_conclusions_en.pdf) [accessed June 2012].

HLPF 2008b; High Level Pharmaceutical Forum. Core principles on relative effectiveness. 2008.

Available at: [http://ec.europa.eu/pharmaforum/docs/rea\\_principles\\_en.pdf](http://ec.europa.eu/pharmaforum/docs/rea_principles_en.pdf). [accessed June 2012].

Hochman M, McCormick D. Endpoint selection and relative (versus absolute) risk reporting in published medication trials. *J Gen Intern Med* 2011;26(11):1246-52. Epub 2011 Aug 13.

Imaz-Iglesia I, González-Enríquez J, Alcaide-Jiménez JF. Guía de Elaboración de Informes de Evaluación de Tecnologías Sanitarias. Agencia de Evaluación de Tecnologías Sanitarias AETS (1999).

Ioannidis JPA, Lau J. Completeness of Safety Reporting in Randomized Trials: An Evaluation of 7 Medical Areas. *JAMA* 2001; 285(4):437-443.

International Network of Agencies for Health Technology Assessment: Health Technology Assessment Glossary 2006. Available at URL:

[http://inahta.episerverhotell.net/upload/HTA\\_resources/Edu\\_INAHTA\\_glossary\\_July\\_2006\\_final.pdf](http://inahta.episerverhotell.net/upload/HTA_resources/Edu_INAHTA_glossary_July_2006_final.pdf) (accessed September 2010).

Kleijnen S, George E, Gouldon S, d'Andon A, Vitre P, Osińska B, Rdzany R, Thirstrup S, Corbacho B, Nagy BZ, Leufkens HG, Boer de A, Goettsch WG. Relative effectiveness assessment of pharmaceuticals: similarities and differences in 29 jurisdictions. *Value Health*. 2012 Sept;15(6):954-60.

Kristensen FB & Sigmund H (ed.). *Health Technology Assessment Handbook*. Copenhagen: Danish Centre for Health Technology Assessment, National Board of Health, 2007.

Liberati A, Sheldon TA, Banta HD. EUR-ASSESS Project Subgroup report on Methodology. Methodological guidance for the conduct of health technology assessment. *Int J Technol Assess Health Care* 1997;13(2):186-219.

Loke YK, Price D, Derry S, Aronson JK. Case reports of suspected adverse drug reactions--systematic literature survey of follow-up. *BMJ* 2006;332(7537):335-339.

Loke YK, Price D, Herxheimer A for the Cochrane Adverse Effects Methods Group. Systematic reviews of adverse effects: framework for a structured approach. *BMC Med Res Methodol* 2007;7:32.

Malmivaara A, Koes BW, Bouter LM, van Tulder MW. Applicability and clinical relevance of results in randomized controlled trials: the Cochrane review on exercise therapy for low back pain as an example. *Spine* 2006;31(13):1405-9.

McIntosh H, Woolacott N, Bagnall A. Assessing harmful effects in systematic Reviews. *BMC Med Res Methodol* 2004;4(1):19.

MacMahon S, Collins R. Reliable assessment of the effects of treatment on mortality and major morbidity, II: observational studies. *Lancet* 2001;357(9254):455-462.

Papanikolaou PN, Christidi GD, Ioannidis JPA. Comparison of evidence on harms of medical interventions in randomized and nonrandomized studies. *CMAJ* 2006;174(5):635-641.

Puhan MA, Soesilo I, Guyatt GH, Schünemann HJ. Combining scores from different patient reported outcomes measures in meta-analyses: when is it justified. *Health Qual Life Outcomes* 2006, 4:94.

Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. *J Clin Epidemiol* 2008;61:102-109.

Sox HC, Greenfield S. Comparative effectiveness research: a report from the Institute of Medicine. *Ann Intern Med* 2009;151: 203-205.

Terwee CB, Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J, Bouter LM, de Vet HC. Quality criteria were proposed for measurement properties of health status questionnaires. *J Clin Epidemiol* 2007, 60:34-42.

Wald NJ, Morris JK. Teleoanalysis: combining data from different types of study. *BMJ* 2003;327(7415):616-618.

World Health Organization (WHO). Global health risks: mortality and burden of disease attributable to selected major risks. 2009. ISBN 978 92 4 156387 1.

[http://www.who.int/healthinfo/global\\_burden\\_disease/GlobalHealthRisks\\_report\\_full.pdf](http://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf)  
(accessed February 2010)

## Appendix 1. Information sources

### Registries

#### Disease registers

Disease registers gather information on the natural history and/or on the management of single diseases. A new case is registered in the database every time a diagnosis of the target disease is made. Some conditions may occur several times in life (i.e. heart attack), thus a single person might be represented several times in the register. When appropriately designed, disease registers allow assessment of the utilisation and diffusion of different diagnostic strategies or technologies in the care of persons with the condition or even to explore variations in the outcomes of different diagnostic interventions (e.g. differences in the consecutive management).

The Swedish National Board of Health and Welfare maintain a number of registers including the pharmaceutical register, the cause of mortality register and the registers containing the diagnoses of all hospitalised patients in Sweden.

[http://www.kvalitetsregister.se/web/Quality\\_Registries.aspx?pageID=8d07dd0a-4079-4ad7-b47b-58759d7055cb](http://www.kvalitetsregister.se/web/Quality_Registries.aspx?pageID=8d07dd0a-4079-4ad7-b47b-58759d7055cb)

#### Quality registers in Sweden

A system of 70 national quality registries has been established in the Swedish health and medical services. It contains individualised data concerning patient problems, medical interventions, and outcomes after treatment. <http://www.socialstyrelsen.se/statistics>

British Heart Foundation's statistics website is an up-to-date source of statistics on the burden, prevention, treatment and causes of heart disease in the UK

<http://www.heartstats.org/homepage.asp>

#### Technology registers

*Technology registers* gather information on the use of a single technology, for example a register on knee total endoprosthesis. A new case is registered in the database every time the technology is used (i.e. a procedure is done, an intervention takes place). In some countries, there is an obligation of reporting indications and consequences of using a technology before marketing authorisation, and when there is no high quality evidence to establish effectiveness and/or safety of the technology.

#### Pharmaceutical registries

On the other hand, registers on pharmaceuticals are initiated to obtain data on safety and effectiveness, after marketing authorisation. Doubt on the generalisability of study data and volume of consumption are a major drive to set up a pharmaceutical reimbursement registry.

-----

#### Utilisation registers

- Norwegian pharmaceutical prescription database: <http://www.norpd.no/>
- Dutch utilisation information:  
<http://www.gipdatabank.nl/index.asp?schermscherm=homepage&infoType=g>

#### ATC INDEX with DDDs

- ATC/DDD system is a tool for exchanging and comparing data on pharmaceutical use at international, national or local levels. <http://www.whocc.no/>

-----

## Regulatory institutions and legal framework

### EMA

The European Medicines Agency [www.ema.europa.eu](http://www.ema.europa.eu) is responsible for the scientific evaluation of applications for European marketing authorisations for both human and veterinary medicines (centralised procedure).

- Once a medicine has been granted a Community marketing authorisation by the European Commission, the EMA publishes a full scientific assessment report called a **European Public Assessment Report (EPAR)**  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar\\_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125&jsenabled=true](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125&jsenabled=true)
- All medicines for human and animal use derived from biotechnology and other high-tech processes must be approved via the centralised procedure. The same applies to all advanced-therapy medicines and human medicines intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases, as well as to all designated orphan medicines intended for the treatment of rare diseases.
- EMA becomes involved in the assessment of medicines that do not require centralised procedure, in cases where they have been referred to the Agency due to a disagreement in authorisation or use of the medicine between two or more Member States, or due to some other issue that requires resolution in the interest of protecting public health.
- EMA constantly monitors the safety of medicines through a pharmacovigilance network, and takes appropriate actions if adverse pharmaceutical reaction reports suggest that the benefit-risk balance of a medicine has changed since it was authorised.
- EMA can be considered as the 'hub' of a European medicines network comprising over 40 national competent authorities in 30 EU and EEA-EFTA countries, the European Commission, the European Parliament and a number of other decentralised EU agencies.
- In many countries over the counter medicines (OTC) are controlled by a regulatory agency. OTC pharmaceuticals are usually regulated by active pharmaceutical ingredients (APIs), not final products.

### FDA

The US Food and Drug Administration (FDA) <http://www.fda.gov/default.htm> is the federal agency responsible for ensuring that human and veterinary drugs, biological products, and medical devices are safe and effective; cosmetics are safe; and electronic products that emit radiation are safe. FDA also ensures that these products are honestly, accurately and informatively represented to the public.

- Drug labeling refers to all of the printed information that accompanies a drug, including the label, the wrapping and the package insert. Food and Drug Administration (FDA) requires that drug labeling be balanced and not misleading. The label must be scientifically accurate and provide clear instruction to health care practitioners for prescription drugs and to consumers for over-the-counter drugs and supplements. Labeling regulations require that the statement of ingredients must include all ingredients, in the order in which they are used in the drug. These ingredients must also be identified by their established name.

## Standardisation and regulatory concerns of medical devices

The government of each European Member State is required to appoint a **Competent Authority** responsible for medical devices. The Competent Authority (CA) is a body with authority to act on behalf of the government of the Member State to ensure that the requirements of the Medical Device Directives are transposed into National Law and are applied. The CA reports to the Minister of Health in the Member State. The CA in one Member State does not have jurisdiction in any other Member State, but they do exchange information and try to reach common positions.

- In UK the Medicines and Healthcare products Regulatory Agency (MHRA) acts as a CA, in Italy it is the Ministero Salute (Ministry of Health).

In the EU, all medical devices must be identified with the [CE mark](#).

The ISO standards for medical devices are covered by

- ICS 11.100.20 standard for biological evaluation of medical devices  
[http://www.iso.org/iso/products/standards/catalogue\\_ics\\_browse.htm?ICS1=11&ICS2=100&ICS3=20&](http://www.iso.org/iso/products/standards/catalogue_ics_browse.htm?ICS1=11&ICS2=100&ICS3=20&) and
- ICS 11.040.01 standard for medical equipment  
[http://www.iso.org/iso/iso\\_catalogue/catalogue\\_ics/catalogue\\_ics\\_browse.htm?ICS1=11&ICS2=040](http://www.iso.org/iso/iso_catalogue/catalogue_ics/catalogue_ics_browse.htm?ICS1=11&ICS2=040) .

The quality and risk management regarding the topic for regulatory purposes is convened by ISO 13485 and ISO 14971. Further standards are IEC 60601-1, for electrical devices (mains-powered as well as battery powered) and IEC 62304 for medical software. The US FDA also published a series of guidances for industry regarding this topic.

### **Packaging standards**

Medical device packaging is highly regulated. Often medical devices and products are sterilised in the package. The sterility must be maintained throughout distribution to allow immediate use by physicians. A series of special packaging tests is used to measure the ability of the package to maintain sterility. Relevant standards include: ASTM D1585- Guide for Integrity Testing of Porous Medical Packages, ASTM F2097- Standard Guide for Design and Evaluation of Primary Flexible Packaging for Medical Products , EN 868 Packaging materials and systems for medical devices which are to be sterilised. General requirements and test methods, ISO 11607 Packaging for terminally sterilised medical devices, and others.

### **Medical Device Directive**

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31993L0042:EN:HTML>

The Medical Device Directive (Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, OJ No L 169/1 of 1993-07-12) is intended to harmonise the laws relating to medical devices within the European Union. The MD Directive is a 'New Approach' Directive and consequently in order for a manufacturer to legally place a medical device on the European market the requirements of the MD Directive have to be met. Manufacturers' products meeting 'harmonised standards'[2] have a presumption of conformity to the Directive. Products conforming with the MD Directive must have a CE mark applied. The Directive was most recently reviewed and amended by the 2007/47/EC and a number of changes were made. Compliance with the revised directive became mandatory on March 21, 2010.

### **National or international safety monitoring systems (databases)**

(which may be managed by a national statutory body or by a supra-national body)

IAEA: Safety standards for diagnostic radiology [http://www-pub.iaea.org/MTCD/publications/PDF/Pub1206\\_web.pdf](http://www-pub.iaea.org/MTCD/publications/PDF/Pub1206_web.pdf)

IAEA: Radiological protection of patients <http://rpop.iaea.org/RPoP/RPoP/Content/index.htm>

ICRP: Publications of International Commission of Radiological Protection <http://www.icrp.org/>

TGA (Therapeutic Goods Administration), <http://www.tga.gov.au/index.htm>

US Food and Drug Administration, MedWatch safety alert system  
<http://www.fda.gov/medwatch/safety.htm>

The Medical Devices section of the UK Medicines and Healthcare Products Regulatory Agency  
[\(http://devices.mhra.gov.uk/\)](http://devices.mhra.gov.uk/)

National Prescription Database for pharmaceuticals.

-----

### A0024&A00025 List of websites where you can find guidelines

Guideline producer	link	requires subscription
American academy of Orthopaedic Surgeons (AAOS)	<a href="http://www.aaos.org/research/guidelines/guide.asp">http://www.aaos.org/research/guidelines/guide.asp</a>	no
American College of Occupational and Environmental Medicine's (ACOEM) <i>Occupational Medicine Practice Guidelines</i>	<a href="http://www.disabilitydurations.com/pr_acoem.htm">http://www.disabilitydurations.com/pr_acoem.htm</a>	yes
National Guideline Clearinghouse, at Agency for Healthcare Research and Quality (AHRQ)	<a href="http://www.guideline.gov/">http://www.guideline.gov/</a>	no
Guidelines International network (GIN)	<a href="http://www.g-i-n.net/">http://www.g-i-n.net/</a>	yes
Current care guidelines (Käypä hoito)	<a href="http://www.kaypahoito.fi">http://www.kaypahoito.fi</a>	no, in Finnish
National Health and Medical Research Council (NHMRC), Australian Government	<a href="http://www.clinicalguidelines.gov.au/">http://www.clinicalguidelines.gov.au/</a>	no
NICE guidance, National Institute for Health and Clinical Excellence (NHS)	<a href="http://guidance.nice.org.uk/CG">http://guidance.nice.org.uk/CG</a>	no
Scottish Intercollegiate Guidelines Network (SIGN)	<a href="http://www.sign.ac.uk/index.html">http://www.sign.ac.uk/index.html</a>	no
See many more guideline producers in the list of Open Clinical	<a href="http://www.openclinical.org/guidelines.html">http://www.openclinical.org/guidelines.html</a>	no

-----

### A0021 List of websites of national agencies with information on reimbursement

AIFA: <http://www.aifa.gov.it/>

Australia:

<http://www.health.gov.au/internet/main/publishing.nsf/Content/Pharmaceutical+Benefits+Schem e+%28PBS%29-1>

Belgium: [http://www.riziv.fgov.be/inami\\_prd/ssp/cns2/pages/SpecialityCns.asp](http://www.riziv.fgov.be/inami_prd/ssp/cns2/pages/SpecialityCns.asp)



Canada: <http://www.cadth.ca/en/products/cdr> or <http://www.pcodr.ca>

Czech Republic: <http://www.sukl.eu>

Finland: <http://www.kela.fi/in/internet/english.nsf>

France: [http://www.has-sante.fr/portail/jcms/j\\_5/accueil](http://www.has-sante.fr/portail/jcms/j_5/accueil) and  
<http://www.codage.ext.cnamts.fr>

The Netherlands: <http://www.medicijnkosten.nl/>

Norway: <http://www.legemiddelverket.no/>

Poland: <http://www.aotm.gov.pl/>

Portugal: <http://www.infarmed.pt/portal/page/portal/INFARMED>

Scotland: <http://www.scottishmedicines.org.uk/>

Spain: <http://www.msc.es/profesionales/farmacia/>

Sweden : <http://www.tlv.se/beslut/sok/lakemedel/>

UK: <http://www.nice.org.uk/>

## Appendix 2. Templates

### Template 1. Format for scoping the assessment

Description	Project scope
<p><b>Population</b></p> <p><i>Describe the disease or health condition of interest. Provide ICD-10 code and MeSH-terms for it.</i></p> <p><i>Describe the target population; possible limitations for instance in age, sex, severity, stage or risk (e.g. men over 65, in low to moderate risk of having the disease, or adult patients with gradus 3-4 disease). Provide Mesh-terms.</i></p> <ul style="list-style-type: none"> <li><i>Describe the intended use of the technology: treatment or prevention, first line/second line treatment,</i></li> </ul>	
<p><b>Intervention</b></p> <p><i>Describe the intervention detailed enough to distinguish it from relevant other technologies: chemical substance and category, mode of administration modes. Provide ATC Code and MeSH term..</i></p>	
<p><b>Comparison</b></p> <p><i>Describe the comparators for this assessment. The technology can be compared to e.g. another specific technology, management pathway without the technology, usual care, not doing anything, or placebo. <b>Include the rationale for choosing the comparator.</b> Provide MeSH-terms. See the guideline <a href="#">‘Comparators and comparisons – Criteria for the choice of the most appropriate comparator(s)’</a></i></p>	
<p><b>Outcomes</b></p> <p><i>Describe the most important effectiveness and safety outcomes for this assessment. <b>Include the rationale for choosing the outcomes.</b> See the guideline <a href="#">‘Endpoints used for REA of pharmaceuticals’.</a></i></p>	

## Template 2. Checklist for potential ethical, organisational, social and legal aspects

The rapid assessment of medicines is based on the EUnetHTA core model. However, due to the nature of the technology (pharmaceuticals) and the purpose of the assessment (to be used in decision-making, usually in the context of reimbursement of newly authorised medicines) with its inherent time limits, the assessment focuses on the first four domains of the Core Model. The economic domain is currently excluded.

The following checklist is a short list of questions in order to determine whether there are specific ethical, organisational, social and legal aspects which also need to be addressed. Since the assessment is comparative in nature, only new issues should be dealt with, which arise from a difference between the medicine to be assessed and its major comparator(s). Already known problems/issues with regard to ethical, organisational, social and legal aspects which are common to the technology to be assessed and its comparator(s) will, as a rule, not be addressed, as it is not to be expected that the addition of a new medicine will lead to changes.

If a question is answered with 'yes', further analysis of these issues may be warranted. If they are answered with no, the domains need not be dealt with further. Examples are provided for clarification.

<b>1. Ethical</b>	
1.1. Does the introduction of the new medicine and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any new ethical issues?	Yes/No
1.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be ethically relevant?	Yes/No
Example: <ul style="list-style-type: none"> <li>The marketing authorisation holder claims that its product is superior, but has decided to limit the amount of the new medicine, which means that it has to be rationed and not all patients who need it can receive it. The comparator is freely available.</li> </ul>	
<b>2. Organisational</b>	
2.1. Does the introduction of the new medicine and its potential use/nonuse instead of the defined, existing comparators require organisational changes?	Yes/No
2.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be organisationally relevant?	Yes/No
Examples: <ul style="list-style-type: none"> <li>The new medicine will replace a surgical intervention which may lead to excess capacity in relevant areas.</li> <li>The new intervention requires the establishment of specialised centers for administration</li> </ul>	
<b>3. Social:</b>	
3.1. Does the introduction of the new medicine and its potential use/nonuse	Yes/No

instead of the defined, existing comparator(s) give rise to any new social issues?	
3.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be socially relevant?	Yes/No
<p>Example:</p> <ul style="list-style-type: none"> <li>• A medicine which is widely used by persons with abuse problems and which colors the tongue blue, thus immediately identifying the user as such. Comparators do not have this property.</li> </ul>	
<b>4. Legal:</b>	
4.1. Does the introduction of the new medicine and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any legal issues?	Yes/No
4.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be legally relevant?	Yes/No
<p>Examples:</p> <ul style="list-style-type: none"> <li>• The comparator for the new medicine is a pharmaceutical which is not licensed in the indication of concern, but widely in use.</li> <li>• The comparator for the new pharmaceutical is a controlled, restricted substance, the new medicine is not.</li> <li>• The most appropriate comparator for the new medicine is available as a pharmacy-compounded medicine, but not as a finished product with marketing authorisation.</li> </ul> <p>Note: The assessment should not address patent-related issues.</p>	

### Template 3. Selecting relevant assessment elements and translating the generic issues into actual research questions

Table [x]. Selected assessment elements

ID	Domain	Topic	Issue <i>[ copy all the generic questions from the Model for Rapid REA in this column (marked in column k)]</i>	Relevance in this assessment Yes/No	Reason for non-relevance/ Research question(s) <i>[If you selected yes, translate the generic issue into actual research question(s). If you selected no, provide an explanation why you deemed this element as not relevant.]</i>

## Template 4. Result card

<b>Name of the project</b>	EUnetHTA JA WP pilot on XXX
<b>Domain</b>	[write the name of the domain]
<b>Topic</b>	[the topic under which this question belongs, copy it from the assessment table in the model]
<b>Issue ID</b>	[from the assessment element table in the model]
<b>Research question</b>	[Copy one research question from Table 3]
<b>Methods</b>	<p>Source of information:</p> <ul style="list-style-type: none"> <li>• Basic documentation <input type="checkbox"/></li> <li>• Domain search <input type="checkbox"/></li> <li>• Other: <input type="checkbox"/> [use also Table 2 to document]</li> </ul> <p>Critical appraisal criteria</p> <p>Method of synthesis</p>
<b>Result</b>	<p>[Plain text and tables. Present result data only; no background information, no interpretations]</p> <p>[Citations in text in the form: Surname of first author Year]</p>
<b>Discussion</b>	[E.g. interpretation of findings, problems identified in identifying or quality of information, pending research, or need for further research.]
<b>References</b>	[Alphabetic order, Vancouver style]
<b>Importance and transferability</b>	<p>How important is this piece of information for decision making?</p> <p>Critical <input type="checkbox"/></p> <p>Important <input type="checkbox"/></p> <p>Optional <input type="checkbox"/></p> <p>How transferable is this piece of information, i.e. can it be used in national decisions as such?</p> <p>Completely <input type="checkbox"/></p> <p>Partly <input type="checkbox"/></p> <p>Not <input type="checkbox"/></p>

## Template 5. Table for reporting results from clinical trials

<b>Title:</b> <title> <i>{as indicated on the study report}</i>			
Study identifier	<code> <i>{list all codes starting with the protocol number followed by – as available – EudraCT number, ISRCT number, other codes that allow cross-referencing to publications}</i>		
Design	<free text> <i>{describe key elements of the design (cross-over, parallel, factorial, dose-escalation, fixed-dose response) including randomisation, blinding, allocation concealment, mono-/multi-centre, etc.}</i>		
	Duration of main phase:	<time>	
	Duration of Run-in phase:	<time> <not applicable>	
	Duration of Extension phase:	<time> <not applicable>	
Hypothesis	<Superiority> <Equivalence> <Non-inferiority> <Exploratory: specify>		
Treatments groups <i>{add as many rows as needed to describe the treatment groups}</i>	<group descriptor> <i>{provide abbreviation for use later in the table of the results section}</i>	<treatment>. <duration>, <number randomised>	
	<group descriptor>	<treatment>. <duration>, <number randomized>	
	<group descriptor>	<treatment>. <duration>, <number randomised>	
Endpoints and definitions <i>{add as many rows as needed to describe the endpoints; for the secondary endpoints select the ones considered most relevant and reported in the results section}</i>	<Co-Primary endpoint>	<label> <i>{generate abbreviation for use later in the table of the results section}</i>	<free text> <i>{provide brief description}</i>
	<Secondary> <other: specify> endpoint	<label>	<free text> <i>{provide brief description}</i>
	<Secondary> <other: specify> endpoint	<label>	<free text> <i>{provide brief description}</i>
Database lock	<date>		
<b>Results and Analysis</b> <i>{present the result separate for each analysis that is considered relevant for the conclusion on the trial; in any case the pre-specified primary analysis should be presented}</i>			
<b>Analysis description</b>	<b>Primary Analysis</b>		
Analysis population and time point description	<Intent to treat> <Per protocol> <other: specify> <i>{consider adding a brief description of the definition of the population}</i> <time point>		

<b>Title:</b> <title> <i>{as indicated on the study report}</i>				
Descriptive statistics and estimate variability	Treatment group	<group descriptor> <i>{as per above terminology}</i>	<group descriptor> <i>{as per above terminology}</i>	<group descriptor> <i>{as per above terminology}</i>
	Number of subject	<n>	<n>	<n>
	<endpoint> <i>{label as above}</i> (<statistic>) <i>{e.g. mean, median, etc}</i>	<point estimate>	<point estimate>	<point estimate>
	<variability statistic> <i>{e.g. standard deviation, confidence interval, etc}</i>	<variability>	<variability>	<variability>
	<endpoint> (<statistic>)	<point estimate>	<point estimate>	<point estimate>
	<variability statistic>	<variability>	<variability>	<variability>
	<endpoint> (<statistic>) <variability statistic>	<point estimate> <variability>	<point estimate> <variability>	<point estimate> <variability>
Effect estimate per comparison <i>{add as many rows as needed to describe the relevant statistical testing performed}</i>	<Co->Primary endpoint	Comparison groups		<group descriptors> <i>{as per above terminology}</i>
		<test statistic> <i>{e.g. difference between groups}</i>		<point estimate>
		<variability statistic> <i>{e.g. confidence interval, etc}</i>		<variability>
		P-value <i>{indicate statistical test used, e.g. ANOVA}</i>		<P-value>
	<<Co->Primary > <Secondary> <other: specify> endpoint <i>{indicate endpoint using terminology as per section "Endpoint and definitions"}</i>	Comparison groups		<group descriptors>
		<test statistic>		<point estimate>
		<variability statistic>		<variability>
		P-value		<P-value>
	<<Co->Primary > <Secondary> <other: specify> endpoint	Comparison groups		<group descriptors>
		<test statistic>		<point estimate>
		<variability statistic>		<variability>
		P-value		<P-value>



<b>Title:</b> <title> <i>{as indicated on the study report}</i>	
Notes	<free text> <i>{consider amongst others the following information:          - reasons for drop-outs          - critical findings with regard to the analysis}</i>
<b>Analysis description</b>	<Secondary analysis> <Co-primary Analysis> <Other, specify: > <i>{also indicate if the conduct of the analysis was pre-specified}</i>
<i>{repeat all the above sections for each analysis that is considered relevant}</i>	

## Template 6. Domain report

Name of the domain domain

Authors:

### Domain methodology

#### Domain framing

[In case it was necessary to deviate from the general scope of the project when reporting the results in certain research questions this should be reported here]

**Research questions** [Here the included assessment elements and the formulated research questions should be listed]

Element ID	Research question
------------	-------------------

#### Sources

[List the sources that were used. In case a domain specific search was performed this should be reported here as well in general terms. Details on the search should be reported in the specific assessment element. In case a own survey was performed to retrieve information this should be described as well]

#### Analysis

[Describe here if it was sufficient (or feasible) to simply retrieve information from one of the sources or whether an analysis was performed (e.g for example an indirect comparison). In case an, analysis was performed the methods should be described (not to detailed, the details should be reported in the specific assessment element)]

[Describe whether and if yes which quality assessment criteria were used]

#### Synthesis

[Include a description on how the data are presented. E.g: Most of the research questions could be answered in plain text format. In addition, evidence tables were used in some instances.]

### Summary of main results

[This section should summarise the most relevant findings from the result cards. Transparency in information retrieval is crucial; therefore the sources of the statements should be included in the summary (e.g. Author, year). In addition this section should limit itself to the results (facts). Interpretation of the data should be included in the discussion section.]

## Discussion

[In this section:

- the interpretation of the findings should be discussed
- issues that may affect the interpretation should be discussed (the quality of the evidence, related uncertainties and the applicability of the evidence)
- evidence gaps and related questions should be discussed]

## Template 7. Summary

### *Summary of relative effectiveness of [XXX]*

*The assessment element ID codes in brackets (e.g. A0001) refer to the result cards in Appendix 1, which give details of the relevant results.*

#### *Scope*

Population	
Intervention	
Comparator(s)	
Outcome(s)	

#### *Introduction*

##### **Health problem**

[Describe the incidence/prevalence] (A0023). [Describe risk factors] (A0003).  
[Describe symptoms] (A0005). [Describe natural course of disease] (A0004).

[Describe how disease is diagnosed] (A0024). [Describe current treatment] (A0025).<sup>1</sup>

##### **Description of technology**

[Describe regulatory status] (A0020).<sup>7</sup> [Describe mode of action] (B0001). [Describe available comparators] (A0025 and/or B0002).

[Describe recommended dose and specific warnings to discontinue treatment] (B0001).  
[Describe monitoring requirements for patients treated with intervention] (C0062).  
[Describe additional pharmacovigilance activities] (C0007)

#### *Results*

##### **Available evidence**

[Describe body of evidence] (safety and clinical effectiveness domain)

##### **Upcoming evidence**

[Describe ongoing trials] (safety and clinical effectiveness domain)

##### **Clinical effectiveness**

[Summarise the result of the most relevant effectiveness endpoints in comparison to the chosen comparator(s)] (D0001, D0005, D0012, D0013)

##### **Safety**

[Summarise the result of the most relevant safety endpoints in comparison to placebo] (C0001)

[Summarise the result of the most relevant differences in safety endpoints compared to the comparator(s)] (C0008)

##### **Reimbursement**

[Summarise the reimbursement status of the pharmaceutical in different countries] (A0021).

## Summary table of relative effectiveness of *[name of pharmaceutical]*

<b>[Indication]</b>						
<i>The assessment element ID codes (e.g. D0001) refer to the result cards in Appendix 1, which give details of the relevant results.</i>						
	Health benefit			Harm		
	OS [numerical estimate, confidence interval]	QoL [numerical estimate, confidence interval]	Endpoint 3 [numerical estimate, confidence interval]	Serious AEs [numerical estimate, confidence interval]	Severe AEs (Grade 3-4) [numerical estimate, confidence interval]	Frequent AEs of any severity grade [numerical estimate, confidence interval]
<b>[pharmaceutical]</b>	<i>[result numerical estimate (confidence interval)]</i>	<i>[result numerical estimate (confidence interval)]</i>	<i>[result numerical estimate (confidence interval)]</i>	<i>[[result numerical estimate (confidence interval)]</i>	<i>[result numerical estimate (confidence interval)]</i>	<i>[result numerical estimate (confidence interval)]</i>
<b>[Comparator 1]</b>	<i>[No of assessment element]</i>	<i>[No of assessment element]</i>	<i>[No of assessment element]</i>	<i>[No of assessment element]</i>	<i>[No of assessment element]</i>	<i>[No of assessment element]</i>
<i>Quality of body of evidence</i>	<i>[summarise quality of evidence for endpoint]</i>	<i>[summarise quality of evidence for endpoint]</i>	<i>[summarise quality of evidence for endpoint]</i>	<i>[summarise quality of evidence for endpoint]</i>	<i>[summarise quality of evidence for endpoint]</i>	<i>[summarise quality of evidence for endpoint]</i>
<b>[pharmaceutical]</b>	.....	....	....	....	....	....
<b>[Comparator 2]</b>	.....	....	....	....	....	....
<i>Quality of body of evidence</i>	.....	....	....	....	....	....

Abbreviations: AE=adverse event; OS=overall survival; QoL=quality of life

### Discussion

[Discuss potential limitations of the endpoints presented and the quality of the available evidence (internal validity)]

[Discuss the applicability of the available evidence (external validity)]

[Discuss the evidence gaps in the currently available evidence, refer to ongoing trials if applicable and provide recommendations on further research required]

### Conclusion

[Conclude whether the pharmaceutical is less/similar/more effective than the comparator(s). In case such a conclusion is not possible, formulate a statement such as: 'there is insufficient evidence to determine whether .....']

[Conclude whether the pharmaceutical has a better/similar/worse safety profile than the comparator(s). In case such a conclusion is not possible, formulate a statement such as: 'there is insufficient evidence to determine whether .....']

[Conclude on further research required]

## Template 8. Reimbursement status

*Table [X]. Reimbursement status of [XXX]*

Country	Reimbursed	Not reimbursed
[Australia]		
[Austria]		
[Belgium]		
[Czech Republic]		
[Denmark]		
[England and Wales]		
[Finland]		
[France]		
[Germany]		
[Italy]		
[Norway]		
[Poland]		
[Portugal]		
[Scotland]		
[Slovakia]		
[Spain]		
[Sweden]		
[The Netherlands]		
[USA (VA Pharmacy Benefits Management Services) ]		

## Appendix 3. Systematic review of the literature

Ideally systematic reviews on randomised controlled trials (RCTs) are the basis of knowledge of effectiveness of an intervention (CRD guidance 2009). The principles on how to conduct a systematic review are nowadays widely agreed upon and most of the methodologies published by different organisations vary only in details. The most widely used methodology applies the principles and instructions of the Cochrane Collaboration (Cochrane Handbook 2011). The same principles and procedures can be applied to systematic reviews of non-randomised comparative study designs or observational studies if there are no or only a few RCTs to answer the HTA question (CCOHTA 2001).

We base our guidance on publications from organisations and expert groups that have shaped the field and that have gained broad consensus: the Cochrane Handbook for Systematic Reviews (Cochrane Handbook 2011), the CRD guidance for systematic reviews (CRD guidance 2009), statement from methodological expert groups such as the CONSORT statement (Altman 2001, Piaggio 2006, Moher 2001) or the PRISMA statement for reporting of systematic reviews (Moher 1999, Clarke 2000), the checklist for HTA reports by INAHTA (Hailey 2003), the PRISMA statement (Liberati 2009) and the GRADE Working Group recommendations for grading quality of evidence and strength of recommendations (Atkins 2004, Guyatt 2006).

This appendix intends to provide a structure for a systematic assessment of interventions. It is not a hands-on textbook on how to perform a systematic review - for this we refer readers to an extended list of further readings which we found helpful in writing the section and which covers those issues in much more detail.

We have aimed at a pragmatic guidance for a health technology report on clinical effectiveness including all the phases from stating the question to the interpretation and judgements about the evidence, and even to stating the recommendations, the latter for those organisations that provide recommendations to policy makers as part of their HTA-report.

### How to plan and conduct a systematic review of effectiveness

#### *Background work*

In the process of conducting a systematic review to assess the effectiveness of a technology, it is wise to check whether others have already published HTA-reports and / or systematic reviews covering the same intervention (Kristensen 2001). In the search for systematic reviews the following databases are suggested:

- Cochrane Database of Systematic Reviews.
- A number of databases provided by the Centre for Reviews and Dissemination (CRD)
  - Health Technology Assessment (HTA) Database
  - Database of Abstracts of Reviews of Effects (DARE)
  - NHS Economic Evaluation Database (NHS EED)

With a bit of luck one may identify a systematic review on the topic of interest, which is sufficiently comprehensive, sufficiently recent, satisfies the requirements on methodological quality, and meets the research questions. If the report is judged to be transferable to one's own health care system and the local setting, then this report could be the basis for the core assessment. It must be noted that such a review is probably only available in the context of a full assessment, a while after marketing authorisation, and not in the context of a rapid assessment shortly after marketing authorisation.

If not, one might need to execute a full systematic review of clinical efficacy / effectiveness. Doing a systematic search will lengthen the timelines within which a rapid

assessment is feasible. The following paragraphs provide a more detailed guidance for this task.

### ***Phrasing the problem as focussed and standardised questions***

The first step for the review is to translate the health care problem into focused, structured and searchable questions that capture the essential elements of the health care problem and the benefit one may achieve with the use of the technology. To accomplish this it can be necessary to break down the problem into several research questions that follow the PICO-structure as described above.

The reviewers need to define the study design(s) they are willing to consider for their review. Following the hierarchy of study designs (Guyatt 2006), reviews on efficacy / effectiveness are generally limited to randomised designs, but it may be necessary to broaden the inclusion to other designs, if data from RCTs are not available or are insufficient (See flowchart)). Sometimes it might be helpful for reviewers and users of the reviews to explicitly state which aspects of a health care problem were not considered in a review. Carefully defined and clearly focused questions will guide the reviewers when doing the review and will help the users of the review to compare the objectives of the review with their own health care problem, and to make decisions about the generalisability and transferability of the findings to their own health care settings.

Reviews should follow an a priori defined protocol, and possible deviations from the protocol should be described.

### ***Databases and other sources***

The focused, structured and searchable question will drive the literature search. The literature search should be comprehensive and transparent. A large variety of sources are available:

- general medical databases (such as Medline, Embase, Cochrane Controlled Trials register),
- topic specific databases for specific questions (such as CINAHL, PSYCINFO, ASSIA, SOCIOLOGICAL ABSTRACTS)
- trial registers (such as Current Controlled Trials (<http://www.controlled-trials.com/>) or Clinical Trials (<http://www.clinicaltrials.gov/>),
- hand searching of journals and the so-called 'grey literature' (e.g. abstract books).
- Especially in the case of rapid assessments of pharmaceuticals also the database of the European Medicines Agency (EMA) and of the Food and Drug Administration (FDA) should be included in the search.

Performing supplementary approaches to identify studies, such as checking reference lists and/or an additional search in Science Citation Index (SCI) of the included articles is a valuable complementary approach. Additional information can be collected from contacts with manufacturers and consultation with experts (domestic and foreign) and agencies. The resources (staff time and cost) required for a comprehensive search can vary considerably for individual sources. Restrictions in locating studies should be given (year, language, population etc).

The reporting of the search is essential for the transparent reporting of a systematic review. The following items should be stated: the databases searched, the platform or provider (such as OVID, Dialog or PubMed), and the start and end dates for the search of each database. The full search strategy should be presented for at least one major database.

Supplementary approaches should be reported. In terms of the attempts to acquire any missing information from investigators or sponsors, it is also useful to describe briefly who was contacted and what unpublished information was obtained (Lefebvre 2008, Institute for Quality and Efficiency in Health Care 2008).



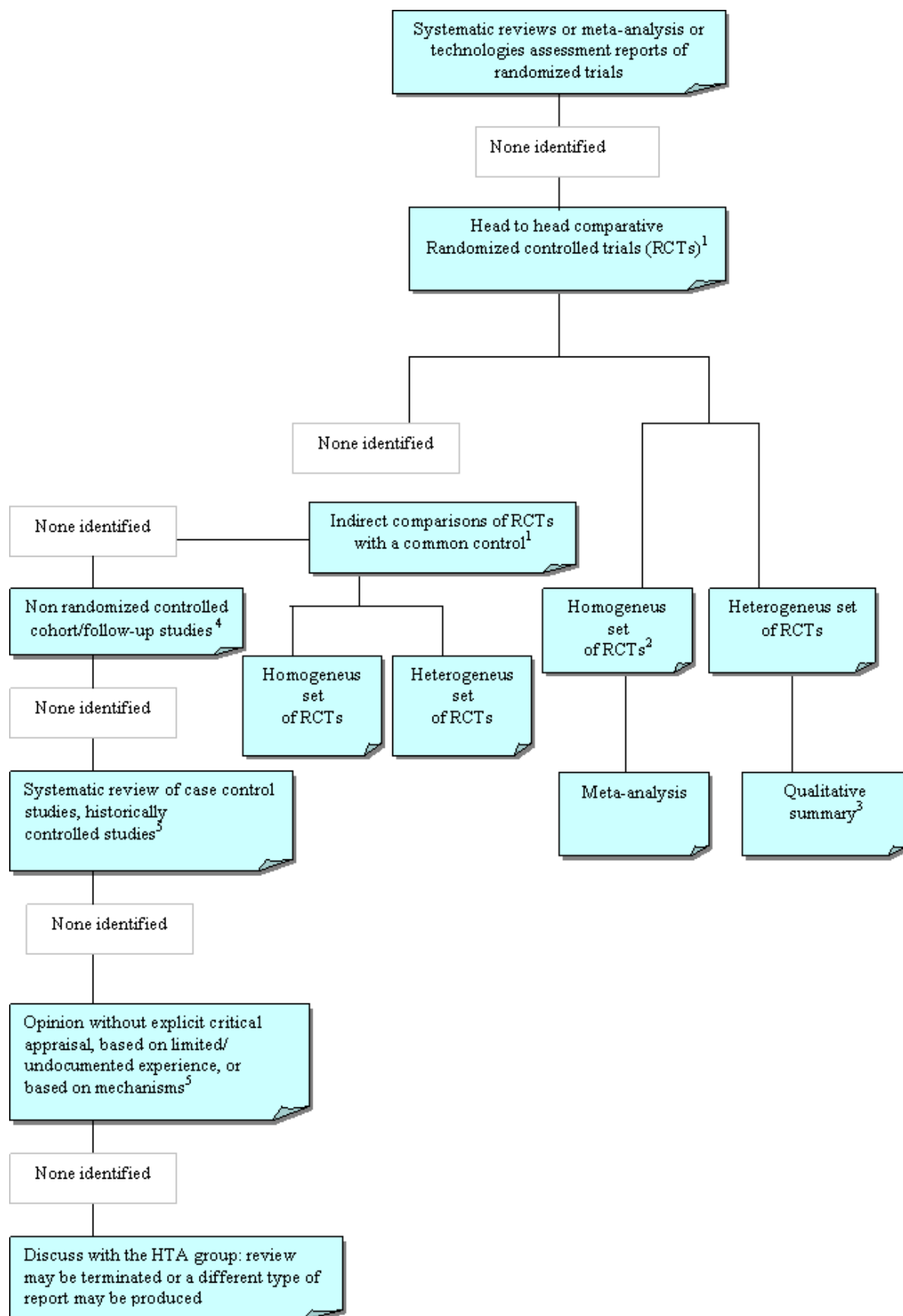
## Selection of studies

The selection process is iterative and includes two or more phases considering the inclusion and exclusion criteria: first the selection of potentially relevant titles and / or abstracts, then the selection of full papers that are considered as potentially relevant, then the selection of the final set of studies. At the end of the review, a general update of the most recent literature should follow the same steps. Since some of the decisions in the selection process will always remain subjective, engaging two or more reviewers in this process will improve transparency and objectivity, especially when the report presents information about the degree of agreement or disagreement among reviewers and how disagreement was solved (e.g. consensus after consulting a third researcher).

Using a flow chart to display the process of study selection as shown below has been proven to be very informative. The flow chart describes the number of citations and studies identified at each step as well as the number excluded, with reasons for exclusion at each stage ending at the final number and types of studies included.

In the European Public Assessment Report (EPAR) regularly data of unpublished clinical trials are included. For a relative effectiveness assessment the information included in the EPAR may not be sufficient. It may be an option to request additional complementary data from the marketing authorisation holder to be able to include important data in the relative effectiveness assessment.

*Flowchart based on CEBM (Centre for Evidence-Based Medicine) Levels of Evidence:*



## Flowchart: Reviews of Clinical Efficacy/Effectiveness Reports (CEBM Levels of Evidence )

1. Direct evidence from good-quality RCTs should be used wherever possible. Without this evidence, it may be necessary to look for indirect comparisons from RCTs, with due consideration of the quality of the indirect comparison.
2. Homogeneous means there is limited clinical heterogeneity in trials, as assessed by their included populations and interventions, plus the absence of evidence of statistical heterogeneity.
3. This may be a systematic qualitative review of trial results without pooling. Qualitative reviews should highlight clinical heterogeneity (differences in participant characteristics, interventions, outcome measures), methodological heterogeneity (study design and quality) and heterogeneity, with respect to results. Tables are useful to describe populations, interventions, settings, outcome measures, etc. It may also be possible to pool results using a random effects model.
4. If only a limited number of poor quality RCTs can be identified, other study designs can be considered. In some cases, even if RCTs are available, studies of other types should be reviewed by the authors, e.g. to identify long-term effectiveness and/or rare or long-term adverse effects.
5. CEBM (Centre for Evidence-Based Medicine) Levels of Evidence). Available at:URL:<http://www.cebm.net/index.aspx?o=5653>. (Accessed: 09-09-2010)

## Critical appraisal

See guideline [Internal validity of randomised controlled trials](#) and [Applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals](#).

## Search strategy for safety data

Combination of different approaches in Medline and Embase is needed insofar available. For rapid REA, it is more likely that study information is not (yet) published nor publicly available. For a pharmaceutical that is already available on the market for other indications, this approach in Medline or Embase makes sense however less for rapid REA. Searches do not detect all relevant studies while indexing terms for adverse events are not always assigned in original studies, and the authors do not mention adverse events in the title or abstract (Derry 2001; Loke 2007). To improve the sensitivity of the search, terms for specified adverse events have to be defined and looked up in each database thesaurus to identify the relevant subject headings to be added in the search strategy (Golder 2006). New, previously unrecognised adverse events remain therefore easily undetected). There is no optimal search strategy for specifically identifying reports of adverse events (Loke 2007, Golder 2010). Following approaches can be used to complement the search strategy with key elements derived from study population and the technology in question:

- Index terms (thesaurus terms, e.g. MeSH in Medline)
  - for specified adverse effects: e.g. Gastrointestinal Hemorrhage, Lymphedema, Pain, Nausea, Lethargy, Fatigue
  - for harm in general: e.g. Adverse Effects (sub-heading), Safety, Toxicity, Drug Toxicity, Complications
- Text words (terms used by the original authors in title and abstract), also taking into account different conventions in spelling and variations in the endings of the terms.
  - for specified adverse effects: nausea, pain, anxiety, tiredness, lethargy, malaise, fatigue, anaemia, QT-prolongation...

- for harm in general: side-effect, adverse event/reaction and complications.
- Search terms to capture certain study design, such as cohort studies
- Describe the rationale for exploratory analyses for adverse events.
- Make a distinction between passive surveillance (e.g. spontaneous reports), stimulated reporting (e.g. in-hospital settings) and active surveillance (e.g. sentinel sites, safety as reason for registries) in reports of pharmacovigilance.
- Specify if searching in susceptible patient groups: elderly, comorbidities, co-prescription, pregnancy.
- Specify if you search for medication errors or other errors or accidental administrations.
- Specify if you search for precaution measures, contraindications or organisational measures to avoid harm.

The methodological approach used in identifying data on adverse events can vary. Therefore, the search strategies should be clearly reported. The search strategy should always be relevant in the context of the natural history of the disease.

In case of including qualitative research on patient safety specific strategies and available filters may be helpful. These filters should never eject data on quantisation of harm nor serious adverse effects.

#### References:

Derry S, Kong Loke Y, Aronson JK. Incomplete evidence: the inadequacy of databases in tracing published adverse drug reactions in clinical trials. *BMC Med.Res.Methodol.* 2001;1:7.

Golder S, McIntosh HM, Duffy S, Glanville J, Centre for Reviews and Dissemination and UK Cochrane Centre Search Filters Design Group. Developing efficient search strategies to identify reports of adverse effects in MEDLINE and EMBASE. *Health.Info Libr.J.* 2006 Mar;23(1):3-12.

Golder S, Loke YK. Sources of information on adverse effects: a systematic review. *Health Information & Libraries Journal* 2010;27(3):176-190.

Loke Y, Price D, Herxheimer A, the Cochrane Adverse Effects Methods Group. Systematic reviews of adverse effects: framework for a structured approach. *BMC Medical Research Methodology* 2007;7(1):32.

## Appendix 4. Development of the Model for Rapid Relative effectiveness assessment

[Back to top](#)

### Background information on EUnetHTA Joint Action work package 5

Several member States of the European Union (EU) have expressed an interest in joint assessments of relative effectiveness of (new innovative) pharmaceuticals. The Directorates General for Health and Consumers (DG Sanco) and General Enterprise and Industry (DG Enterprise) of the European Commission have indicated in earlier communications that they have no intentions to develop new central institutions. Upon the completion of the Pharmaceutical Forum, the EUnetHTA network was identified as an appropriate candidate for developing scientific recommendations for improvements in relative effectiveness assessment (REA).

Work package 5 (WP5) on Relative Effectiveness Assessment in EUnetHTA  
WP5 was developed as part of the new proposal for a EUnetHTA Joint Action between 2010-2012 that was filed to DG Sanco on May 20, 2009. The EUnetHTA Joint Action grant agreement was signed in December 2009 on behalf of 33 participating partners.

The objectives of WP5 (as defined in the EUnetHTA Grant Agreement 2010-2012) are:  
Development of health technology assessment tools and methods: Improved REA by identifying areas where methodological guidance is needed and by providing it, suggesting ways to integrate relative effectiveness assessment of pharmaceuticals as a special version of the HTA Core Model;  
Application and field testing of developed tools and methods: a REA of (a group) of pharmaceuticals in line with the core health technology assessment development.

### Course of development

It was soon noticed while starting to develop this model that people give different meaning to the phrase 'relative effectiveness assessment'. The purpose of a REA is to inform health care professionals, patients and decision makers about the added therapeutic benefit of an intervention compared to already existing interventions and focuses on the clinical implications of the intervention. However, the exact scope is undefined. It is rather a basket term for which no clear boundaries are available. Therefore the following agreements were done for the development of the model:

In line with the recommendation of the Pharmaceutical Forum that relative effectiveness and cost-effectiveness should be considered as two separate entities, the **domain of cost-effectiveness is excluded from the scope of WP5**.

Originally, two models were to be developed in WP5:

a) Model for Rapid REA for (single) rapid assessments which are in general assessments of a new pharmaceutical at the time of introduction to the market in comparison to one or more alternative interventions.

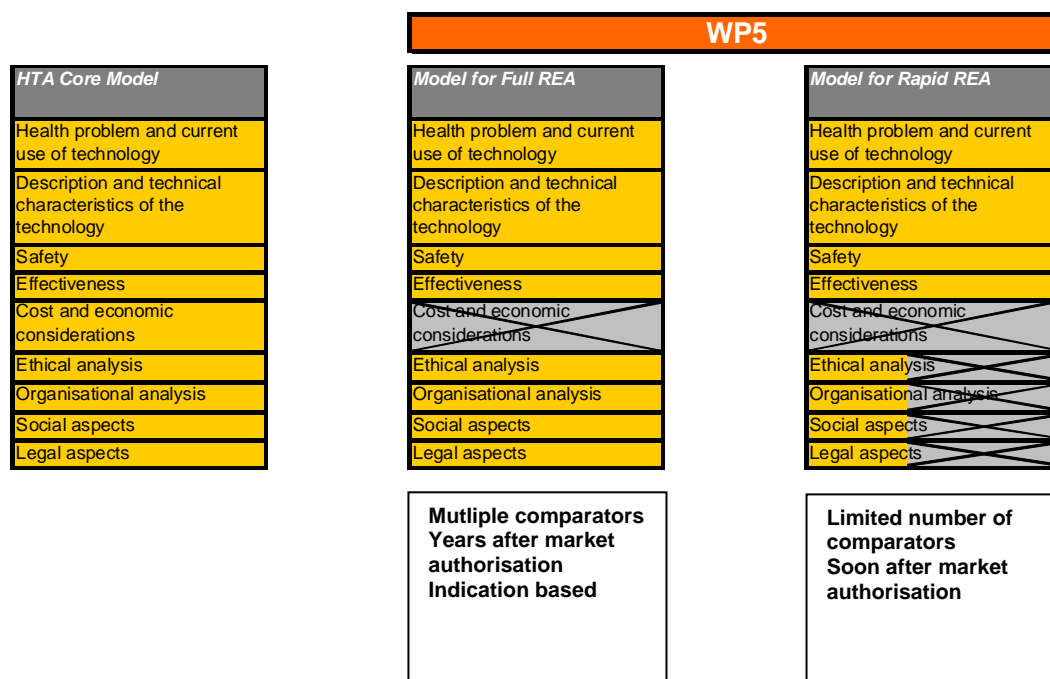
b) Model for Full REA assessments of pharmaceuticals (non-rapid) of (all) available technology(ies) for a particular step in a treatment pathway or a specific condition. This is generally done some years after marketing authorisation.

For a rapid assessment a limited number of comparators is used as opposed to a full assessment, where multiple technologies are considered. Additionally, even though similar methodology is followed in the collection of evidence, due to tim(e)ing and sometimes scope limitations, the rapid assessment is less comprehensive than the full assessment model.

As presented in Figure 3 the scope of the Model for Full REA is all domains of the HTA Core Model except for cost and economic considerations. The scope of the Model for Rapid REA is also all domains of the HTA Core Model, except for cost and economic considerations, however only a

limited number of elements of the ethical analysis, the organisational analysis, the social aspects and the legal aspects are included.

**Figure 3. Model development within WP5**



In 2011, the first version of the Model for Rapid REA was tested in a pilot. Based on this pilot the following decisions were made regarding further development of the models:

- WP5 Joint Action will focus on the further development of the Model for Rapid REA. The Model for Full REA will further be developed in WP8 Joint Action 2;
- The main focus of the Model for Rapid REA should be the first four domains. A short checklist should be developed to check if there may be relevant social/legal/ethical/organisational issues to add to the first four domains during the scoping phase (see [Figure 1](#));
- A REA submission file by the marketing authorisation holder should serve as the basic document in a rapid assessment with additional literature search only if required.

### Most relevant deviations from the HTA Core Model

The following principles were considered very relevant during the development of the Model for Rapid REA of Pharmaceuticals:

- From a legal viewpoint, following the European transparency guideline (Transparency Directive 89/105/EEC), some countries have the legal obligation to do an assessment of pharmaceuticals within a certain time period (90/180 days). The Model for Rapid REA of Pharmaceuticals is developed bearing in mind that the assessment should meet these strict timelines;
- The Model for Rapid REA of Pharmaceuticals is developed for a different collaboration model than the traditional way of working for a HTA Core Model. In contrast to the traditional way of working in which many agencies are collaborating as authors the amount of authoring agencies should be limited to two. In addition, all domains should be written by the same authors. To preserve the benefit of broad participation of agencies that is ensured in the traditional collaboration model, several agencies should be involved to do in-depth review;

The principles have led to a Model for Rapid REA of Pharmaceuticals that differs from the traditional HTA Core Model on the following points:

- Only the first four domain are included.
- In addition, a short checklist is included to check if there may be relevant social/legal/ethical/organisational issues to add to the first four domains during the scoping phases;
- It includes only a selection of the assessment elements of the traditional HTA Core Model (the ones that are considered relevant for a REA)
- A REA submission file by the marketing authorisation holder and the European Public Assessment Report are the primary sources for the assessment (instead of doing a de novo assessment);
- The general scope of the subject under assessment includes all PICO elements (instead of Technology Indication Comparison [TIC]). In addition, domains specific scopes are not intended;
- There is only a general methods section instead of domain specific methods sections
- Guidance on how to produce a 'relative effectiveness section' that combines data from all domains

### ***Definitions specific to the Rapid and Full models for relative effectiveness assessment of pharmaceuticals***

*Relative effectiveness:* 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 (HLPF 2008b).

*Relative efficacy:* the extent to which an intervention does more good than harm, under ideal circumstances, compared to one or more alternative interventions (HLPF 2008b).

*Rapid assessment of relative effectiveness of pharmaceuticals:* A rapid assessment is an assessment of a specific technology within a limited timeframe in comparison with one or more relevant alternative interventions. It may assess a new pharmaceutical launched onto the market, or (re)assess a pharmaceutical for a new indication or when new relevant data are available (Kleijnen et al. 2012).

*Full assessment of relative effectiveness of pharmaceuticals:* The assessment of multiple technologies within a disease area. It is typically conducted several years after the technologies have been introduced to the market and may not have to be carried out within a certain time frame (Kleijnen et al. 2012).

## **Working process for developing the Model for Rapid Relative Effectiveness Assessment**

### ***First version of the Model for Rapid Relative Effectiveness Assessment***

The first version of the model was developed in 2010-2011.

The first version was produced by several working groups called *Domain teams*. Each team focused on one domain. The roles were divided into *authors* and *reviewers*. The authors used the existing text of the medical & surgical interventions application (EUnetHTA 2008a and b) as well as draft versions of the screening application as base text and had as task to update the generic

Model and to consider adding specific elements and methodological guidance considering pharmaceuticals. Reviewers commented the draft versions of authors' work.

The task was divided into three sections:  
Updating the *Domain description*,  
updating the *Assessment elements table*, and  
updating the *Domain methodologies*.

The authors got the task to modify the base text so that it remains generic, i.e. is applicable to all types of technologies; medical & surgical interventions, diagnostic, and screening technologies. If there is a need to amend information that is specific for pharmaceuticals only, it should be marked in italics or placed under separate subheading.

The domain descriptions in the earlier Model applications were heterogeneous across domains; they were of different length and different in content. In some domains, there were actually two quite different domain descriptions from the earlier model applications, and the current investigators had to start with combining these two into one generic domain description. The investigators got the task to harmonise the texts within and across the domains, and make the text shorter and friendlier to readers, considering the fact that the text will finally appear in the online tool.

Regarding the assessment elements the authors were encouraged to go through the topics and issues in the table, one by one, asking the following questions:

Does this issue apply/ should we keep this issue in the application on pharmaceuticals?

If no, suggest removing it from the pharmaceuticals model

If yes, ask yourself, does the issue need some modification?

If yes, please modify. Notice that the issues should be generic questions. You should formulate them to be pharmaceuticals specific.

Are there issues missing, that are relevant to pharmaceuticals?

If yes, add new element (row)

Is the topic-issue hierarchy logical and useful

If not, suggest changes

Suggest amendments or changes to the Clarification, Information sources and Reference fields

Consider the Importance and Transferability of each element. Suggest changes to the existing numbers.

Suggest amendments or changes to the Relations fields. Identify elements with relevance for order of doing a core HTA (Do certain elements need to be answered before one can continue working with this element?) or possible overlapping (Are there elements which require same original studies and where there is a possibility to duplication of work?).

The methodological guidance that is applicable in several, or even in all domains, were moved to the 'Common methodologies' section.

It was made explicit that the style should not be a text book, neither a methodological article. Instead of lengthy descriptions, the investigators were encouraged to write brief sentences and use lists and links to useful sources and tools.



## ***Second version of the Model for Rapid Relative Effectiveness Assessment***

The 2<sup>nd</sup> version of the model was produced in 2012. The experience gathered in a pilot rapid assessment that was conducted in 2011 with the 1<sup>st</sup> version of the model was used to make the model more practical and easy to use for a rapid assessment.

Based on the pilot the following changes were implemented:

- The model is limited to the first four domains
- In addition, a short checklist is included to check if there may be relevant social/legal/ethical/organisational issues to add to the first four domains during the scoping phases;
- Only a limited selection of the assessment elements of the traditional HTA Core Model (the ones that are considered relevant for a REA) are included
- A REA submission file by the marketing authorisation holder and the European Public Assessment Report are the primary sources for doing an assessment (instead of doing a de novo assessment);
- The general scope of the subject under assessment includes all PICO elements. ;
- There is only a general methods section instead of domain specific methods sections
- Guidance on how to produce a 'relative effectiveness section' that combines data from all domains is included
- The formulation of text in the assessment elements was improved

The changes were implemented by CVZ, after which the domain teams from the first version of the model functioned as dedicated reviewers.

### **References:**

EUnetHTA. 2008a. Work Package 4. HTA Core Model for diagnostic technologies v 1.0r. Available at: [http://www.eunetha.net/Public/EUnetHTA\\_Deliverables\\_project\\_2006-2008/](http://www.eunetha.net/Public/EUnetHTA_Deliverables_project_2006-2008/).

EUnetHTA. 2008b. Work Package 4. HTA Core Model for medical and surgical interventions v 1.0r. Available at: [http://www.eunetha.net/Public/EUnetHTA\\_Deliverables\\_project\\_2006-2008/](http://www.eunetha.net/Public/EUnetHTA_Deliverables_project_2006-2008/)

## Appendix 5. Recommendations of guidelines on methodological issues

Endpoints used in REA of pharmaceuticals:

### *Clinical endpoints*

Click [here](#) for the full text of the “Clinical endpoints” guideline.

Recommendations – Clinical endpoints
1. All clinical endpoints should be comprehensively defined and justified in the study protocol(s) and report. They should be clinically relevant to the disease being treated.
2. Endpoint estimates should be presented to show both statistical significance and clinical relevance.
3. Where appropriate, endpoints should be expressed in natural units (e.g. post-operative infections prevented).
4. The implications of the observed treatment effect on clinical endpoint should be easy to interpret.
5. Clinical endpoints should be sensitive to treatment differences.
6. Measurement of clinical endpoints:
a. Clinical endpoints should be measurable within a reasonable period of time for all or a high proportion of patients.
b. Both relative and absolute measures should be presented. Responder analysis may be presented when appropriate.
c. A clinical endpoint should be measured with minimal measurement or assessment error.
7. Where a continuous or ordinal endpoint is converted to dichotomous, there should be a clear justification for the choice of cut-point.
8. Clinical endpoint estimates should come from unbiased studies, especially with respect to detection bias (e.g. appropriate blinding).
9. An endpoint should be independent of jurisdiction or region to maximise comparability.
10. The analysis of endpoint data should explicitly state the handling of missing data.
11. Clinical endpoints should be long-term or final endpoints where possible, although short-term endpoints are acceptable for acute conditions with no long-term consequences. All-cause mortality should be used where relevant as it is the most unbiased endpoint. Overall survival is the preferred clinical endpoint in a survival analysis.
12. Any extrapolation from intermediate to final endpoints should be underpinned by a clear biological or medical rationale or a strong or validated link.

<b>Recommendations – Clinical endpoints</b>	
13.	Multiple endpoints can be presented, including adverse event endpoints. It might be helpful to determine a hierarchy of endpoints.
14.	Appropriate adjustment should be considered for multiple hypothesis testing.
15.	Composite endpoints should be presented in disaggregated form, be based on endpoints of clinical importance for REA and ideally show a homogenous response across all components.

### *Composite endpoints*

Click [here](#) for the full text of the “Composite endpoints” guideline.

<b>Recommendations – Composite endpoints</b>	
1	Composite endpoints should generally not be used if a suitable single primary endpoint is available. If a single primary endpoint is not available or if a composite endpoint can be justified to be more suitable (e.g. rare disease/event), it may be chosen instead.
2	There should be prior empirical and clinical evidence of the value of each chosen component for the composite outcome.
3	The number of components of the composite endpoint should be limited to 3 or 4 in order to avoid problems in the analysis and interpretation.
4	Trials using composite endpoints should follow CONSORT guidelines and report pre-specified primary and secondary endpoints to allow appropriate interpretation. Changes in the definition of a composite endpoint should not occur during the trial.
5	All components of a composite endpoint should be separately defined as secondary endpoints and reported with the results of the primary analysis.
6	Components of similar clinical importance and sensitivity to intervention should preferably be combined. Heterogeneity (mix of subjective and objective endpoints) should be avoided.
7	Inclusion of components in which influence of the intervention is known to be small or unlikely should be avoided. If adequate, mortality should however be included if it is likely to have a censoring effect on the observation of other components.
8	Composite endpoints can be used to assess not only effectiveness but also harms of a pharmaceutical.
<b>CE reporting</b>	
9	Treatment effects should be reported on the CE at the first place. Results should also be reported for each component of a composite endpoint in the way it contributed to the result within the composite endpoint. All results should be reported separately even if they lack statistical power. A list of results for all components should be provided in a table with confidence intervals.
10	Separate components can be reported according to hierarchical levels, for example L1, all- cause mortality, L2, cause-specific mortality, L3, nonfatal clinical events, L4, symptoms.
11	In cases where the composite endpoint includes fatal and non-fatal events, it is recommended to report results on relevant combinations of components of the CE.
12	All data should be reported. The number of patients with partially missing values on some components should be reported in detail.
13	If there are relevant subgroups or special patient populations at risk (such as elderly, or patients with renal failure), results should be provided for these subgroups.
<b>Analysis and synthesis of the evidence from CE studies in REA</b>	

Recommendations – Composite endpoints	
14	Treatment effects should be interpreted based on the CE at the first place. However, treatment effect on each component of a composite endpoint in the way it contributed to the result within the composite endpoint should also be analyzed to assess whether an intervention had similar effects on all endpoint components.
15	It is recommended to check that clinically important components of the composite endpoint are not affected negatively by the treatment, as some treatments may have negative effect on one component which can be masked by a large beneficial effect of the remaining components. In these cases it may not be possible to conclude that the treatment has a clinically relevant effect on the composite endpoint as a whole. It should be stated and/or identified by the REA process which component is mainly responsible for the overall effect
16	If valid and comparable composite endpoints from several studies are available, consider basing the overall conclusion on a meta-analysis.
17	If – according to this table – there is a single <u>relevant</u> problem or a significant accumulation of problems associated with a given CE, considerable uncertainty concerning the validity of study results has to be concluded. The position of this study in the hierarchy of evidence and its usefulness for REA will have to be downgraded.

### *Surrogate endpoints*

Click [here](#) for the full text of the “Surrogate endpoints” guideline.

Recommendations – surrogate endpoints
<p><b>Recommendation 1</b></p> <p>The REA of pharmaceuticals should be based whenever possible on final patient-relevant clinical endpoints (e.g. morbidity, overall mortality).</p>
<p><b>Recommendation 2</b></p> <p>In the absence of evidence on final patient-relevant clinical endpoint that directly measures clinical benefit, both biomarkers and intermediate endpoints will be considered as surrogate endpoints in REA if they can reliably substitute for a clinical endpoint and predict its clinical benefit.</p>
<p><b>Recommendation 3</b></p> <p>If surrogate endpoints are used for REA, they should be adequately validated: the surrogate-final endpoint relationship must have been demonstrated based on biological plausibility and empirical evidence. The level of evidence, the uncertainties associated and the limits of their use should be explicitly explained. Complete validation data should always be provided. For adequately validated surrogate endpoints, a second validation for REA purposes will not be necessary.</p>
<p><b>Recommendation 4</b></p> <p>Validation of a surrogate versus patient-relevant clinical endpoint is normally undertaken in a specific population and for a specific drug intervention i.e. validation is disease-specific, population-specific and pharmaceutical class (technology) specific. Demonstration of surrogate validation both within and across drug classes should be thoroughly justified.</p>
<p><b>Recommendation 5</b></p>

## Recommendations – surrogate endpoints

For the **first assessment**, even if final endpoints are preferred, surrogate endpoints might be accepted if the validity of the surrogate/final clinical endpoint relationship has been previously clearly established on clinical endpoints of interest for REA. The availability of a sufficiently large safety database is particularly important. Evidence on safety outcomes should always be reported.

### Recommendation 6

For the **re-assessment**, effectiveness should in principle be demonstrated on morbidity and mortality endpoints (e.g. stroke, myocardial infarction, fracture). Comparative clinical data (or evidence that data will be provided in a reasonable timeframe) on relevant clinical endpoints and safety coming from post-marketing clinical trials and other sources should be provided whenever possible before the re-assessment of the pharmaceutical can be carried out.

The absence of data on clinical endpoints relevant for REA might be acceptable when a clinical endpoint is difficult or impossible to study (very rare or delayed) or target population is too small to obtain meaningful results on relevant clinical endpoints even after very long follow-up (very slowly progressive and/or rare diseases). However, these exceptions need to be carefully argued and agreed in advance of an REA.

### Recommendation 7

Re-assessment requirements for further data regarding relevant clinical endpoints should be clearly defined when a REA has been previously made based on surrogate endpoints for the first assessment.

### Recommendation 8

Further methodological research on the use of surrogate outcomes is needed to inform future REA approaches for the handling of surrogates.

## *Safety*

Click [here](#) for the full text of the “Safety” guideline.

## Recommendations – safety

### Recommendation 1

In relative safety assessment of pharmaceuticals main objectives of HTA assessors are summarised as follows:

- To identify the adverse reactions
- To quantify the adverse reactions in terms of frequency categories, incidence, severity and seriousness
- To compare the safety profile of the pharmaceutical with its comparator(s)/best standard of care.

### Recommendation 2

HTA assessors may focus their investigation on the following areas:

<b>Recommendations – safety</b>
<ul style="list-style-type: none"><li>- The most frequent adverse reactions.</li><li>- The “important identified” and “potential” risks associated with use of the product, according to the RMP. These should include only the important identified and potential adverse events/reactions, important identified and potential interactions with other medicinal products, foods and other substances, and the important pharmacological class effects.</li></ul>
<b>Recommendation 3</b> The HTA assessors should use consistent and precise terminology to avoid misleading results. They should use the MedDRA Dictionary for describing adverse reactions.
<b>Recommendation 4</b> Main sources of information of HTA assessors are: <ul style="list-style-type: none"><li>- EPAR, SPC and RMP (when available)</li><li>- Published and unpublished (where acceptable under the specific HTA system guidelines) randomised clinical trials</li><li>- Manufacturer dossier</li><li>- Unpublished full study reports (where acceptable under the specific HTA system guidelines)</li><li>- Observational studies</li></ul>
<b>Recommendation 5</b> It is necessary to evaluate both the risk of bias of sources of information and the quality of data on adverse reactions. Methods used to assess the risk of bias should be clearly described and results should be reported. It should be clearly explained how the information on risk of bias will be used in the synthesis of data. To assess the data on adverse reactions, how the adverse effects were collected and reported should be evaluated.  Useful questions to assess how the adverse reactions are collected: <ul style="list-style-type: none"><li>- Were definitions given of reported adverse effects?</li><li>- How were adverse effects data collected: prospective/routine monitoring, spontaneous reporting, patient checklist/ questionnaire/diary; systematic survey of patients?</li></ul> Useful questions to assess how the adverse effects are reported: <ul style="list-style-type: none"><li>- Were any patients excluded from the adverse effects analysis?</li><li>- Did the report give numerical data by intervention group?</li><li>- Which categories of adverse effects did the investigators report?</li><li>- Did investigators report on all important or serious adverse effects, and how were these defined?</li><li>- Were methods used for monitoring adverse effects reported?</li><li>- Was an independent data safety monitoring board established?</li></ul>
<b>Recommendation 6</b> Characteristics of selected studies should be summarised in a table. Useful information on studies characteristics are the following: <ul style="list-style-type: none"><li>- methods (study design, follow-up period);</li><li>- participants for both arms (setting, age, sex and country/geographic area),</li><li>- intervention and comparators (for pharmaceuticals: the name, dose, frequency, way of administration and duration);</li><li>- outcomes;</li><li>- methods to collect adverse effects.</li></ul>

<b>Recommendations – safety</b>
Different tables should be elaborated for RCTs and observational studies.
<p><b>Recommendation 7</b>                  Results from individual studies should be presented by group in tabular form, using the following measures:</p> <ul style="list-style-type: none"> <li>- Number of participants in both study arms</li> <li>- Number of patients excluded from the analysis dataset</li> <li>- Patient-years of exposure</li> <li>- Number of participants with the event</li> <li>- Number of events</li> <li>- Absolute risk; incidence rate (95% CI)</li> <li>- Relative risk (95% CI)</li> <li>- Quality of evidence</li> </ul> <p>Different tables should be elaborated for RCTs and observational studies.                  Adverse effects should be grouped according to the System Organ Class (SOC).                  Adverse effects which are common and serious should be reported separately.                  If possible, adverse effects should also be provided by severity grade.                  When adverse effects are collected from different study designs and when the degree of heterogeneity is high the data cannot all be pooled together using standard meta-analysis principles. Therefore in these circumstances adverse effects data is best summarised in a qualitative or descriptive manner.</p>
<p><b>Recommendation 8</b>                  The safety profile of the pharmaceutical is described in comparison to the comparator(s), with special regard to the most frequent, serious and severe adverse reactions.                  A table is preferable for the comparison of the safety profile of the new pharmaceutical and the comparator(s).                  HTA assessors should describe if there is a clinically significant difference in adverse reactions between products.                  In the discussion of results limitations and external validity should be investigated and discussed, considering all factors (e.g. patient characteristics, co-morbidities, type and severity of disease) which may contribute to the occurrence of adverse reactions.</p>
<p><b>Recommendation 9</b>                  The assessment of relative safety together with relative benefits will contribute to establish a balanced assessment of the relative effectiveness of the intervention, and to decide upon possible consequences on coverage decision.</p>

### ***Health-related quality of life and utility measures***

Click [here](#) for the full text of the “Health-related quality of life and utility measures guideline”.

<b>Recommendations – Health-related quality of life and utility measures</b>
<ol style="list-style-type: none"> <li>1. HRQoL instruments used in the context of REA should first and foremost be <b>valid for the purpose the REA intends to serve.</b>(paragraph 1.2Fout! Verwijzingsbron niet gevonden.) REA assessors should thus first consider for what purpose the REA will be used: to inform reimbursement decisions or to inform clinical decision making. The recommendations apply to both full REA and rapid REA.</li> <li>2. A general recommendation applicable to all types of REA irrespective of their particular purpose, is to require the inclusion of a <b>disease- or population specific and a generic</b></li> </ol>

<b>Recommendations - Health-related quality of life and utility measures</b>
<p><b>HRQoL measure</b> for most adequately capturing the impact of a disease on daily life. In case there is a need for the calculation of QALYs, a utility measure (Time Trade-Off or Standard Gamble) or generic HRQoL, instrument associated with a reference set of utility values (generic utility instrument) is recommended.</p>
<p>a) For countries that require an economic evaluation to support a product reimbursement application, it is recommended to require data emerging from the administration of a generic utility instrument in the clinical trial(s). Utility values should be derived from the general public (indirect utility measurement) or from patients (direct utility measurement). There is no consensus across jurisdictions about the most appropriate source. The choice between the sources of utility values is a normative one and should be based on careful consideration of the expected consequences for the decisions for which the HRQoL measurements are used, especially in case of decisions across indications. Consistency in the application of the chosen source is required. In both decision contexts, the use of other estimates for the HRQoL benefit in the REA than in the economic evaluation should be avoided. To improve comparability and consistency, countries might also consider recommending the use of one particular instrument for national reimbursement requests that is widely used (e.g. the EQ-5D).(paragraph 2.1.3)</p>
<p>b) For countries that do not require an economic evaluation to support a product reimbursement decision, a disease-specific or generic HRQoL measure may be sufficient. Utility measures remain useful for REA in this context, however, especially for the calculation of QALYs, which are particularly useful for comparing interventions affecting both mortality and morbidity.</p>
<p>3. <b>REA performed for informing resource allocation decisions across indications</b> should primarily be based on HRQoL data obtained with a <b>generic HRQoL</b> instrument, encompassing all HRQoL dimensions in which improvements are considered important by the general public. If no improvement on such generic HRQoL instrument is observed, the alleged benefit of an intervention is less likely to be considered meaningful <i>from a societal point of view, given the range of existing health problems between which public resources need to be allocated</i>. REA should consider the effect of an intervention on the HRQoL of a typical real life patient population, taking the impact of patient's co-morbidities on HRQoL into account.(paragraph 2.1)</p>
<p>4. <b>REA performed for informing resource allocation decisions within indications</b> can be based on <b>validated comprehensive disease-specific HRQoL</b> data, as comparability across indications is in this case less important. Nevertheless, the consideration of <b>generic HRQoL</b> data remains useful for reasons of coherence in the valuation of health benefits, and in consequence, transparency of the decision-making process.(paragraph 2.1.2) <b>Verwijzingsbron niet gevonden.</b></p>
<p>5. <b>REA performed for the purpose of informing health care professionals and patients</b> could be based on <b>disease-specific HRQoL instruments</b>. They can be considered as complementary to generic instruments in REA performed for policy purposes. Disease-specific HRQoL instruments may be useful for more in-depth assessment of the generic HRQoL dimensions affected by an intervention. It should be borne in mind that the burden imposed on respondents increases with the number of questionnaires used.(paragraph 2.1.2)</p>
<p>6. HRQoL benefits of interventions should be demonstrated by means of <b>repeated measurements</b> in both the intervention and the control group.(paragraph 2.1.5.1)</p>
<p>7. <b>Single item scores</b> for HRQoL alone are considered insufficient to demonstrate relative effectiveness because they are subject to bias and often too crude to detect changes in health. Single item scores are scores derived from one single question asking to value current overall health on a specific scale.(paragraph 2.1.5)</p>
<p>8. <b>Mapping</b> of disease-specific or generic instruments to preference-based instruments to</p>



<b>Recommendations - Health-related quality of life and utility measures</b>
obtain utility values is generally not recommended for REA. Authorities should encourage researchers to always include a preference-based instrument in their clinical trial protocol in order to avoid the need for mapping. (paragraph 2.1.3.3)
9. Documentation of the <b>validity, reliability, responsiveness and acceptability</b> of the HRQoL instruments used in REA should be provided, taking into account the applied mode of administration and possible cultural and/or language adaptations. (paragraphs 2.1.4, 2.1.5.2 and 2.1.5.3)
10. Evaluation of HRQoL by “ <b>proxy judges</b> ” is not recommended. Its acceptance is limited only to cases where the patient cannot contribute him/herself or where the use of proxies can be justified by the nature of the judgements to be made.( paragraph 2.1.5.4)
11. <b>Transparent reporting within due time</b> of the results of all HRQoL measurements is recommended. If not (yet) published, it is required to make these results accessible for HTA bodies to allow critical appraisal.
12. When changes in survival and HRQoL are combined in one outcome measure such as the <b>QALY</b> , separate reporting of changes in survival and HRQoL and a description of the methods to combine the measurements should be requested to allow for separate consideration of both endpoints.( paragraph 2.2).

## Comparators and comparisons

### *Criteria for the choice of the most appropriate comparator(s)*

Click [here](#) for the full text of the “Criteria for the choice of the most appropriate comparator(s) guideline”.

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 pharmaceutical compared with routine clinical care, the most used, or what would be replaced by the introduction of that new pharmaceutical.

<b>Recommendations - Criteria for the choice of the most appropriate comparator(s)</b>
<p><b>Recommendation 1</b></p> <p>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 for the respective indication and line of treatment.</p>
<p><b>Recommendation 2</b></p> <p>Where there is no European-wide agreed reference comparator</p> <ul style="list-style-type: none"> <li>• evidence needs to be available that the chosen comparator intervention is routinely used in clinical practice (Recommendation 3)</li> <li>• the comparator intervention is validated for the respective clinical indication/population and evidence is available (Recommendation 4)</li> </ul>
<p><b>Recommendation 3</b></p> <p>Evidence that the intervention is used in routine clinical care could come, in order of</p>

<p><b>Recommendations – Criteria for the choice of the most appropriate comparator(s)</b></p>
<p>preference, from:</p> <ul style="list-style-type: none"> <li>• National reimbursement lists if available</li> <li>• Prescription statistics (if appropriate)</li> <li>• Market surveys</li> <li>• Discussion with clinical specialists and patient organisations</li> <li>• Registries</li> <li>• Validated clinical protocols</li> <li>• If the above are not available: Internet searches, in particular patient and professional websites</li> </ul>
<p><b>Recommendation 4</b></p> <p>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.</p>
<p><b>Recommendation 5</b></p> <p>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.</p> <p>Where the comparator is not a pharmaceutical, it should be used according to evidence based methodology and its instructions for use.</p>
<p><b>Recommendation 6</b></p> <p>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.</p>
<p><b>Recommendation 7</b></p> <p>The most appropriate comparators for an assessment should be identified before the assessment begins or in the early phase of an assessment.</p>
<p>The following recommendations relate to specific national procedural rules, and are only relevant for specific countries</p>
<p><b>Recommendation 8</b></p> <p>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.</p>
<p><b>Recommendation 9</b></p> <p>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.</p>
<p><b>Recommendation 10</b></p> <p>If required by national procedural rules, and depending on the assessment question, the comparator may need to be from a similar pharmaceutical class.</p>

## ***Direct and indirect comparisons***

Click [here](#) for the full text version of the “Direct and indirect comparisons guideline”.

<b>Recommendations - Direct and indirect comparisons</b>
1. A systematic literature search is a pre-requisite to conducting a direct or indirect comparison. This must be documented according to existing guidelines. A comprehensive review will maximise the evidence base.
2. The application of direct or indirect comparisons relies on the assumption that only comparable studies should be combined. Studies that differ substantially in one or more key characteristics (e.g. participants, interventions, outcomes measured) should not be combined. Methods such as meta-regression that account for study level covariates may be used, although the power to detect effect differences is reduced.
3. The choice between a fixed and random effects model should be made based on the characteristics of the studies being analysed. Heterogeneity should be assessed and a clear justification for the choice of model must be provided. Where a random effects model is preferred, results from a fixed effect model can still be presented in special situations (e.g. few studies and where sample sizes vary considerably).
4. Potential sources of bias should be investigated, if identified (e.g. funnel plots for publication bias).
5. Attention should be given to determining the presence of outliers or influential observations that may have an undue impact on results. Sensitivity analysis should be used to determine the impact of those influential or outlying studies.
6. The choice between direct and indirect comparison is context specific and dependent on the question posed as well as the different evidence available. Where sufficient good quality head-to-head studies are available, direct comparisons are preferred as the level of evidence is high. Should substantial indirect evidence be available, then it can act to validate the direct evidence. When there is limited head-to-head evidence or more than two treatments are being considered simultaneously, the use of indirect methods may be helpful.
7. If both direct and indirect evidence are available, they can be evaluated separately. Attempts should be made to explain any discrepancies between the results obtained in terms of study characteristics. In the event of indirect results differing substantially from the direct evidence, there must be close scrutiny of the data, although there is no consensus in the literature on how to deal with these discrepancies.
8. Only adjusted methods of indirect comparison that maintain randomisation should be used. Unadjusted indirect comparisons are not recommended.
9. The choice of indirect comparison method relies on the network of available evidence. Preference should be given to the most transparent method available (i.e. one should favour Bucher’s method of adjusted indirect comparison over MTC if the data permit its usage and the appropriate assumptions are satisfied).

<p>10. An indirect comparison should only be carried out if underlying data from comparable studies are homogeneous and consistent, otherwise the results will not be reliable.</p>
<p>11. The assumptions made for indirect comparisons must be explicitly stated. Particular attention should be given to the homogeneity, similarity and consistency assumptions. A general assumption of indirect comparisons is that the relative effectiveness of a treatment is the same across all studies included in a meta-analysis.</p>
<p>12. When Bayesian methods are applied, the choice of the prior distributions should be justified and documented. In the case of non-informative priors, where alternative specifications exist they should be applied as part of a sensitivity analysis. When informative priors are used, the source of that data must be clearly documented and consideration given to testing the impact of using a non-informative prior in place of the informative prior.</p>
<p>13. The complexity of a model is not a measure of its accuracy or utility and preference is for the most parsimonious model whose assumptions can be justified.</p>

## Levels of evidence

### *Internal validity of randomised controlled trials*

Click [here](#) for the full text version of the “Internal validity of randomised controlled trials guideline”.

<p><b>Recommendation - Internal validity of randomised controlled trials</b></p>
<p><b>Recommendation 1</b></p> <p>Use the risk of bias concept of the Cochrane Collaboration to assess the internal validity of RCTs within an REA. Chapter 8 and table 8.5.d of the Cochrane Handbook (Higgins &amp; Green 2011) provide detailed guidance.</p>
<p><b>Recommendation 2</b></p> <p>Provide appropriate training and clear and consistent decision rules to achieve acceptable reproducibility of the risk of bias assessments. The use of standardized extraction sheets is also recommended.</p>
<p><b>Recommendation 3</b></p> <p>Within an REA, specify in advance how to deal with studies with a high or unclear risk of bias. There are at least 4 options: (i) rely only on studies with a low risk of bias; (ii) perform sensitivity analyses according to the different risk of bias categories; (iii) describe the uncertainty with regard to the different levels of risk of bias, so that subsequent decisions can be made considering this uncertainty; (iv) combine option (ii) and (iii).</p>
<p><b>Recommendation 4</b></p> <p>Use a validated tool to assess the methodological quality of systematic reviews: the Oxman and Guyatt index (Oxman &amp; Guyatt 1991, Jadad &amp; Murray 2007) and the AMSTAR instrument (Shea et al. 2007) are recommended. Both instruments are useful, without a</p>

<b>Recommendation - Internal validity of randomised controlled trials</b>
preference for either one.

### ***Applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals***

Click [here](#) for the full text version of the “Applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals guideline”.

<b>Recommendation - Applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals</b>
<b>Recommendation 1</b>  Applicability is defined as the extent to which the effects observed in clinical studies are likely to reflect the expected results when a specific intervention is applied to the population of interest. Applicability should be considered in each assessment of relative effectiveness of pharmaceuticals. The aim of assessing applicability is to consider whether a relevant effect modification is likely in the population of interest as compared to the results in the clinical studies.  (section 2.1 of the guideline)
<b>Recommendation 2</b>  Prior to assessing the applicability, causality between treatment and outcome should be established (internal validity is a pre-requisite of applicability).  (section 2.1 of the guideline)
<b>Recommendation 3</b>  To assess the relative effectiveness of interventions, trials with a pragmatic approach are more suitable than trials with an explanatory approach as the results are more likely to occur in clinical practice. If available, data from trials with a pragmatic approach should always be included in the assessment (if the trial has been performed in the population of interest).  (section 2.1 of the guideline)
<b>Recommendation 4</b>  If available, analysis that addresses effect modification of results to a specific/general patient population/setting (e.g. effect model, meta-analysis) should be included in the assessment.  (section 2.2.1 of the guideline)
<b>Recommendation 5</b>  Assessors should describe differences between available evidence and the ideal evidence to address the question being asked. They should offer a qualitative judgement about the importance and potential effect of those differences.  a) First, the authors should carefully identify and describe the target population

b) It should be noted that the size of the effect modifications (the numerical value of the effect) can only be addressed by statistical methods.

c) The most applicable evidence may differ when considering benefits or harms since these often depend on distinct physiological processes. Therefore applicability should be judged separately for different outcomes.

d) To address the applicability in a report the 4-step process developed by Atkins et al (2011) is recommended:

**Step 1.** Determine the most important factors that may affect applicability (the table in Annexe 1 can be helpful)

**Step 2.** Systematically abstract and report key characteristics that may affect applicability in evidence tables (highlight studies with a pragmatic approach and data on effect size of effect modification).

**Step 3.** Make and report judgements about major limitations to applicability of individual studies.

**Step 4.** Consider and summarize the applicability of a body of evidence (use format of table below)

For details we refer to the guideline by [Atkins et al](#) (2011)

e) For a rapid assessment (limited timeframe) the 4-step process described above may not be feasible. In any case, it is recommended to at least fill in the summary table which will help envisage potential applicability issues.

f) The following aspects are important to include in the description:

- It is likely that not all data are available to complete the table. In case of missing data this should be described as well.
- The section on outcomes should include a comment regarding which effect measure is less likely to be subject to effect modification (e.g. which effect measure is more/less likely to be different in the population of interest in a particular setting than in the available trials).
- It should always be considered and addressed whether a specific element that is relevant for the applicability can be assessed in general or whether this should be done in the local (national) context.

(section 2.2.2 of the guideline)

#### Recommendation 6

It should be noted that evaluating the applicability of the evidence is not a pre-defined formula. Depending on the topic interpretation of the applicability may vary. For example, for a rare disease other considerations and requirements may be relevant compared to a non-rare disease. Regardless of the topic it is very relevant that *the considerations are transparently reported in the assessment report.*