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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

WORK PACKAGE 5 JOINT ACTION 2

The HTA Core Model® for Rapid Relative Effectiveness Assessments

Developed by
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Authorship in collaborative writing of a living document

This model was developed in Work Package (WP5) Joint Action 1 and updated in WP5 Joint Action 2. The update process was coordinated by the Dutch National Health Care Institute (ZIN, the Netherlands) and the Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA, Austria).
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.

This document represents collaborative writing by multiple authors at multiple time points. The authors worked on the previous versions of the HTA Core Model® updating and editing text written by others. Strong editorial input is present. While this may challenge long-held concepts of property, credit and authority, it 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 that, for instance, 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 modify subsequent versions.

HTA Core Model for Rapid REA V4.1

The first published version of the HTA Core Model for Rapid REA (V3.0) has been developed for pharmaceuticals only with the intention to produce a rapid assessment within a limited time frame, since countries are legally obliged to assess pharmaceuticals within a specified time period (90-180 days) based on 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).
The current version (V4.1) was extended to cover also applications for medical and surgical interventions, and for screening and diagnostic technologies. Even though strict time frames do not apply to other technologies, such as medical interventions, the rationale for rapid assessments can be justified by the need for producing timely information for, e.g. pending decisions in countries of assessment producers.
The scope of V4.1 was amended, to provide guidance for producers of HTA information in general. EUnetHTA specific information and processes were removed and will be included in the Procedure Manuals of WP5 Strand A (Rapid Relative Effectiveness Assessments on pharmaceuticals) and Strand B (Rapid Assessments of other technologies).

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LIST OF ABBREVIATIONS

AIDS	Acquired immune deficiency syndrome
AE	Adverse event
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
CHMP	Committee for Medicinal Products for Human Use
CEC	Costs and economic considerations
CSR	Clinical Study Report
CUR	Health problem and current use domain
DDD	Defined Daily Dose
DOR	Diagnostic Odds Ratio
EEA	European Economic Area
EFF	Clinical effectiveness
EFTA	European Fair Trade Association
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ETH	Ethical analysis
EUnetHTA	European network for Health Technology Assessment
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
INAHTA	The International Network of Agencies for Health Technology Assessment
IAEA	International Atomic Energy Agency
ICD	International Classification of Diseases
ICRP	Publication of International Commission of Radiological Protection
IEC	International Electrotechnical Commission
ISO	International Organization for Standardization
LEG	Legal aspects
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical subject headings
MHRA	Medicines and Healthcare products Regulatory Agency
NNH	Number needed to harm
NNT	Number needed to treat
ORG	Organisational aspects
OTC	Over the counter
PICO	Patient, intervention, comparison, outcome
POP	Planned and ongoing projects

PSUR	Periodic safety update report
QALY	Quality-adjusted life years
QoL	Quality of life
RCT	Randomised controlled trial
REA	Relative effectiveness assessment
RMP	Risk management plan
SAE	Serious adverse events
SAF	Safety
SDOR	Summary Diagnostic Odds Ratio
SOC	Social aspects
SPC	Summary of Product Characteristics
TEC	Description and technical characteristics of the technology domain
TGA	Therapeutic Goods Administration
WHO	World Health Organisation
WP	Work package

1 INTRODUCTION

1.1. The HTA Core Model® for Rapid Relative Effectiveness Assessment

The HTA Core Model® for Rapid Relative Effectiveness Assessment abbreviated as 'Model for Rapid REA' is a methodological framework for the collaborative production and sharing of HTA information. Because the objective of the framework is sharing of commonly required elements of information, only information that is considered both important and transferable is collected.

The aim is:

- to improve the applicability of HTA information in other (e.g. national or regional) HTA projects
- to enable actual collaboration between HTA agencies by providing a common framework for the production of rapid Relativeness Effectiveness Assessments and
- to avoid duplication of work.

Resting on the HTA Core Model®, the Model for Rapid REA provides an overview for producers of rapid REAs on important generic research questions which should be considered and on the basic steps involved. Rapid REAs are assessments of a specific technology within a limited time frame in comparison with one or more relevant alternative interventions. It covers generic research questions (i.e. issues) considered most relevant for four different applications each focusing on the assessment of specific types or uses of health technologies:

- Pharmaceuticals
- Diagnostic Technologies
- Medical and Surgical Interventions
- Screening Technologies

For a detailed description of the domains, guidance concerning assessment of specific types of technologies and for further potentially relevant research questions to be considered within a rapid REA the different applications from the HTA Core Model® should be consulted.

What is relative efficacy/effectiveness?

Two definitions are commonly used in the context of an REA:

- **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 relative effectiveness, the focus is on determining the magnitude of the health benefits and harms of a (new) technology, compared with other existing technologies. As stated in the principles on relative effectiveness, an REA should include a comparison with the most appropriate health-care intervention(s). The REA should focus primarily on data derived from usual circumstances of health-care practice, although these are usually not available right after marketing authorisation or market entry of the technology. Additionally, the REA should present the uncertainties affecting interpretation of reliability and clinical relevance of the results. Rapid REAs may assess a new technology recently introduced to the market, or (re)assess a technology for a new indication or when new relevant data are available [1].

1.2. Background

The HTA Core Model for Rapid REA is based on The HTA Core Model®. which consists of three main components:

1. A list of generic questions that can be asked in a HTA. The model also identifies relations between the questions.
2. Methodological guidance helps researchers to find answers to the questions defined by the model.
3. The common reporting structure provides a standard format for the output of HTA projects.

Figure 1: Domains of HTA Core Model® and of the HTA Core Model® for Rapid Relative Effectiveness Assessment

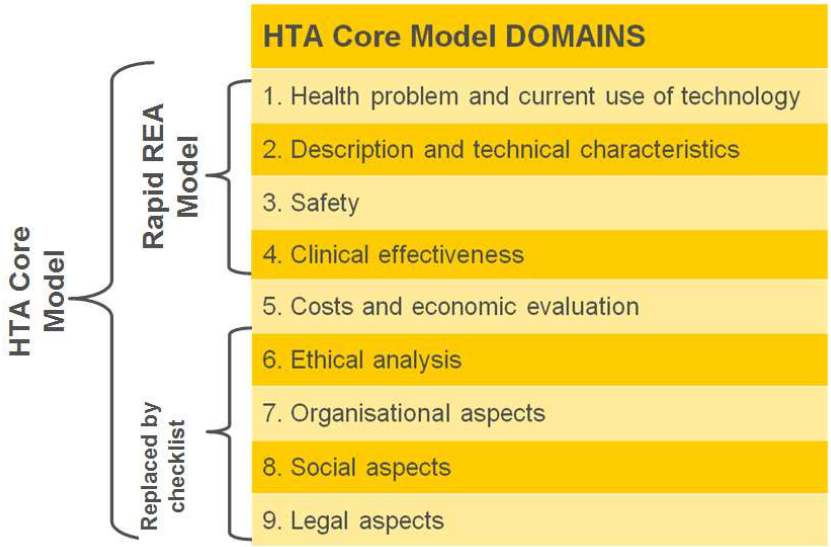
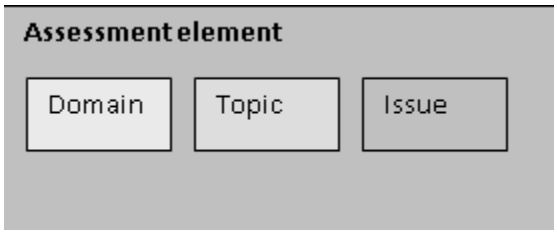


Figure 2: An assessment element



The HTA Core Model® organises the information by dividing it first into nine *domains* (*see Figure 1*). Each domain is divided into *topics*, and each *topic* is further divided into several *issues (see Figure 2)*. The *issues* are the generic questions that should be considered when assessing a health technology. The combination of a domain, topic, and issue defines an *assessment element* within the HTA Core Model® (more information at HTA Core Model®).

Since the Model for rapid REA is intended for assessments within a limited time frame, it covers only the first four domains of the HTA Core Model® *(see Figure 1)* and within these domains only a subset of issues. The purpose of dividing the assessment into specific domains is to facilitate the systematic presentation of information. The domains covered in the Model for rapid REA are briefly described below.

1.3. Domains

Description and technical characteristics of technology (TEC)

The information presented in this domain describes the technology (or a sequence of technologies) and its technical characteristics, e.g. mode of action/mechanism of action, when it was developed, for what purpose(s), who will be using it, in what manner, and at which level of health care. The regulatory and reimbursement status of the technology is listed when applicable.

The issues in this domain should be described in sufficient detail to differentiate the technology from its comparators. The relevant terms and concepts used should be used in a way that allows those unfamiliar with the technology to get an overall understanding of its use. It is important to distinguish between scientifically proven versus suggested mechanisms of action. Important terms should be defined and a glossary or list of product names provided. The section may include pictures, diagrams, videos or other visual material, in order to facilitate understanding for persons who are not experts in the field.

Health problem and current use of the technology (CUR)

The information presented in this domain describes the target conditions, target groups, epidemiology and the availability and patterns of use of the technology in question. Furthermore, it describes the burden – both on individuals and on society – caused by the health problem, as well as the alternatives to the technology in question. Some of the topics considered relevant for this domain have generally referred to 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, which is covered in this domain, includes the condition's underlying mechanism (pathophysiology), natural history (i.e. course of disease), available screening, diagnostic methods, prognosis and epidemiology (incidence, prevalence), underlying risk factors for acquiring the condition, as well as available treatments. A description of subgroups or special indications should be included especially when the technology does not target the whole population.

Clinical Effectiveness (EFF)

The information presented in this domain discusses the relative benefits of a (new) technology, which can be determined under experimental conditions (e.g. efficacy/ within the protocol of a randomised controlled trial (RCT)) or under routine conditions (e.g. effectiveness/ 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:
(a) the most relevant interventions should be directly compared where possible, and,
(b) studies should include patients who are typical of day-to-day health-care settings (Sox et al. 2009).
The scope of REAs is to determine the relative benefits of a technology under routine conditions, i.e. its effectiveness. Ideally, both types of data would be available from RCTs, allowing the assessment under ideal circumstances underpinned by data obtained under routine conditions.
Effectiveness could as well, as supportive measure of the two data sources mentioned above, be estimated with real world data (non-RCT studies). Once the extent of the effect obtained in experimental designs is known, it can be additionally checked by observational designs to evaluate the external validity or generalizability of the effect.

The assessment of health benefits should primarily consider clinically meaningful endpoints such as mortality, morbidity and quality of life (QoL). Surrogate endpoints act as substitutes for clinically meaningful endpoints and are expected to predict the effect of the technology (benefit and/or harm). Surrogate endpoints should only be used if they are validated adequately. The level of evidence, the associated uncertainties and the limits of their use should be explained explicitly.

Safety (SAF)

The information presented in this domain describes the direct and indirect harms of a technology for patients and staff and how to reduce the risk of harms. There is usually a spectrum of known and unknown harms, which can be intended or unintended, of different seriousness, and dose or time dependent. The harmful effects of a technology are essential in quantifying the net benefit (benefit minus harms) of an intervention. The harms are identified and quantified in terms of frequency, incidence, severity and seriousness, and are then compared to those of the comparator(s).

Uncertainties due to restricted knowledge base (small numbers, short follow-up) should be addressed when serious or late harms can be expected foremost if the technology is compared to well-established comparator(s).

Checklist for potential ethical, organisational, social and legal aspects

The other five domains (i.e. on costs, ethical, legal, social and organizational issues) were excluded from the Model for Rapid REA because the information contained therein is highly context dependent and has therefore limited transferability. However, ethical, organisational, social and legal aspects that may need to be addressed in-depth are covered by a short checklist (See Appendix 3: *Template 3. Checklist for potential ethical, organisational, social and legal aspects*). If the response to a question in the checklist is 'yes', further analysis may be warranted, otherwise the checklist of questions does not need to be considered further. Since the assessment is comparative in nature, only those issues for which a difference exists between the technology to be assessed and its major comparator(s) should be described.

Relevant assessment elements from these four domains may be selected from the HTA Core Model®. Pre-established 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 technology will lead to changes.

2 METHODS

2.1. Setting the general scope of the assessment

Key messages for scoping

- Scoping should be performed according to the PICO structure (See Appendix 3 *Template 1. Format for scoping the assessment*).
- The choice of comparator and outcomes should be justified explicitly in the assessment.
- Consultation with the sponsors of technologies under assessment regarding the scope of the assessment may be a valuable source.
- During the scoping phase, the *Checklist for potential ethical, organisational, social and legal aspects* should be completed.
- At the end of the scoping phase, a final project plan will have been completed.

The first step in a rapid REA is to specify what should be assessed (i.e. the scope) following the so-called PICO structure. PICO stands for:

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

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 because of, e.g. a subpopulation of special interest, or the absence of data for the population defined in the scope. The following considerations are relevant regarding the PICO elements in the context of a rapid REA.

- **Population/patients with the disease of interest.** For pharmaceuticals, an initial definition of patients who will receive the intervention is generally provided by the marketing authorisation, which in turn is based on the evidence provided by the manufacturer/marketing authorisation holder. For other technologies, HTAs, guidelines, reviews and developers/manufacturers are relevant sources that can be used. The purpose of use of the technology should be specified, for example, first- or second- line treatment or whether the intended purpose is treatment or prevention.

- **Intervention(s).** The dose(s) and frequency of the technologies and their comparators is a crucial issue. This is true for direct, as well as indirect, comparisons. For example, when the comparator (or one of the comparators) is a pharmaceutical administered at low doses, this will lead to over-estimation of the technology's efficacy or effectiveness and estimation of safety will be compromised. For pharmaceuticals specifically, dose comparisons are useful when the doses, dosing schedules and the route of administration are consistent with those recommended in the marketing authorisation. Familiarity with the recommended doses (including equivalent doses) of each comparator and knowledge of their dose–response relationships are a prerequisite for interpreting the results of the comparisons.

- **Comparison(s).** The comparator(s) should be chosen carefully, preferably based on 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. In the context of a rapid REA, the number of comparators should be limited. **The choice of comparators should be justified explicitly in the report.**

- **Outcomes.** For the assessment of relative effectiveness, consideration must be given to the appropriateness of the outcome variables on which information on the intervention's effect is available.
  When surrogate variables (e.g. low-density lipoprotein cholesterol concentration; blood pressure) are used as outcome measures, the clinical validity of these measures needs to be considered. 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.
  When possible, adverse events relevant for the assessment should be identified in advance and should be listed in the scope. **The choice of outcomes should be justified explicitly in the report.**

A template for reporting the scope is included in Appendix 3 (*Template 1. Format for scoping the assessment*).

2.2. How to work with the assessment elements

Assessment elements are the standardised parts of HTA information. Every answer to the issues defined by the assessment elements is recorded as a structured piece of information.

Key messages for the assessment elements table

- Assessment elements are standardised pieces of HTA information.
- Each domain has specific assessment elements that contain issues, i.e. generic research questions that can be answered for that domain.
- In all domains, each issue should be considered individually for its relevance for the rapid REA.
- The selected issues should be translated into actual research questions (answerable questions).

Selecting relevant issues from the model

In this phase the research team(s) should go through all the domains they are interested in and consider each issue (i.e. the generic questions in the relevant assessment element table) one by one. Each issue should be defined either as relevant or irrelevant.
The issues defined as relevant will be studied in the assessment or they can be tagged as "consider later" to allow flexibility in the working process. The relevance is based on whether the issue presented is relevant in the context of the particular technology that is being assessed. One should be practical: not to try to find "artificial" relevance, but not to reject issues too easily as irrelevant either.
If an issue is considered relevant, but no data are available to answer the question, it should be reported in the assessment. Thus, issues should not be excluded based on a lack of data, but the gap in evidence should be identified and reported. In these cases, further studies can be recommended, after their feasibility has been confirmed.

Further assessment elements from the HTA Core Model® applications for *medical and surgical interventions, screening,* pharmaceuticals or *diagnostic technologies,* which are not contained in the Model for Rapid REA, could also be screened and included in rapid REAs when deemed relevant.

Formulating research questions

In this phase, the authors should translate the issues 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 with which the authors can proceed.

2.3. Collecting and analysing data

Information sources

The following information sources can be used (see also Appendix 1):

- General medical databases: e.g, Medline, Embase
- Specialised databases: e.g. CINAHL, ERIC
    - Administrative databases: e.g Emerald Library, Pub Med Central
- Trial registers: e.g. Clinical Trials, WHO International Clinical Trials Registries Platform portal
- Databases on specific study designs: e.g. DARE, NHS EED
- Useful other sources:
    - Surveys, epidemiological research, national and regional guidelines, routine statistics and administrative databases, conference proceedings (Web of Science Database), expert opinions
    - Additional information can be collected also from contacts with manufacturers, e.g. Submission Files

For pharmaceuticals:

- EPAR including the Summary of Product Characteristics (SPC), of the pharmaceutical of interest. The availability of the EPAR and SPC depends greatly on the timing of the assessment. In case of an early assessment (before marketing authorisation), the documents may not yet be available. Therefore, the Committee for Medicinal Products for Human Use (CHMP) report, or a draft of the EPAR can be used initially for drafting first versions of the rapid REA. However in the final stages of the assessment preparation, information should be checked against the EPAR and SPC for inconsistencies.
- EPARs, including SPCs of comparators.
- Original unpublished studies that are relevant for the rapid REA in the format of Clinical Study Reports (CSRs). Unpublished data should only be included in the assessment if the authors are allowed to present the data in the report.

Literature search

A systematic literature search needs to be performed. This literature search can be provided either within a submission file completed by the sponsors or it should be conducted by the authors.

All final search strategies should be included in the rapid REA, including searches for ongoing trials in clinical trial registries, e.g. ClinicalTrials.gov.

For guidance on domain specific information sources please refer to Summarized Research in Information Retrieval for HTA (SuRe Info); available from: http://vortal.htai.org/?q=sure-info).

Appropriate study types

Health problem and current use and *Description and technical characteristics of the technology*
There is no single methodological approach that can be applied to all issues in these domains. Descriptive and observational study designs, narrative reviews, surveys, observational and qualitative research, registry analyses and market research reports, as well as guidelines and consensus statements, can be used for compiling the domains.

Efficacy and effectiveness data
The generally accepted standard for demonstrating a causal relationship between an intervention and health outcomes is an appropriately designed and conducted RCT. Therefore, as a general rule, RCTs should be considered for assessing the health benefits of a technology and ideally, for a rapid REA most of the data should be retrieved from RCTs. A (well-conducted) meta-analysis of the results of more than one RCT provides the highest level of evidence. Non-randomised intervention studies or observational studies can be considered where an RCT has not been conducted, published yet or is not feasible, or complementary data are 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 access/authorisation. Generally, information on the benefit under routine conditions may be collected in trials with a pragmatic approach (a trial setting that corresponds to usual circumstances of health care 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.

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 a higher risk of bias may be necessary when harms are unknown, rare, or occur only in long follow-up. Such sources may include observational studies, country registries and published case reports.

Quality appraisal

Health problem and current use and *Description and technical characteristics of the technology*
Quality assessment of the information retrieved may be difficult, as there is often no standard way of assessing it and because many aspects and facets must be taken into account when information is evaluated in terms of its quality. The validity of the information may differ considerably depending on the type and source of information requested (quantitative or qualitative; registries, administrative data, etc.). Appropriate methods for appraising the available evidence should be selected considering the target level of detail and precision in providing information on these domains.

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 risk of bias. The risk of bias concept should be used to assess the internal validity of clinical studies within a rapid REA. The risk of bias should be assessed on two levels, i.e. first, 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 a rapid REA, guidance on how to deal with studies with a high or unclear risk of bias should be specified in advance. There are three main options:

a. Rely only on studies with a low risk of bias;
b. Perform sensitivity analyses according to the different risk of bias categories; or
c. Describe the uncertainty with regard to the different levels of risk of bias, so that subsequent decisions can be made considering this uncertainty.

Safety data
Methods used to assess bias should be described clearly, and the risk of bias regarding the information sources and how the data was collected should be reported. The way risk of bias information was used in the rapid REA should be explained clearly.

Timelines 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.

Effect measures and confidence intervals

A number of measures of the intervention's 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 Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiler (See 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 versus 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.

A measure of the precision of the effect estimate (standard error or confidence interval [CI]) 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 AEs 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). Randomised trials are methodologically most solid, and may alone be an appropriate source of evidence for some review questions about harm. However, safety reporting in randomised trials is heterogeneous and often inadequate. Rare adverse effects are not usually detected in randomised trials, and even relatively frequent harms with a longer latency period cannot be quantified easily. Information about new, serious, rare or long-term adverse effects are thus typically found in observational studies (cohort, case-control and cross-sectional studies). Risk of late-onset harms (e.g. number of radiation-induced cancers) can be estimated based on analogies and assumptions from epidemiological studies. In cases where AEs are incorporated in utility values of QoL, the source of the quantification should be accessible.

Extrapolation of efficacy to give relative effectiveness data

Ideally, for a rapid REA most of the data is retrieved from high-quality 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).

In the case of surrogate outcomes, **transformation** into patient-relevant final outcomes of treatment should be considered (AGDH, 2008).

It may be relevant for a rapid 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.

Interpreting evidence

At this stage, the authors of a rapid REA should check that the data extracted are relevant to the research questions formulated at the start of the process, and that analysing and synthesising the data continues to answer the questions. Often, the evidence available is not quite as useful as anticipated; in such cases, a clear report should be made on how well the evidence answers the original research question. Cases in which no data were available should also be reported.

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 report. There are several ways to provide this information. In many cases, plain text is sufficient; in others, an evidence table would be helpful.

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 a rapid REA 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.

Evidence tables, therefore, should be part of each rapid 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 elements but that could have an impact on the results. Although the items reported in each cell will be driven by the review questions, 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.

To interpret 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% CI 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 primary and secondary outcome as is done when developing the project plan).
    - Identify knowledge gaps by comparing the research questions (including the predefined outcome) with the available evidence.

To allow transfer of data across countries, rapid 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, but rapid REAs should not contain recommendations for or against technologies assessed.

2.4. Reporting

In order to assess relative effectiveness, 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). The following, at least, should be included:

- Scope: description of the technology; description of comparators; description of the health problem; description of the current treatment.
- Results: description of available evidence and ongoing trials; description of relative effectiveness results; description of relative safety results;
- Summary table of relative effectiveness (a template for writing the summary can be found in Appendix 3 *(Template 2: Summary 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 technology is less, similarly, or more effective and safe; conclusion as to whether further research is required.

3 ASSESSMENT ELEMENTS TABLE

This table presents all the selected assessment elements for the Model for rapid REA. The ID, topic, issue and clarification is provided.

ID	Topic	Issue	Clarification
Description and technical characteristics of the technology			
B0001	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 that scope and elaborate them here in more detail. Technology may include a single device, a questionnaire, imaging or sequence of technologies. The HTA may address one or several similar technologies. Describe separately for the technology and the comparator: the type of device, technique, procedure or therapy, its biological rationale and mechanism of action; and also, describe how the technology differs from its predecessors, and the various current modifications or different manufacturers' products, especially if the differences affect performance.
A0020	Regulatory status	For which indications has the technology received marketing authorisation or CE marking?	There are both international and national market authorisation systems. The systems differ between countries and are more established for pharmaceuticals than for medical devices. An overview of the status with regard to key processes, e.g. CE marking, EMA/US Food and Drug Administration (FDA) approval is recommended. In case the technology is authorised under a different process, e.g. adaptive licensing or conditional reimbursement, information should be presented. Also, information on national data and an analysis of possible discrepancies can be useful. <u>Specific to diagnostic technologies:</u> Imaging devices may require approval. Substances needed for obtaining images may require additional approval (e.g. radiotracers). In some cases, the approval for primary screening is different to that for clinical use (FDA recently licensed tests explicitly for screening), but in most cases, approval is obtained for diagnostic use and the test is proposed for screening without any other formal approval. <u>Specific to screening technologies:</u> Imaging devices may require approval. Substances needed for obtaining images may require additional approval (e.g. radiotracers). In some cases the approval for primary screening is different to that for clinical use (FDA recently licensed tests explicitly for screening), but in most

ID	Topic	Issue	Clarification
			cases approval is obtained for diagnostic use and the test is proposed for screening without any other formal approval.
B0002	Features of the technology	What is the claimed benefit of the technology in relation to the comparators?	This issue is especially relevant in new technologies with uncertain expectations and claims of benefit. Describe the following aspects: • How is it expected to be an improvement over previous/existing technologies used for the same health problem? • 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 is it intended to replace or to supplement existing technologies?
B0003	Features of the technology	What is the phase of development and implementation of the technology and the comparator(s)?	Most technologies will be introduced at approximately the same time in several countries. 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. For end-users it is useful to know whether new versions or adaptations of the technology are expected in the near future. Describe the following aspects: • Is the technology an innovation? • When was it developed? • Is the technology only partially innovative (i.e. a modification of an existing technology), and in that case, is it possible to specify the degree of innovation the technology may represent? • When was the technology introduced into health care? • Is the technology an already established one, but now used in a different way, for instance for a new indication? This issue may be less relevant for new pharmaceuticals. • Is it experimental, emerging, established in use or obsolete (implementation level)? • Is the technology field changing rapidly? • How does this technology differ from its predecessors (other technologies used for similar purposes)? • Are there new aspects that may need to be considered when applying it? • 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,

ID	Topic	Issue	Clarification
			organisational, social and ethical domains?
B0004	Features of the technology	Who administers the technology and the comparators and in what context and level of care are they provided?	This issue should be answered in case there is a relevant difference between the technology and the comparator. Describe the following aspects: • Which professionals (nurses, doctors, and other health-care 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 the technology or interpret the outcome? • Are there certain criteria (skills, function, training requirements) for the patients or professionals who will administer the technology? 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. Its role in the management pathway can be presented as a replacement, an add-on or for triage.
B0008	Investments and tools required to use the technology	What kind of special premises are needed for the technology and the comparator(s)?	This issue should be answered in case there is a relevant difference between the technology and the comparator. Many technologies require purpose-built premises, such as radiation-secured areas, Faraday cages, dressing rooms for the patient, or specific premises equipped with fume cupboards for storage and reconstitution of chemotherapy pharmaceuticals. Typical premises in primary or secondary care may differ markedly from country to country. A clear description of necessary facilities is needed instead of a general statement (e.g. to be used in hospitals only). This issue may be less relevant for pharmaceuticals.
B0009	Investments and tools required to use the technology	What supplies are needed for the technology and the comparator (s)?	This issue should be answered in case there is a relevant difference between the technology and the comparator. Examples are syringes, needles, pharmaceuticals and contrast agents, fluids, bandages and tests to identify patients eligible for treatment.
A0021	Regulatory status	What is the reimbursement	Information on national reimbursement status from different countries for the technology as well as the comparators, including key dates and anticipated licensing time frame. Information on full

ID	Topic	Issue	Clarification
		status of the technology?	coverage, co-payments and coverage under special circumstances/conditional coverage is useful.
Health problem and current use of technology			
A0002	Target condition	What is the disease or health condition in the scope of this assessment?	Use the target condition and International Classification of Diseases (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, subtype, 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 for the society (A0006).
A0003	Target condition	What are the known risk factors for the disease or health 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 prevalence of the various risk factors might differ in different geographic areas and among different subpopulations.
A0004	Target condition	What is the natural course of the disease or health condition?	This assessment element should provide information on the prognosis and course of the health condition when untreated. This information is relevant for appraising the overall value of the technology. 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. This element should also provide information on the time lag between the onset of disease and the symptoms or other findings that eventually trigger the need of diagnostics and care.
A0005	Target condition	What are the symptoms and the burden of disease or health condition	This element should describe the patients' relevant symptoms before intervention with the technology, their severity and whether they are persistent, intermittent or undulating taking into account different stages of the disease. Patients' perceptions of the burden of the disease are not always in line with the clinical seriousness of the disease or its societal burden.

ID	Topic	Issue	Clarification
		for the patient?	
A0006	Target condition	What are the consequences of the disease or health condition for the society?	Describe consequences and burden of the disease or health condition by providing information on 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, QoL, quality-adjusted life years (QALYs).
A0024	Current management of the condition	How is the disease or health condition currently diagnosed according to published guidelines and in practice?	The effectiveness of an intervention may vary in populations which are diagnosed by different diagnostic pathways. 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.
A0025	Current management of the condition	How is the disease or 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 different disease stages? Deviation from evidence-based guidelines may suggest over- or under-use of the technology. Identification of practice variations due to the differences in the forms, stages or severity of the disease may imply differences in the quality of health care. Different stages of disease may call for different therapeutic procedures (e.g. aortic insufficiency is first treated with medication, and at a certain point of cardiac structural changes, an operation is preferred). Provide an overview of other treatment alternatives. Likewise, diagnostic or monitoring methods used for various diseases may vary depending on the stage of disease.
A0007	Target population	What is the target population in this	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

ID	Topic	Issue	Clarification
		assessment?	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. Point out e.g. if certain populations should be excluded from the analysis.
A0023	Target population	How many people belong to the target population?	This information can be used to give an idea of the resource requirements in general for implementing the technology. Estimates of incidence and prevalence should be provided. Estimates of likely relevant increases or decreases in the size of the target population in the future should also be included.
A0011	Utilisation	How much are the technologies utilised?	Provide national estimates for current and future utilisation rates for the indication under assessment, 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 technology by 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. Specific to screening technologies : What is the current rate of screening adherence?
Clinical Effectiveness			
D0001	Mortality	What is the expected beneficial effect of the technology on mortality?	Report the results both in absolute terms and relative to the comparator. Mortality is the preferred, objective endpoint for assessments of life-threatening conditions. Overall mortality, disease-specific mortality and mortality due to causes other than the target disease are distinguished. 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 HR (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. 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). Disease-specific mortality is a proportion of all-cause mortality. It should be noted that even if a

ID	Topic	Issue	Clarification
			given treatment reduces one type of death, it could increase the risk of dying from another cause, to an equal or greater extent. Disease-specific mortality is typically presented as rates and as age- and risk-adjusted measures such as HR. 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. Mortality due to causes other than the target disease includes all unintended, either positive or negative effects of the technology on mortality. There may be e.g. a 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. Supplement with relevant data if differences can be expected for specific subgroups. 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 cause, to an equal or greater extent. Disease-specific mortality is typically presented as rates and as age- and risk- adjusted measures such as HR. It is a frequently used endpoint in screening trials, where it is considered to be subject to bias. Supplement with relevant data if differences can be expected for specific subgroups. Specific to diagnostic technologies: In diagnostic and screening technologies, this issue refers to the expected beneficial effect of the test-treatment chain. Specific to screening technologies: In diagnostic and screening technologies, this issue refers to the expected beneficial effect of the test-treatment chain. With screening tests, one should consider the effects of lead-time bias, length-time bias and selection bias to the mortality.
D0005	Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or	Report the results both in absolute terms and relative to the comparator. Describe the efficacy and effectiveness of the technology on relevant disease outcomes (symptoms and findings). Outcomes such as function, QoL and patient satisfaction are reported in other assessment elements of this domain. Report changes in severity, frequency and recurrence of symptoms and findings. Supplement with relevant data if differences can be expected for specific subgroups. (See guideline on *Endpoints used for REA of pharmaceuticals – Clinical endpoints*).

ID	Topic	Issue	Clarification
		health condition?	
D0006	Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	Report the results both in absolute terms and relative to the comparator. Report here efficacy and effectiveness outcomes such as complete cure, progression-free survival, time-to-event, next stage of disease, relapse. Describe here the duration of treatment effect on symptoms and findings: permanent, short-term, long-term, intermittent, undulating. Supplement with relevant data if differences can be expected for specific subgroups.
D0011	Function	What is the effect of the technology on patients' body functions?	Report the results both in absolute terms and relative to the comparator. 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. Supplement with relevant data if differences can be expected for specific subgroups.
D0016	Function	How does the use of the technology affect activities of daily living?	Report the results both in absolute terms and relative to the comparator. Supplement with relevant data if differences can be expected for specific subgroups. Activities of Daily Living (ADL) is used in rehabilitation as an umbrella term relating to self-care, comprising those activities or tasks that people undertake routinely in their everyday life. The activities can be subdivided into personal care and domestic and community activities.
D0012	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. Supplement with relevant data if differences can be expected for specific subgroups. Health related quality of life (HRQoL) is typically measured with self- or interviewer-administered questionnaires to measure cross-sectional differences in QoL between patients at a point in time (discriminative instruments) or longitudinal changes in HRQoL within patients during a period of time (evaluative instruments). Two basic approaches to HRQoL measurement are available: generic instruments that provide a summary of HRQoL; and specific instruments that focus on problems associated with single disease states, patient groups, or areas of function. Generic

ID	Topic	Issue	Clarification
			instruments include health profiles and instruments that generate health utilities. Each approach has its strengths and weaknesses and may be suitable for different circumstances.
D0013	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. Supplement with relevant data if differences can be expected for specific subgroups. HRQoL is typically measured with self- or interviewer-administered questionnaires to measure cross-sectional differences in QoL between patients at a point in time (discriminative instruments) or longitudinal changes in HRQoL within patients during a period of time (evaluative instruments). Two basic approaches to HRQoL measurement are available: generic instruments that provide a summary of HRQoL; and specific instruments that focus on problems associated with single disease states, patient groups, or areas of function. Generic instruments include health profiles and instruments that generate health utilities. Each approach has its strengths and weaknesses and may be suitable for different circumstances.
D0017	Patient satisfaction	Were patients satisfied with the technology?	Describe patients' overall perception of the value of the intervention and their satisfaction with the treatment. For further information, see guideline on *Endpoints used for REA of pharmaceuticals – Clinical endpoints*.
D0032 (for diagnostics and screening technologies only)	Morbidity	How does the test-treatment intervention modify the magnitude and frequency of morbidity?	A more accurate replacement test could improve treatment and effectiveness. A satisfactory triage test may decrease the number of adverse outcomes from another test. An add-on test may increase sensitivity so that more patients receive proper treatment and thus improved outcomes.
D1001 (for diagnostics and screening technologies only)	Test accuracy	What is the accuracy of the test against reference standard?	Accuracy in terms of sensitivity and specificity, and other measures such as likelihood ratios, pre-test probabilities, SDORs, area under the curve (AUC) or Q*.
D1005	Test	What is the	Sensitivity and specificity vary according to the threshold value. Optimal combination of sensitivity

ID	Topic	Issue	Clarification
(for diagnostics and screening technologies only)	accuracy	optimal threshold value in this context?	and specificity defines optimal threshold value. The optimum depends on the consequences of the test results, e.g. whether it does more harm to overlook a case or to treat someone unnecessarily. Specific to screening technologies: In screening programmes, one should consider separately the screening test and the subsequent diagnostic tests.
Safety			
C0008	Patient safety	How safe is the technology in relation to the comparator(s)?	Here, one should identify and describe the direct harms of the use and the administration of the technology and the comparator(s). Highlight the differences in the most important risks (i.e. the most severe and frequent harms) of the technology and its comparator and consider if there are uncertainties with regard to safety because of small numbers and/or short duration of follow-up. Consider: • What is the frequency and what are serious adverse events (SAEs) of the technology in relation to the comparator(s)? • What are the most frequent AEs of the technology in relation to the comparator(s)? • What is the frequency of discontinuation of treatment due to AEs of the technology in relation to the comparator(s)? • What is the frequency of SAEs leading to death for the technology in relation to the comparator(s)? • What is the frequency of unexpected AEs in participants and comparison groups?
C0002	Patient safety	Are the harms related to dosage or frequency of applying the technology?	This is usually relevant with pharmaceuticals but may also be relevant with medical 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 HTAs. 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. Specific to pharmaceuticals:

ID	Topic	Issue	Clarification
			For further information, see guideline on *Endpoints used for REA of pharmaceuticals – Safety*.
C0004	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?
C0005	Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	Typically, people with comorbidities and co-medication, pregnancy, intolerances, specific genetic profiles, elderly people, children and immunosuppressed patients. Are there any relevant contraindications or interactions with other technologies?
C0007	Patient safety	Are the technology and comparator(s) associated with 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 guideline on *Endpoint used for REA of pharmaceuticals – Safety*.
B0010	Investments and tools required to use the technology	What kind of data/records and/or registry is 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 clinical indications, specified populations, prescriber information, inpatient or outpatient use, test results, review period and health outcomes. In case of new technologies, consult the EVIDENT database. Specific to pharmaceuticals: refer to the SPC and EPAR.

ID	Topic	Issue	Clarification
		of the technology and the 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.
C0006 (for diagnostic and screening technologies only)	Patient safety	What are the consequences of false-positive, false-negative and incidental findings generated by using the technology from the viewpoint of patient safety?	What are the consequences of false-positive, false-negative and incidental findings generated by using the technology? False-negative test results (Type II error) identify sick people incorrectly as healthy with the possible consequence of incorrectly rejected or delayed treatment. The volume of false-negative test results can be estimated to be 1-sensitivity of the test. False-positive test results (Type I error) identify healthy people incorrectly as sick with the possible consequence of over-treatment. The volume of false-positive test results can be estimated to be 1-specificity of the test. Incidental findings in tests carry major risk of over-diagnosis and over-treatment. <u>Specific to screening technologies :</u> In screening programmes, one should consider separately the false-negative screening test results and the subsequent false-negative diagnostic test results.

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Appendix 1. Information sources

Registries

Registries may act as an important information source for those involved in the conduct of health technology assessments (HTAs). Although registries are usually managed by medical societies, scientific associations, or government institutions, industry-managed registries also exist. Registries collect data for a defined geographical area, usually a single country; however, regional or even European registries also exist. Registries commonly release periodic reports for disseminating findings and results. The reports are often open-access and downloadable free of charge from the homepage of the registry. Dissemination is also achieved by publishing specific studies or reports in specialised peer-reviewed journals. Types of registries included are disease, technology and procedure registries.

Disease registries

Disease registries gather information on the natural history and/or 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 one's life (e.g. heart attack), thus a single person might be represented several times in the registry. When appropriately designed, disease registries allow assessment of the utilisation and dissemination of different diagnostic strategies or technologies in the care of persons with the target 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 maintains a number of registries including the pharmaceutical registry, the cause of mortality registry, and the registries containing the diagnoses of all hospitalised patients in Sweden.
(Available from:
http://www.kvalitetsregister.se/hittaregister/allaregister.4.72f32ee2142b812430434f.html).

The 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. (Available from: https://www.bhf.org.uk/research/heart-statistics).

Technology registries

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

Quality registries 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. (Available from: http://www.socialstyrelsen.se/statistics).

Pharmaceutical registries

In contrast to technology registries, pharmaceutical registries are initiated to obtain data on safety and effectiveness *after* marketing authorisation. Doubt on the generalisability of study data and volume of consumption are major drivers to set up a pharmaceutical reimbursement registry.

Utilisation registries

- Norwegian pharmaceutical prescription database. (Available from: http://www.norpd.no/).
- Dutch utilisation information. (Available from: http://www.gipdatabank.nl/index.asp?scherm=homepage&infoType=g).
- The Anatomical Therapeutic Chemical (ATC) classification system with the Defined Daily Dose (DDD): The ATC/DDD system is a tool for exchanging and comparing data on pharmaceutical use at international, national, or local levels. (Available from: http://www.whocc.no/).

Regulatory institutions and legal framework

The European Medicines Agency

The European Medicines Agency (EMA; www.ema.europa.eu) is responsible for the scientific evaluation of applications for European marketing authorisations for 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 an European Public Assessment Report (EPAR) (Available from: 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 human immunodeficiency virus/acquired immune deficiency syndrome (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.
- The EMA becomes involved in the assessment of medicines that do not require the centralised procedure; such cases may be referred to the EMA because of a disagreement in authorisation or use of the medicine between two or more member states, or because of some other issue that requires resolution in the interest of protecting public health.
- The 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.
- The EMA can be considered as the 'hub' of a European medicines network comprising over 40 national competent authorities in 30 European Union (EU) and European Economic Area–European Free Trade Association (EEA–EFTA) countries, the European Commission, the European Parliament, and a number of other decentralised EU agencies.
- In many countries, over-the-counter (OTC) medicines are controlled by a regulatory agency. OTC pharmaceuticals are usually regulated by active pharmaceutical ingredients (APIs), not final products.

The US Food and Drug Administration

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; that cosmetics are safe; and that electronic products, which emit radiation, are safe. The FDA also ensures that these products are honestly, accurately, and informatively represented to the public.

- Drug labelling refers to all of the printed information that accompanies a drug, including the label, the packaging, and the package insert. The FDA requires that drug labelling be balanced and not misleading. The label must be scientifically accurate and provide clear instruction to healthcare practitioners for prescription drugs and to consumers for OTC drugs and supplements. Labelling 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 requirements for medical devices

The government of each European member state is required to appoint a **Competent Authority (CA)** responsible for medical devices. The CA is a body with authority to act on behalf of the government of that member state to ensure that the requirements of the Medical Device Directive are transposed into national law and are applied. The CA reports to the Minister of Health in the specific 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 the 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. There is no common database for CE marked products. Although, under the European Directives on technical harmonisation, certain bodies, so called Notified Bodies are responsible for assessing the conformity of the products covered by 'New Approach' Directives[1] and there is a database that lists these Notified Bodies. In the NANDO database **(New Approach Notified and Designated Organisations)** you can fi nd the Notified Bodies appointed by the Member States for conformity assessment of products covered by the Directives. Notified Bodies can be located by Directive or by country via the **NANDO** homepage: http://ec.europa.eu/growth/tools-databases/nando/. Therefore knowing the CE mark code the NB that issued the CE mark can be located.

The International Organization for Standardization (ISO) standards for medical devices are covered by:

- ICS 11.100.20 standard for biological evaluation of medical devices (Available from: 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 (Available from: http://www.iso.org/iso/iso_catalogue/catalogue_ics/catalogue_ics_browse.htm?ICS1=11&ICS2=040).

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

Packaging standards

Packaging and size/content of drugs and packaging of medical devices 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 health care professionals. A series of special packaging tests is used to measure the ability of the package to maintain sterility. Relevant standards include: American Society for Testing and Materials (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 – Part 1: General requirements and test methods; and ISO 11607 Packaging for terminally sterilised medical devices.

Medical Device Directive

The Medical Device Directive (Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, Official Journal of the European Union L 169 of 12/07/1993; available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31993L0042:EN:HTML) is intended to harmonise the laws relating to medical devices within the EU (currently under revision). The 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 Directive have to be met. Manufacturers' products meeting 'harmonised standards' have a presumption of conformity to the Directive. Products conforming to the Directive must have a CE mark applied. The Directive was most recently reviewed and amended by Council Directive 2007/47/EC and a number of changes were made. Compliance with the revised Directive became mandatory on March 21, 2010.

There is a specific **in vitro diagnostic** (IVD) Directive (European Council Directive 98/79/EC on IVD medical devices).

[1] The European Union directives, known as the "New Approach Directives", define "essential requirements" related to health, safety and environmental issues. Products must meet these requirements in order to be placed on the European market.

National and international safety-monitoring systems (databases)

These systems may be managed by a national statutory body or by a supranational body.

- International Atomic Energy Agency (IAEA): Safety standards for diagnostic radiology (Available from: http://www-pub.iaea.org/MTCD/publications/PDF/Pub1206_web.pdf)
- IAEA: Radiological protection of patients (Available from: http://rpop.iaea.org/RPoP/RPoP/Content/index.htm)
- ICRP: Publications of International Commission of Radiological Protection (Available from: http://www.icrp.org/)
- Australian Government – Department of Health: Therapeutic Goods Administration (TGA) (Available from: http://www.tga.gov.au/index.htm)
- FDA MedWatch safety alert system (Available from: http://www.fda.gov/medwatch/safety.htm)
- The MHRA: Medicines & Healthcare products Regulatory Agency (Available from: https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency)

Current diagnostic and treatment guidelines (A0024 & A0025)

Name	Link
AHRQ – The Agency for Healthcare Research and Quality (US Department of Health and Human Services)	http://www.ahrq.gov/
CADTH – Canadian Agency for Drugs and Technologies in Health	http://www.cadth.ca/en
EDQM – The European Directorate for the Quality of Medicines & HealthCare	http://www.edqm.eu/en/Homepage-628.htm I
FDA – U.S. Food and Drug Administration	http://www.fda.gov/
MSAC – Medical Services Advisory Committee (Australia)	http://www.msac.gov.au/
NHS Evidence – Free access to clinical and non-clinical health information and evidence, guidance and government policy	http://www.evidence.nhs.uk/default.aspx
PBAC – Pharmaceutical Benefits Advisory Committee (Australia)	http://www.health.gov.au/internet/main/publishing.nsf/Content/health-pbs-general-listing-committee3.htm#pbac
SIGLE – OpenSIGLE, System for grey literature in Europe (until 2005)	http://opensigle.inist.fr /
TGA – Therapeutic Goods Administration (Australia)	http://tga.gov.au/
TRIP database – Clinical search tool to identify evidence for clinical practice	http://www.tripdatabase.com/
WHO – World Health Organization	http://www.who.int/en/
National Guidelines Clearinghouse	http://www.guidelines.gov
SIGN	http://www.sign.ac.uk/guidelines/

NICE	http://guidance.nice.org.uk/CG/Published
Cochrane collaboration	http://www.cochrane.org

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

List of websites

National agencies information on reimbursement status or recommendations on reimbursement (A0021)

Country and Agency	Website
Australia: Australian Government – Department of Health	http://www.health.gov.au/internet/main/publishing.nsf/Content/Pharmaceutical+Benefits+Scheme+%28PBS%29-1
Belgium: Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (RIZIV)/l'institut national d'assurance maladie invalidité (INAMI) Belgian Healthcare Knowledge Centre (KCE)	http://www.riziv.fgov.be/inami_prd/ssp/cns2/pages/SpecialityCns.asp http://kce.fgov.be/
Canada:Canadian Agency for Drugs and Technologies in Health (CADTH)	http://www.cadth.ca/en/products/cdr http://www.pcodr.ca
Czech Republic: State Institue for Drug Control (SÚKL)	http://www.sukl.eu
Finland: Social Insurance Institution of Finland (Kela)	http://www.kela.fi/in/internet/english.nsf
France: French National Authority for Health (HAS) Securite Sociale l'Assurance Maladie	http://www.has-sante.fr/portail/jcms/j_5/accueil http://www.codage.ext.cnamts.fr
Italy: Italian Medicines Agency (AIFA)	http://www.aifa.gov.it/
The Netherlands:Zorginstituut Nederland	http://www.medicijnkosten.nl/
Norway: Norwegian Medicines Agency	http://www.legemiddelverket.no/
Poland: Ministerstwo Zdrowia	http://www2.mz.gov.pl/wwwmz/index?mr=b4&ms=0&ml=pl&mi=0&mx=0&ma=2151
Portugal: National Authority of Medicines and Health Products (INFARMED)	http://www.infarmed.pt/portal/page/portal/INFARMED
Scotland: Scottish Medicines Consortium (SMC)	http://www.scottishmedicines.org.uk/
Spain: Ministerio de Sanidad, Servicios Sociales e Igualdad	http://www.msc.es/profesionales/farmacia/
Sweden: Dental and Pharmaceutical Benefits Agency (TLV)	http://www.tlv.se/beslut/sok/lakemedel/
Switzerland: Federal Office of Public Health (FOPH)	http://www.bag.admin.ch/themen/krankenversicherung/00263/00264/06695/10387/index.html?lang=en
UK: National Institute for Health and Care Excellence (NICE)	http://www.nice.org.uk/

1 Other sources
2

Agency	Website
AHRQ – The Agency for Healthcare Research and Quality (US Department of Health and Human Services)	http://www.ahrq.gov/
Canadian Agency for Drugs and Technologies in Health (CADTH)	https://www.cadth.ca/
The European Directorate for the Quality of Medicines & HealthCare (EDQM)	http://www.edqm.eu/en/Homepage-628.html
Medical Services Advisory Committee (MSAC) (Australia)	http://www.msac.gov.au/
NHS Evidence – Free access to clinical and non-clinical health information and evidence, guidance and government policy	http://www.evidence.nhs.uk/default.aspx
Pharmaceutical Benefits Advisory Committee (PBAC) (Australia)	http://www.pbs.gov.au/browse/medicine-listing
Open Grey: System for Information on Grey Literature in Europe	http://www.opengrey.eu/
TRIP database – Clinical search tool to identify evidence for clinical practice	http://www.tripdatabase.com/
World Health Organization (WHO)	http://www.who.int/en/
The Cochrane Collaboration	http://www.cochrane.org

Appendix 2. Shared methodologies

General guidance to critical appraisal of published studies and other information

Important notice: This appendix represents auxiliary content of the HTA Core Model® and will be updated and amended according to the HTA Core Model® during Joint Action 2 by November 2015.

Critical appraisal of systematic reviews
AMSTAR

Critical assessment of indirect comparisons

- http://www.ispor.org/workpaper/interpreting-indirect-treatment-comparison-and-network-meta-analysis-studies-for-decision-making.pdf
- http://www.ispor.org/workpaper/conducting-Indirect-treatment-comparison-and-network-meta-analysis-studies.pdf

Critical appraisal of guidelines

- AGREE is an international collaboration improving the quality of clinical practice guidelines by establishing a shared framework for development, reporting and assessment http://www.agreecollaboration.org
- GRADE Working Group recommendations for grading quality of evidence and strength of recommendations. http://www.gradeworkinggroup.org

Critical appraisal of observational studies
There are several checklists or scales on quality available but no consensus about using those. The most appropriate are:

- Newcastle Ottawa Scale http://www.cochrane.org/training/cochrane-handbook
- AHRQ: Systems to Rate the Strength Of Scientific Evidence http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=erta4 7
- Checklist of items that should be included in reports of observational studies (actually not meant for assessing quality): STROBE http://www.strobe-statement.org

Critical appraisal of diagnostic accuracy studies

- QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies
- STARD: The Standards for Reporting of Diagnostic Accuracy (STARD)
- PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
- GRADE: Grading of Recommendations Applicability, Development and Evaluation

Critical appraisal of modelling studies
International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has published a useful article describing the basic guidelines for conducting and reporting modelling studies (Weinstein 2003). It can be used also as guidance for using and critically appraising modelling studies. Furthermore, ISPOR is developing more specific guidelines on different modelling methods.

Critical appraisal of qualitative studies
Examples of quality assessment instruments:

- Critical Appraisal Skills Programme – CASP www.phru.nhs.uk/Doc_links/Qualitative%20Appraisal%20Tool.pdfQARI software by Joanna Briggs Institute. www.joannabriggs.edu.au/services/sumari.php
- EPPI-review by the EPPI Centre. http://eppi.ioe.ac.uk/eppireviewer/login.aspx
- Quality Framework UK Cabinet Office http://www.gsr.gov.uk/downloads/evaluating_policy/a_quality_framework.pdf
- Checklist of items that should be included in reports of qualitative studies (not checklist for assessing quality) COREQ http://www.aaz.hr/dokumenti/odjel-raz-ist-i-zdra-teh/edukativni-materijali/smjernice/7.%20Guidelines%20for%20qualitative%20research.pdf

- Popay et al (1998)
- The Mays & Pope criteria (2000)

Quality assessment of routine collected statistics and administrative data

Routine collected administrative data (e.g. DRG, discharge databases, reimbursement claims databases) can be useful too, when available. For example sickness funds collect great amounts of information which could be used to analyse utilisation of technology etc. However, analysis of this kind of data might be very time consuming, since data need to be "prepared" before analysis. By definition, these data has been collected for other purposes than research and they cannot be used to answer scientific questions without previous processing. This might not be feasible in the context of an HTA project, due to resource constraints.
The use of routine collected statistics has several limitations. The reliability of the diagnosis varies and usually it is not possible to differentiate between different stages of the disease. Even the validity of the coding of causes of death may be variable, and in some countries it is known to be very limited.
Own analysis of administrative data often requires authorization from the data owner, which in some countries might be difficult to obtain due to issues of privacy protection and confidentiality.

Critical appraisal of register data
ISPOR is developing guidelines for patient registry data:
http://www.ispor.org/sigs/PR_analysis_data_mgt.asp

Further information and tools provided by EUnetHTA

- Core Model Applications contain further potentially relevant assessment elements and methodological guidance for the different applications (i.e. pharmaceuticals, medical and surgical interventions, screening and diagnostic technologies).
- EUnetHTA Guidelines: Currently 11 guidelines have been published, 3 further are in development:
    1. Clinical endpoints
    2. Composite endpoints
    3. Surrogate endpoints
    4. Safety
    5. Health-related quality of life
    6. Criteria for the choice of the most appropriate comparator(s)
    7. Direct and indirect comparison
    8. Internal validity
    9. Applicability of evidence in the context of a relative effectiveness assessment
    10. Meta-analysis of diagnostic test accuracy studies
    11. Methods for health economic evaluations - A guideline based on current practices in Europe
    12. Internal validity of non-randomised studies (NRS) on interventions (in development)
    13. Therapeutic medical devices (in development)
    14. Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness (in development)
- Procedure Manual for Pharmaceuticals provides detailed information on the processes, organisation, timelines and organisation for the joint production of rapid REAs on pharmaceuticals within EUnetHTA (will be updated)
- Procedure Manual for other technologies provides detailed information on the processes, organisation, timelines and organisation for the joint production of rapid assessments on other technologies (i.e. medical and surgical interventions, diagnostic and screening technologies within EUnetHTA (will be updated)
- Submission File Template for pharmaceuticals and medical devices (link will be added, once published).

Appendix 3. Templates

Template 1. Format for scoping the assessment

Description	Project scope
Population	*[Describe the disease or health condition of interest. Provide corresponding ICD-10 code and medical subject headings (MeSH) terms]* *[Describe the target population; possible limitations for instance in age, sex, severity, stage or risk (e.g. men over 65 years, with low-to-moderate risk of having the disease, or adult patients with grade 3–4 disease). Provide MeSH terms]* *[Describe the intended use of the technology: treatment or prevention, first-line/second-line treatment]*
Intervention	*[Describe the intervention in sufficient detail to distinguish it from other relevant technologies: administration modes. Provide MeSH terms, if applicable]* *[Describe the intended use of the technology, e.g. if it is to be used for diagnostic, screening or therapeutic purposes]*
Comparison	*[Describe the comparator(s) for this assessment. The technology can be compared to e.g. another specific technology, management pathway without the technology, usual care, no intervention, or placebo.* ***Include the rationale for choosing the comparator.*** *Provide MeSH terms, if applicable]* *[See the guideline on Comparators and comparisons – Criteria for the choice of the most appropriate comparator(s)]*
Outcomes	*[Describe the most important effectiveness and safety outcomes for this assessment.* ***Include the rationale for choosing the*** *outcomes. See the guideline on Endpoints used for REA of pharmaceuticals – Clinical endpoints]*

Template 2: Summary of relative effectiveness

The following table will be provided as a summary of the quality of the body of evidence. This judgement is derived based on the risk of bias on study level and the risk of bias on outcome level. An overview of these findings for ALL outcomes is provided in the Table “Risk of bias – outcome level: summarised assessment”. Of these, the most critical outcomes, as defined in the project scope, are displayed in the summary table. For each endpoint, the quality of the body of evidence should be stated and the corresponding references should be cited.

Provide details on how the quality of the body of evidence was rated and explain what the judgements mean. For example, if you have used GRADE use:

- High = We are very confident that the true effect lies close to that of the estimated effect.
- Moderate = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimated effect, but there is a possibility that it is substantially different.
- Low = Our confidence in the estimated effect is limited: the true effect may be substantially different from the estimated effect.

If no evidence was found, indicate finding in the table.

[Indication] *The assessment element ID codes (e.g. D0001) refer to the result cards, which give details of the relevant results.*						
	Health benefit [add the no. of assessment elements]			**Harm [add the no. of assessment elements]**		
	Endpoint 1 [numerical estimate, CI]	**Endpoint 2** [numerical estimate, CI]	**Endpoint 3** [numerical estimate, CI]	**SAEs** [numerical estimate, CI]	**Other AEs** [numerical estimate, CI]	**Frequency of AEs** [numerical estimate, CI]
[Technology] **[Comparator 1]**	***[result numerical estimate (CI)]*** ***[add the references used for this endpoint]***	***[result numerical estimate (CI)]*** ***[add the references used for this endpoint]***	***[result numerical estimate (CI)]*** ***[add the references used for this endpoint]***	***[result numerical estimate (CI)]*** ***[add the references used for this endpoint]***	***[result numerical estimate (CI)]*** ***[add the references used for this endpoint]***	***[result numerical estimate (CI)]*** ***[add the references used for this endpoint]***
Quality of body of evidence+	***[summarise quality of evidence for endpoint]***	***[summarise quality of evidence for endpoint]***	***[summarise quality of evidence for endpoint]***	***[summarise quality of evidence for endpoint]***	***[summarise quality of evidence for endpoint]***	***[summarise quality of evidence for endpoint]***
[Technology] **[Comparator 2]**	***…..***	***….***	***….***	***….***	***….***	***….***
Quality of body of evidence+	***…..***	***….***	***….***	***….***	***….***	***….***

Abbreviations: AE=adverse event; CI=confidence interval; SAE=serious adverse event.
+Explain how the quality of evidence was rated, e.g. GRADE.

Template 3. Checklist for potential ethical, organisational, social and legal aspects

The following checklist is a short list of questions to determine whether there are specific ethical, organisational, social and legal aspects that also need to be addressed. Since the assessment is comparative in nature, only new issues, which arise from a difference between the technology to be assessed and its major comparator(s), should be dealt with. As a rule, already known problems/issues related to ethical, organisational, social and legal aspects, which are common to the technology to be assessed and its comparator(s), will not be addressed, as it is not expected that the addition of a new technology will lead to changes.
If the answer to a question is 'yes', further analysis of these issues may be warranted; if the answer is 'no', the domains need not be dealt with further. Examples are provided for clarification.

1. Ethical	
1.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	Yes/No
If answered with 'yes', please provide a short statement explaining why. *Example:* Routine introduction of prenatal genetic screening tests, which could lead to pregnancy termination, may cause ethical issues for the couple as well as for the health-care provider.	
1.2. Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	Yes/No
If answered with 'yes', please provide a short statement explaining why. *Example:* 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.	
2. Organisational	
2.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes?	Yes/No
If answered with 'yes', please provide a short statement explaining why. *Example:* The new intervention requires the establishment of specialised centres for administration.	
2.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	Yes/No
If answered with 'yes', please provide a short statement explaining why. *Example:* The new technology will replace a surgical intervention, which may lead to excess capacity in relevant areas.	
3. **Social**	
3.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any	Yes/No

new social issues?	
If answered with 'yes', please provide a short statement explaining why. *Example:* A new technology allows patients to return to the workplace, but since the technology can be seen by co-workers, it may lead to stigmatisation.	
3.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	Yes/No
If answered with 'yes', please provide a short statement explaining why. *Example:* A technology, which is widely used by persons with abuse problems, colours the tongue blue, thus, immediately identifying the user. Comparators do not have this property.	
4. **Legal**	
4.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	Yes/No
If answered with 'yes', please provide a short statement explaining why. *Example:* The comparator for the new technology is a pharmaceutical that is not licensed for the indication of concern, but is widely in use.	
4.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	Yes/No
If answered with 'yes', please provide a short statement explaining why. *Examples:* • The comparator for the new technology is a controlled, restricted substance, but the new medicine is not. • The most appropriate comparator for the new technology is available as a pharmacy-compounded medicine, but not as a finished product with marketing authorisation. *Note:* The assessment should not address patent-related issues.	

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2