EUnetHTA JA2
WP7 DELIVERABLE

Evidence submission templates to support production of core HTA information and rapid assessments: adaptation notes

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WP 7 Lead Partner: Haute Autorité de Santé (HAS)
WP Subgroup Coordinator: National Institute for Health and Care Excellence (NICE)

Abbreviations

ATC: Anatomical Therapeutic Chemical
CE: Conformité Européene (European Conformity)
CI: confidence interval
CONSORT: consolidated standards of reporting trials
DSM: Diagnostic and Statistical Manual of Mental Disorders
EEA: European Economic Area
EPAR: European Public Assessment Report
EU: European Union
GMDN: global medical device nomenclature
HRQOL: health-related quality of life
HTA: health technology assessment
ICD: International Classification of Diseases
ITT: intention-to-treat
PIL: patient information leaflet
PRISMA: preferred reporting items for systematic reviews and meta-analyses
QOL: quality of life
RCT: randomised controlled trial
REA: relative effectiveness assessment
RIS: Research Information Systems
RMP: risk management plan
SPC: summary of product characteristics
STROBE: strengthening the reporting of observational studies in epidemiology
US: United States
VnR: Nordic article number

Contents

Background

Agencies responsible for reimbursement often request an evidence submission from companies to support decisions on the reimbursement of pharmaceuticals and medical devices. The EUnetHTA evidence submission template is a flexible tool that can be used by reimbursement agencies as the basis of a company's evidence submission for regional or national processes and for joint assessments. The scope of the EUnetHTA evidence submission template is relative effectiveness assessment (defined by the HTA Core Model for rapid relative effectiveness assessment as health problem and current use of the technology, description and technical characteristics of the technology, safety and clinical effectiveness). Therefore currently, it does not include pricing, health economics or budget impact issues, or other domains of the HTA CORE model.

The evidence submission template was developed for use with pharmaceuticals and medical devices, and these are in separate documents, though the majority of sections are common to both types of health technology. The evidence submission template does not specifically cover other health technologies such as diagnostic technologies, procedures or services, although some sections may also be relevant.

The evidence submission template does not replace agencies' existing methods and processes. The template is a flexible tool, that is, agencies should choose sections and questions that are relevant to their specific decision-making criteria. The evidence submission template is available as a 'Word' template and agencies can add, remove and adapt questions. Agencies should also customise the evidence submission template to add further explanatory text so that it reflects their requirements. To support agencies with the adaptation process this document has been produced. These adaptation notes highlight areas that agencies should consider when adapting the evidence submission template.

The adaptation notes also link the questions in the evidence submission template to the HTA CORE model assessment elements and also to the existing EUnetHTA methodological guidance that supports the production of HTA assessments. In some instances questions in the submission template relate one-to-one to questions in the HTA CORE model (for example questions relating to the health problem), in other instances multiple questions may relate to a single assessment element in the HTA CORE model (for example questions relating to features of the technology). A single question in the evidence submission template may also relate to multiple assessment elements in the HTA CORE model (for example presentation of study results and conclusions). These differences reflect the different purposes of the evidence submission template and the HTA CORE model.

There are 2 versions of the evidence submission template that agencies can use to start the adaptation process. There is a 'long' version that includes all national evidence requirements from reimbursement agencies in Europe and a 'short' version

that includes only the most frequently requested information. The ‘long’ version of the evidence submission template contains more questions asking the company to describe the methodology of developing the submission (for example questions about study identification, critical appraisal and evidence synthesis) and therefore may be more suitable for agencies who do not do their own independent assessment. The ‘short’ version focuses on providing evidence (for example a list of studies and a summary of study results) and may be a suitable starting point for agencies that primarily use company submissions to support their own independent assessment of the technology. The adaptation notes include an index showing which questions are included in the short version of the evidence submission template. The ‘short’ version of the evidence submission template is currently used as the basis of the company submission in the EUnetHTA joint assessments.

Other documentation used to support reimbursement

The information requested in the evidence submission template should be used for assessments together with information from other commonly used documents, such as:

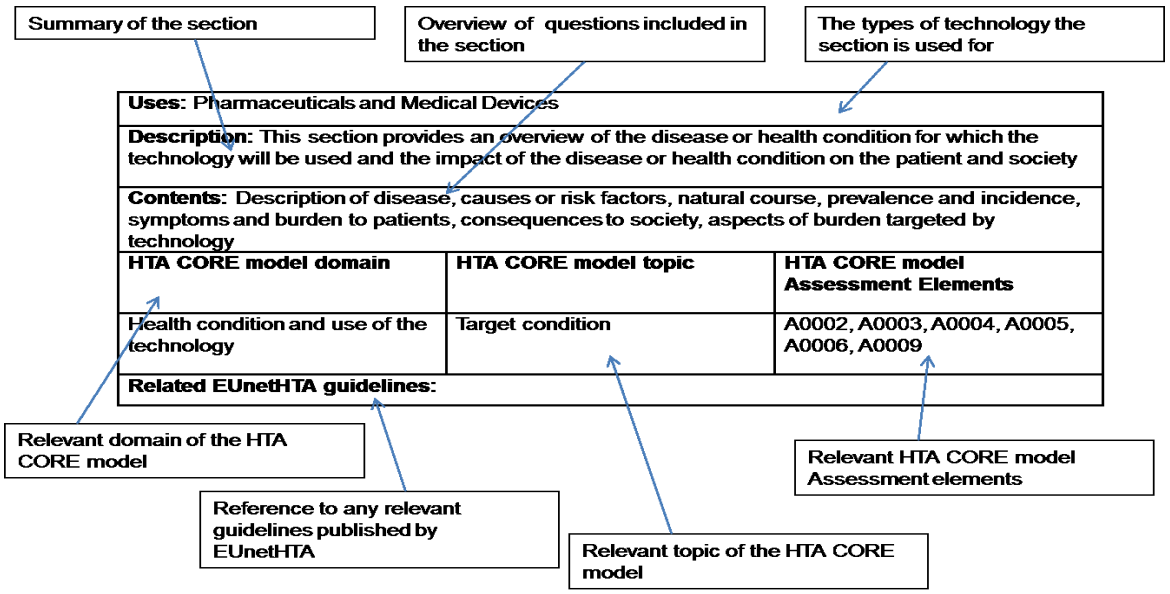
- Full text papers of cited articles.
- Clinical study reports, statistical plans and protocols.
- CE certificates and declarations of conformity.
- Instructions for use.
- User manuals and package inserts.
- Product diagrams, photographs, videos and samples.
- Draft or final regulatory documents (summary of product characteristics (SPC), Patient information leaflets (PIL), European public assessment reports (EPAR)).
- For products already on the market regulatory safety documents, such as periodic safety updates and other vigilance information.
- Research Information Systems (RIS)-files of references cited in the submission.

When adapting the evidence submission template, it is necessary to state which other documents are required. If there are restrictions about accepting unpublished and confidential data, or alternatively copyright issues with replicating published material, these should be highlighted in the adaption process.

To support health technology assessment EUnetHTA has produced a series of methodological guidelines and the HTA CORE model. These can be found at: http://www.eunethta.eu/eunethta-guidelines and http://meka.thl.fi/htacore/ respectively. These sources may be useful to support the adaptation process and to provide guidance to companies completing the evidence submission template.

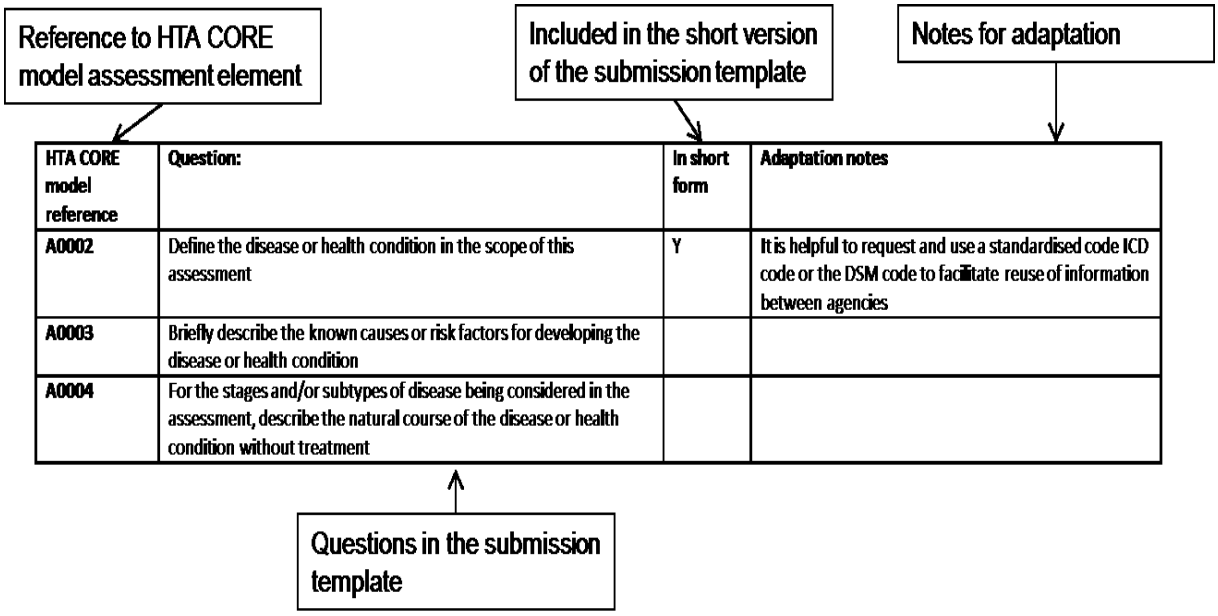
Using the adaptation notes

The evidence submission template and adaptation notes are divided into sections. A section includes a group of questions related to a particular theme. For each section there is a table in the adaptation notes that provides an overview of the section. This is designed to help agencies decide whether the questions are relevant to their decision-making. It also shows how the section relates to existing EUnetHTA tools. Assessment elements used in the relative effectiveness assessment (REA) application of the HTA CORE model are suffixed as '(REA)' with an indication of whether they are mandatory or non-mandatory for the REA application.



Some sections in the evidence submission template are for technologies that are already launched and available, for example extensions to the authorisation. These sections are highlighted in the 'uses' section of the above table.

Underneath the summary table there is a second table. The first column contains a link to any relevant HTA CORE model assessment elements, the second column provides a summary of the question in the evidence submission template, the third column shows whether the question is included in the short form version of the submission template. The final column includes adaptation notes.



HTA CORE model reference	Question:	In short form	Adaptation notes
A0002	Define the disease or health condition in the scope of this assessment	Y	It is helpful to request and use a standardised code ICD code or the DSM code to facilitate reuse of information between agencies
A0003	Briefly describe the known causes or risk factors for developing the disease or health condition		
A0004	For the stages and/or subtypes of disease being considered in the assessment, describe the natural course of the disease or health condition without treatment		

In the submission template, notes for companies are written in *italics* highlighted in blue. Further italics can be added to provide information on the specific details or level of detail required by the company to meet the agency requirements. When adapting the submission template it is helpful to provide an overall idea of the length of the submission expected from the company and whether any questions should be considered either only briefly or in-depth.

As well as amending questions and sections, it is possible to rearrange sections and to add other sections to cover areas such as pricing, costs, budget impact, economic information and expert opinion. Tables are included in the template showing how information can be presented, but these can also be adapted.

1. Description and technical characteristics of the technology

1.1 Characteristics of the technology (pharmaceuticals)

Uses: Pharmaceuticals (the next section is for use with medical devices)		
Description: This section provides details of the pharmaceutical technology under assessment.		
Contents: Technology names, marketing authorisation holder, class, active substance, formulation, codes, mechanism of action, claimed benefits and innovation, package information, administration and dosing, context of care and personnel.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Description and technical characteristics of the technology	Features of the technology	B0001 (mandatory REA); B0002 (mandatory REA), B0004 (REA non-mandatory)
Related EUnetHTA guidelines: -		

HTA CORE model reference	Question:	In short form version	Adaptation notes
B0001	An overview of the technology including:		A table is provided to capture this information.
	• Non-proprietary name	Y	
	• Proprietary name	Y	
	• Marketing authorisation holder	Y	
	• Class	Y	
	• Active substance(s)	Y	
	• Pharmaceutical formulation(s)	Y	
	• Anatomical Therapeutic Chemical (ATC) code	Y	
	• The mechanism of action.	Y	
B0001	Information about administration and dosing:		A table is provided to capture this information.
	• Method of administration	Y	
	• Doses and dose frequency	Y	
	• Treatment course	Y	
	• Dose adjustments	Y	
-	Information about the different packs available		A table is provided to capture this information. State which pack code should be requested e.g. pack barcodes or VnR code.
	• Pack size	Y	
	• Strength	Y	
	• Form	Y	
	• Pack codes	Y	
B0004	State the context and level of care for the technology, e.g. primary healthcare, secondary healthcare, tertiary healthcare, outside	Y	

	health institutions or as part of public health or other.		
B0004	State who administers the technology, include:		
	• the professionals who apply and make decisions about starting or stopping the technology		
	• whether patients or their carers administer the technology.		
B0002	State the claimed benefits of the technology, including whether the technology should be considered innovative.	Y	

1.1 Characteristics of the technology (medical devices)

Uses: Medical devices (the previous section is for use with pharmaceuticals)		
Description: This section provides details of the medical device technology under assessment.		
Contents: Names, product codes, authorisation holder, class, mechanism of action, claimed benefits and innovation; description of the medical device, diagram, how the medical device is used, different models, package contents, history of development.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Description and technical characteristics of the technology	Features of the technology	B0001 (mandatory REA); B0002 (mandatory REA), B0003 (non-mandatory REA), B0004 (mandatory REA)
Related EUnetHTA guidelines: Therapeutic Medical Devices (in development)		

HTA CORE model reference	Question:	In short form	Adaptation notes
B0001	Overview of the technology including:		A table is provided to capture this information.
	• Name	Y	
	• Manufacturer	Y	
	• Names for the technology in other countries		
	• Product codes	Y	
	• Class of device and Global Medical Device Nomenclature (GMDN) code	Y	
	• Mechanism of action	Y	
B0001	Describe the characteristics of the technology, including a diagram, photograph or illustration of the technology, details of the materials used and any accessories required.	Y	
B0001	Outline the purpose of the technology and provide a brief description of how the technology is used.	Y	There is a separate section for information about procedures used with the technology and the requirements to use the technology.
B0001	Specify the different models or version of the technology that are available.		
B0003	Describe the history of development of the technology.		
-	Describe the pack contents and whether any accessories or ancillary substances are included in the packs.	Y	
B0004	State the context and level of care for the technology, e.g. primary healthcare, secondary healthcare, tertiary healthcare, outside health institutions or as part of public health or other.	Y	

B0004	State who administers the technology, include:		
	• the professionals who apply and make decisions about starting or stopping the use of the technology		
	• whether patients or their carers administer the technology.		
B0002	State the claimed benefits of the technology, including whether the technology should be considered innovative.	Y	

1.2 Regulatory status of the technology (pharmaceuticals)

Uses: Pharmaceuticals (the next section is for medical devices)		
Description: This section provides the (anticipated) regulatory information for pharmaceutical technologies.		
Contents: Approval status, wording of indication, other available indications, date of approval, launch date, conditions attached to authorisation.		
Uses: Pharmaceuticals		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Health condition and use of the technology Description and technical characteristics of the technology	Regulatory status	A0020 (mandatory REA)
Related EUnetHTA guidelines: -		

HTA CORE model reference	Question:	In short form	Adaptation notes:
A0020	The marketing authorisation status of the technology in the country of application and if applicable in other European countries and the US, Canada and Australia.		A table is provided to capture this information. The list of countries for which the information is required may be placed in the first column of the table. Agencies should amend the question to define which countries regulatory data are required from e.g. European Union, European Economic area, Europe, any other countries or a selection of other countries. For joint assessment the question and table should be amended to remove the reference to country of application. In the short form the detailed regulatory information about the technology is limited to the country of application and a list of other countries in which the product has marketing authorisation.
	• the verbatim wording of the indication(s)	Y	
	• date of approval (or date approval is expected)	Y	
	• type of approval (full, conditional, exceptional)		
	• whether the technology is launched or when it is expected to be launched	Y	
	• approval number		
A0020	State the authorisation procedure.		Companies are asked to indicate if the product is following a centralised, mutual recognition, or de-centralised procedure.
A0020	State whether the technology has any special status.		Companies are asked to indicate if the product has orphan, generic, biosimilar classification.
A0020	State any other indications not included in the assessment for which the technology has marketing authorisation in any European country.	Y	

A0020	State any contraindications or groups for whom the technology is not recommended.	Y	
A0020	State whether there are any ongoing procedures for new indications for the technology or ongoing procedures relating to existing indications in Europe.		Companies are asked to indicate changes to the marketing authorisation currently in progress.
A0020	Describe the main issues discussed by the EMA or other regulatory organisation in granting a marketing authorisation for the indication under assessment.		
A0020	Describe any undertakings in the context of the marketing authorisation.		Companies are asked to indicate any formal requests from regulatory authorities for additional clinical studies or follow-up studies or any special pharmacovigilance monitoring/RMP.

1.2 Regulatory status of the technology (medical devices)

Uses: Medical devices (the section for pharmaceuticals is before this)		
Description: This section provides the (anticipated) regulatory information for medical device technologies.		
Contents: Approval status, wording of indication, other available indications, contraindication, date of approval and next if any approval, launch date.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Health condition and use of the technology Description and technical characteristics of the technology	Regulatory status	A0020 (mandatory REA)
Related EUnetHTA guidelines:		

HTA CORE model reference	Question:	In short form	Adaptation notes
A0020	The authorisation status of the technology in the country of application and if applicable in other European countries and the US, Australia and Canada:		Agencies should amend to define which countries regulatory data are required from: European Union, European Economic area, Europe, wider than Europe or a selection of European countries. A table is provided to capture this information. The list of countries for which the information is required may be placed in the first column of the table. For joint assessment the question and table should be amended to remove the reference to country of application. In the short form the regulatory status of the technology is limited to the country of application and a list of other countries in which the product has authorisation.
	• the verbatim wording of the (expected) indication(s)	Y	
	• date of approval (or date approval is expected)	Y	
	• expiry date of the approval		
	• whether the technology is launched or when it is expected to be launched	Y	
	• approval number (if available)		
A0020	State any contraindications or groups for whom the technology is not recommended.	Y	
A0020	State whether there are any ongoing procedures for new indications for the technology in Europe.		Companies are asked to indicate changes to authorisations currently in progress.

1.3 Details of manufacture, distribution and follow up (medical devices)

Uses: Medical devices		
Description: This section provides information about manufacturing and distribution, as well as information about the follow-up of the medical device including spares and replacements, maintenance and medical surveillance.		
Contents: Location of manufacture, distribution mechanism, availability of spares and replacements, maintenance requirements, quality control requirements, sterilisation, medical surveillance requirements, statistics of repairs.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Description and technical characteristics of the technology	-	B0007
Related EUnetHTA guidelines:		

HTA CORE model reference	Question:	In short form	Adaptation notes
-	Give the location(s) of manufacture of the technology.		
-	Describe the mechanism of distribution (including the distributor) and how availability of the technology is ensured.		
B0007	Describe the availability of spare parts or replacements, including how repairs are completed and the length of time required for repair.		
B0007	Describe any technical surveillance measures necessary to ensure optimal functioning of the medical device.		
B0007	State whether any maintenance is necessary and if so what maintenance needs to be done, how often and by whom.		
B0007	Provide details of sterilisation procedures (whether by heat/chemicals/irradiation/other) and how often sterilisation should be done.		
-	If the technology is launched, include the number and frequency of any repairs needed for the previous 2 years.		The evidence submission template requests that this information is provided as an appendix.

1.4 Duration of life, guarantees and warranties (medical devices)

Uses: Medical devices		
Description: This section gives information about manufacturer guarantees and device life.		
Contents: Life of the medical device and component parts, details of guarantees and warranties.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
-	-	-
Related EUnetHTA guidelines:		

HTA CORE model reference	Question:	In short form	Adaptation notes
-	Indicate the life span of the technology, and of any component parts, if applicable. Include the assumptions about frequency of use that support this.	Y	In the short form this question is included in the section 'characteristics of the technology'.
-	Give details of the guarantees and warranties that accompany the technology and its component parts, including the guarantee period.		

2. Health problem and current clinical practice

2.1 **Overview of the disease or health condition**

Uses: Pharmaceuticals and medical devices		
Description: This section provides a descriptive overview of the disease or health condition that is the subject of the assessment and the impact of the disease or health condition on the patient and society.		
Contents: Definition of the disease or health condition, causes or risk factors, natural course of disease, prevalence and incidence, symptoms and burden to patients, consequences to society, aspects of burden targeted by the technology under assessment.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Health condition and use of the technology	Target condition	A0002 (mandatory REA), A0003 (Non-mandatory REA), A0004 (mandatory REA), A0005 (mandatory REA), A0006 (Non-mandatory REA), A0009
Related EUnetHTA guidelines: -		

HTA CORE model reference	**Question:**	**In short form**	**Adaptation notes**
A0002	Define the disease or health condition in the scope of this assessment.	Y	It is helpful to request and use a standardised code *ICD code or the DSM code* to facilitate reuse of information between agencies.
A0003	Briefly describe the known causes or risk factors for developing the disease or health condition.		
A0004	For the stages and/or subtypes of disease being considered in the assessment, describe the natural course of the disease or health condition without treatment.		
A0006	Present an estimate of prevalence and/or incidence for the disease or health condition including recent trends.	Y	Indicate to companies whether there is a preference for the estimates to come from national statistics or published literature. When using for joint or collaborative assessment indicate if the prevalence or incidence is required across Europe or within individual countries. Mark the scope of the countries e.g. EU, EEA, Europe.
A0005	Describe the symptoms and burden of the disease or health condition for patients.	Y	This question considers the impact of the disease or health condition from the patient perspective.
A0006	Describe the consequences of the disease or health condition for society.		This question considers the impact of the disease or health condition from a population perspective.
A0009	Describe the aspects of the burden of disease that are targeted by the technology, i.e. those that are expected to be reduced by the use of the technology.	Y	

2.2 Target population

Uses: Pharmaceuticals and medical devices		
Description: This section describes the company's proposed positioning of their technology and target population e.g. this may be the population identified in the authorisation or a target group of patients using the technology for which the company wants reimbursement.		
Contents: Description and justification of the target population, size of target population, patient pathway of care with new technology.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Health condition and use of the technology	Target population	A0007 (mandatory REA), A0023 (mandatory REA)
Related EUnetHTA guidelines: -		

HTA CORE model reference	Question:	In short form	Adaptation notes
A0007	Describe the target population and the proposed position of the target population in the patient pathway of care.	Y	Adapt this question to reflect whether a company should submit for the whole population in the authorisation, the whole population in the indication or if they may submit for a subgroup of an indication.
A0007	Provide a justification for the proposed positioning of the technology and definition of the target population.	Y	
A0023	Estimate the size of the target population. Include a description of how the size of the target population was obtained and whether it is likely to change (e.g. increase or reduce) over time.	Y	When using for joint assessment indicate if the size of the target population is required across Europe or within individual countries. Mark the scope of the countries e.g. EU, EEA, Europe.

2.3 Clinical management of the disease or health condition

Uses: Pharmaceuticals and medical devices		
Description: This section describes the diagnosis and clinical management of the disease or health condition.		
Contents: Current clinical management and diagnosis, issues, uncertainties, variations and unmet needs in clinical management, currently available guidelines on clinical management, alternatives to the technology, justification of alternatives.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Health condition and use of the technology	Current management of the condition	A0017, A0018, A0024 (mandatory REA medical devices; non-mandatory REA pharmaceuticals), A0025 (mandatory REA)
Related EUnetHTA guidelines: Criteria for the choice of the most appropriate comparator(s): http://5026.fedimbo.belgium.be/outputs/methodological-guideline-rea-pharmaceuticals-criteria-choice-most-appropriate-comparators		

HTA CORE model reference	Question:	In short form	Adaptation notes
A0024 A0025	Describe the clinical pathway of care for different stages and /or subtypes of the disease being considered in the assessment.	Y	A table is provided for companies to include relevant guidelines where there are multiple guidelines. For joint assessment mark the scope of the countries from which guidelines should be provided e.g. EU, EEA, Europe.
A0018	State the technologies currently used in the clinical pathway for which the proposed technology is an alternative, or an additional treatment.	Y	Indicate how the alternative technologies should be identified e.g. those most commonly used, or all treatments in use. The template includes a separate section for the company to define the comparators that are to be used in the assessment.
A0017	Describe any issues relating to current clinical management, e.g. unmet needs, uncertainty about best practice, variations in management and management of specific patient groups.		
-	Describe the pathway of care that incorporates the new technology if the technology were to be adopted for use.	Y	

2.4 Comparators in the assessment

Uses: Pharmaceuticals and medical devices		
Description: This section describes the comparators that the company is using in the assessment.		
Contents: Statement of the comparators and justification for the choice of comparator.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Health condition and use of the technology	Description of the technology	B0001 (mandatory REA)
Related EUnetHTA guidelines: Criteria for the choice of the most appropriate comparator(s): http://5026.fedimbo.belgium.be/outputs/methodological-guideline-rea-pharmaceuticals-criteria-choice-most-appropriate-comparators		

HTA CORE model reference	Question:	In short form	Adaptation guide
B0001	On the basis of the alternatives presented, identify the technologies to be used as comparator(s) for the assessment.	Y	Add guidance for choice of comparator (e.g. best available care, established care, most cost-effective treatment, alternative comparable product) including guidance on use of off label comparators.
B0001	Provide a justification for the choice of the comparators in the assessment.		

3. Current use of the technology and comparators

3.1 Current use of the technology

Uses: Pharmaceuticals and medical devices Use only for assessments of technologies that are already available in one or more countries.		
Description: This section describes how the technology is currently being used.		
Contents: Experience of using the new technology, scale of current use, and changes in use expected if the technology is introduced.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Health condition and use of the technology	Utilisation	A0001, A0011 (mandatory REA medical devices; non-mandatory REA pharmaceuticals), A0018
Related EUnetHTA guidelines:		

HTA CORE model reference	Question:	In short form	Adaptation notes
A0001 A0018	Describe the experience of using the technology, e.g. the health conditions and populations, and the purposes for which the technology is currently used. Include whether the current use of the technology differs from that described in the (expected) authorisation.	Y	For joint assessment define the level of detail required for this question, e.g. major indications for which it is used across Europe or a breakdown of the information on use across individual countries. Mark the scope of the countries e.g. Country of application, EU, EEA, Europe, World.
A0011	Indicate the scale of current use of the technology, e.g. the number of people currently being treated with the technology, or number of settings in which the technology is used.	Y	For joint assessment define how this information should be presented e.g. if the amount of existing use is required across Europe or within individual countries Mark the scope of the countries e.g. Country of application, EU, EEA, Europe, World.
A0011	Indicate how the scale of current use is expected to change in the future if the technology is introduced.		

3.2 Reimbursement and assessment status of the technology

Uses: Pharmaceuticals and medical devices Use only if the technology has been launched in a European country.		
Description: This section provides information about the reimbursement status of the technology under assessment in the country of application and other countries. The section can also be used to collate recommendations from other health technology assessments that do not necessarily result in reimbursement.		
Contents: Reimbursement status in Europe, indications, restrictions and level of reimbursement, date of decision, summary of reimbursement recommendations.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Health condition and use of the technology Description and technical characteristics of the technology	Regulatory status	A0021 (non-mandatory REA)
Related EUnetHTA guidelines:		

HTA CORE model reference	Question:	In short form	Adaptation notes
A0021	Provide information about the reimbursement status of the technology in Europe. Include:		A table is provided to capture this information. Mark the scope of the countries e.g. Country of application, EU, EEA, Europe.
	• whether the reimbursement status is technology specific (e.g. for all indications) or if it is indication specific (e.g. reimbursement is made on an indication-by-indication basis)		
	• the indications [populations, restrictions, settings] covered by existing reimbursement decisions for the technology		
	• the reimbursement status of the technology in European countries (positive/negative/ongoing/not assessed)	Y	
	• the date(s) on which the reimbursement decision was made, and		
	• the level of reimbursement.	Y	
A0021	Summarise the existing reimbursement and assessment recommendations in European countries.		A table is provided to capture this information. This information is only requested for the indication under assessment.

3.3 Current use of the comparators

Uses: Pharmaceuticals and medical devices		
Definition: This section provides information about the regulatory and reimbursement status and current use of the comparators.		
Contents: Regulatory status, reimbursement status, levels of reimbursement, date of decision.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Health condition and use of the technology	Utilisation	A0011 (mandatory REA medical devices; non-mandatory REA pharmaceuticals), A0012, A0020 (mandatory REA), A0021 (non-mandatory REA)
Related EUnetHTA guidelines:		

HTA CORE model reference	Question:	In short form	Adaptation notes
A0011	Indicate the number of people in the target population estimated to receive treatment with each of the comparators.		When using for joint assessment indicate if data on the use of different comparators is required across Europe or within individual countries.
A0012	Describe the variations in the degree to which the comparators are used across countries/regions/settings, if any.		
	For each of the comparators in the assessment provide		A table is provided to capture this information. This question and table should be adapted for countries requiring comparator treatments to be authorised and/or reimbursed.
A0020	• the regulatory authorisation status		
A0021	• reimbursement status		
A0021	• date of the decision		
A0021	• level of reimbursement		
A0021	• restrictions placed on reimbursement		

4. Investments and tools required

4.1 Requirements to use the technology

Uses: Pharmaceuticals and medical devices		
Description: This section describes resources and personnel that are needed in order to be able to use the technology.		
Contents: Associated technologies (pharmaceuticals, medical devices and procedure), restrictions applied to the authorisation, concomitant treatments, concomitant tests, monitoring and investigations, facilities, equipment and supplies required.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Description and characteristics of the technology	Investments and tools required to use the technology	A0020 (REA mandatory); B0008 (REA non-mandatory); B0009 (REA non-mandatory)
Related EUnetHTA guidelines:		

HTA CORE model reference	Question:	In short form	Adaptation guide
A0020 B0008 B0009	State whether using the technology requires another technology.		
	• Pharmaceutical		
	• Medical device		
	• Procedure		
A0020	Special conditions attached to the regulatory authorisation:		Companies are asked to reference relevant sections of the SPC, EPAR or user manual.
	• conditions relating to settings for use e.g. inpatient or outpatient, presence of resuscitation facilities	Y	
	• restrictions on professionals who can use or may prescribe the technology	Y	
	• conditions relating to clinical management e.g. patient monitoring, diagnosis, management and concomitant treatments.	Y	
B0009	Describe the treatments (e.g. for side-effects) that may be required by patients using the technology.		
B0009	Describe the tests, investigations and monitoring required by patients using the technology.		
B0008	Describe the facilities required to use the technology.	Y	Only included in the short form version of the evidence submission template for medical devices.
B0009	Describe the equipment required to use the technology.	Y	
B0009	Describe the supplies required to use the technology.	Y	

4.2 Procedures required to use the technology

Uses: Pharmaceuticals and medical devices where these are associated with a procedure.		
Description: This section describes in detail any procedures that are associated with the technology.		
Contents: Type of procedure and approach, technical platform, anaesthesia requirements, whether the device is required to complete the procedure, similarities and differences where more than one procedure may be used.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Description and characteristics of the technology	Features of the technology Investments and tools required to use the technology	B0001 (mandatory REA), B0008 (non-mandatory. REA), B0009 (non-mandatory REA)
Related EUnetHTA guidelines:		

HTA CORE model reference	Question:	In short form	Adaptation notes
B0001	State whether the procedure was developed alongside the technology or was previously carried out with a different technology or without the technology.		
B0001	Describe the procedure. Include:		Only included in the short form for the medical device evidence submission template.
	• the type of approach (direct, percutaneous, vascular, endoscopic, etc.)	Y	
	• whether or not guidance is required (ultrasound, echo-Doppler, X-ray, etc.)	Y	
	• for each step of the procedure, the duration of the step and the type and role of each person involved (e.g. physician performing the procedure, anaesthetists, nurses, etc.).	Y	
B0008 B0009	Describe the technical platform (that is, equipment in the room in which the procedure is performed, etc.) and the environment necessary for performing the procedure: In particular, specify whether or not the procedure must be performed in an operating theatre and, if this is not the case, whether a particular pre-existing technical platform is required.		
B0001	State the number of times the procedure needs to be repeated for the treatment to be complete.		
B0009	Describe whether anaesthesia is required, include details about the methods used (general, local, loco-regional, sedation,		

	analgesia, etc.).		
B0001 B0008 B0009	If more than one procedure may be used, highlight the similarities/differences in terms of technicality, duration of the procedure, technical platform, etc.		

4.3 Investments, disinvestments and changes in service organisation

Uses: Pharmaceuticals and medical devices		
Description: This section describes the material investments and additional services, personnel and skills that need to be invested in, in order to introduce the technology (i.e. the resources not currently available but needed if the technology were to be introduced). It includes changes in service organisation that may result if the technology is introduced and also resources that are used currently but will no longer be needed if the technology is introduced		
Contents: Skills and training, employment of personnel, purchase of equipment and supplies, construction of infrastructure, changes to current services, resources no longer required.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Description and characteristics of the technology	Investments and tools required to use the technology	B0007, B0012, B0013, B0014
Related EUnetHTA guidelines:		

HTA CORE model reference	Question:	In short form	Adaptation notes
B0012 B0013	Describe any additional skills and training that will need to be provided for the professionals who will administer the technology:		
	• describe the type of training and any training materials required (individual and/or group sessions, number and length of sessions, number and qualifications of trainers)		
	• if the technology requires a specific skill that is developed over a period of time using the technology, an estimate should be provided of the number of patients a professional needs to treat (as a total number or per year) in order to reach an acceptable minimum standard		
	• explain the extent to which the training and quality assurance measures may affect the efficacy and safety of the technology.		
B0013 B0014	Describe any training that will be needed for patients and / or their carers.		
B0007	Describe any additional human resources required to implement the technology, e.g. new employees.		
B0007	Describe any changes to current services that are needed to introduce the technology. Include:	Y	
	• any tests or investigations needed for selecting or monitoring patients that are over and above usual clinical practice	Y	

	• any equipment, or organisational and technical conditions that will require investment before the technology can be introduced	Y	
	• any investment in infrastructure	Y	
	• any programmes and services that will have to be increased due to introduction of the technology (rehabilitation, nursing etc.).	Y	
	Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed if the technology is introduced.	Y	

5. Clinical effectiveness and safety

5.1 Identification and selection of relevant studies

Uses: Pharmaceuticals and medical devices		
Description: This section is used to record the details of the literature search(es). If applicable, the same section can also be used to record the searches used to find studies of the comparators for evidence synthesis or safety studies if different criteria are used for the identification of safety studies.		
Contents: Research question guiding searches, databases and registries searched, search dates, search terms and strategies, inclusion and exclusion criteria, PRISMA flow chart, methods for identifying ongoing and unpublished studies, citation hits.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Clinical effectiveness Safety	Domain methodology	-
Related EUnetHTA guidelines: Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness: http://www.eunethta.eu/outputs/eunethta-methodological-guideline-process-information-retrieval-systematic-reviews-and-healt Therapeutic Medical Devices (under development)		

General notes on using and adapting this section:

Consider whether systematic identification of both studies of the intervention and of the comparators is required for the assessment process and adapt the template text accordingly.

As well as copies of the search strategies the following appendices may also help review the searches and the robustness of the identification of the studies:

- List of studies excluded from the result of the searches of bibliographic databases (full text screening) with reason for exclusion.
- List of studies excluded from the search result from trial registries with reason for exclusion.
- RIS-Files of all references identified in the systematic searches of bibliographic databases and study registries.

Agencies who want to appraise a companies' network meta-analysis should also request this section on the process of identification of studies.

HTA CORE model reference	Question:	In short form	Adaptation notes
EUnetHTA methodology guidelines and HTA CORE model methodology	Specify the research question or problem statement used to guide the searches.		
	State the databases and trial registries searched and, when relevant, the platforms used to do this.	Y	Add a list of the databases that the company should search.
	State the date the searches were done and any limits (e.g. date, language) placed on the searches.	Y	
	Include as an appendix the search terms and strategies used to interrogate each database or registry.	Y	An example search strategy is included in the submission template to support companies to provide this information.
	State the inclusion and exclusion criteria used to select studies and justify these.	Y	A table is provided to facilitate completion. The template text can be amended if a particular method of identifying studies is expected, e.g. independent screening by 2

			people.
	Provide a flow chart showing the number of studies identified and excluded.	Y	The PRISMA statement is recommended http://prisma-statement.org/. The PRISMA statement and reference to the PRISMA statement is included in the evidence submission template. For copyright reasons do not replicate the PRISMA statement in documents without the citation.
	Describe any additional methods to those described above, that were used to identify ongoing and unpublished studies.		

5.2 Relevant studies

Uses: Pharmaceuticals and medical devices		
Description: This section is used to record the administrative details of each study providing evidence in the submission, this can include studies of the intervention and comparators and studies providing efficacy, effectiveness and/or safety data.		
Contents: Study reference, registration name/number, conflicts of interest, study dates, study location, source of identification, references to linked publications, publication status.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Clinical effectiveness Safety	-	-
Related EUnetHTA guidelines: -		

General notes on using and adapting this section:
The agency's definition of a relevant study needs to be included in the evidence submission template e.g. this could include all studies in the indication under assessment, only randomised controlled data or only studies that reflect the PICO aspects defined in the submission.
The text and the table will need adapting depending on agency methods and acceptability of randomised and non-randomised data as well as acceptability of published, ongoing and unpublished data.

HTA CORE model reference	Question:	In short form	Adaptation notes
	For each study identified, provide		
	• Study reference, e.g. author and year or ID number	Y	
	• Trial name and registration number		
	• Conflicts of interest (indicate studies sponsored by the company)		
	• Dates of study (date of study start and (expected) completion date)		
	• Study location or regions		
	• Source of identification (e.g. company-sponsored trial, trial registry, bibliographic database)		
	• References for available documentation	Y	The company is asked to include published and unpublished documentation.
	• Status (e.g. ongoing or complete): include expected completion date for ongoing studies.	Y	

5.3 Main characteristics of studies

Uses: Pharmaceuticals and medical devices		
Description: This section is used to record the descriptive and methodological characteristics of each study used as evidence in the submission.		
Contents: Study objective, design, eligibility criteria, intervention, comparator, follow-up, primary and secondary outcomes, randomisation methods, methods of blinding, methods of recruitment, methods of allocation concealment, sample size determination, patient withdrawal, baseline comparison.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Clinical effectiveness Safety	-	-
Related EUnetHTA guidelines: Therapeutic Medical Devices (under development) Further information on the presentation of study information can be found in the CONSORT statement: http://www.consort-statement.org/consort-statement/overview0/ for randomised controlled trials, and STROBE guidelines for observational studies: http://www.strobe-statement.org/		

General notes on using and adapting this section: Agencies who want to appraise a companies' network meta-analysis should request this section.			
HTA CORE model reference	**Question:**	**In short form**	**Adaptation notes**
	Main characteristics of the studies		Consider whether systematic description is required for both studies of the intervention and of the comparators for the assessment process and adapt the template text accordingly.
	• Study objective(s)	Y	
	• Study design or type	Y	
	• Study population (eligibility criteria)	Y	
	• Intervention (including timing and duration of administration)	Y	
	• Comparator (if usual care, please describe what this constitutes)	Y	
	• Follow-up	Y	
	• Primary outcome measure	Y	
	• Secondary outcome measures	Y	
	Provide the following information about the study methodology:		This question is used to describe the methods used in the study. The adequacy of the method is assessed in the risk of bias sections of the submission 5.7, 5.8, 5.9.
	• Method of recruitment		
	• If applicable, method of randomisation (include unit of randomisation)		
	• Method of allocation concealment		

	• Methods of blinding (patients, treating physicians and outcome assessors)		
	For the technology under consideration, describe any groups of patients excluded from the studies and the rationale for their exclusion. Indicate if these groups are included (or expected to be included) in the marketing authorisation.		
	For each study describe how sample size was determined.		
	For each study provide a flow diagram of the numbers of patients moving through the trial.	Y	For pharmaceutical technologies, the company may be able to use tables from the regulatory documents.
	For each study provide a comparison of study participants (including demographic, clinical and social information (where applicable)) in treatment arms at baseline.	Y	For pharmaceutical technologies, the company may be able to use tables from the regulatory documents.

5.4 Individual study results (clinical outcomes)

Uses: Pharmaceuticals and medical devices		
Description: This section is used to record the clinical outcomes of each study used as evidence in this submission. The section records direct comparisons of study data. Indirect comparisons are included in the synthesis of evidence and conclusions (sections 5.10 and 5.11).		
Contents: relevant endpoints, definition of endpoint, methods of data collection and analysis, study results (including assessment measure, time point, n with event, n without event, mean, standard deviation, difference, confidence interval, p value).		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Clinical effectiveness	Mortality Morbidity Function Health related quality of life Patient satisfaction	D0001 (mandatory REA); D0005 (mandatory REA); D0006 (mandatory REA), D0011(mandatory REA); D0014; D0016 (non-mandatory REA); D0012 (mandatory REA), D0013 (mandatory REA); D0017 (non-mandatory REA)
Related EUnetHTA guidelines: Endpoints used for relative effectiveness assessment of pharmaceuticals: clinical endpoints http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf Endpoints used for relative effectiveness assessment of pharmaceuticals: composite endpoints http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Composite%20endpoints.pdf Endpoints used in relative effectiveness assessment of pharmaceuticals: surrogate endpoints http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Surrogate%20Endpoints.pdf Endpoints used for relative effectiveness assessment of pharmaceuticals: HRQOL and utility measures http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Health-related%20quality%20of%20life.pdf		

General notes on using and adapting this section: Agencies may wish to identify whether the company should focus on particular outcomes when reporting study outcomes. The evidence submission template currently reflects those included in the HTA CORE model REA application: mortality, morbidity, function, health-related quality of life and patient satisfaction. Agencies who want to appraise a companies' network meta-analysis should request this section as well.			
HTA CORE model reference	**Question:**	**In short form**	**Adaptation notes**
	Describe the relevant endpoints, including the definition of the endpoint, methods of data collection and methods of analysis.	Y	A table is provided to facilitate completion. In the short form the company is requested only to provide a definition of the endpoint and methods of analysis.
	If any outcomes, studies or study arms are excluded from the summary of clinical outcomes provide a justification for their exclusion.		A table is provided to facilitate completion.
D0001, D0005	Provide a summary of the study results for each relevant	Y	Example tables are provided for dichotomous and continuous

D0006, D0016 D0012, D0013 D0014, D0017	comparison and outcome.		data and for comparative and non-comparative data and can be adapted to suit stated methods. Adapt the text in the template to reflect requirements for outcomes data e.g. all clinical trial outcomes data or only a defined selection of outcomes relevant to the agency.

5.5 Individual study results (safety outcomes)

Uses: Pharmaceuticals and medical devices		
Description: This section is used to record the safety results of each study used as evidence in this submission. The section records direct comparisons of study data. Indirect comparisons are included in the synthesis of evidence and conclusions (sections 5.10 and 5.11).		
Contents: Exposure, relevant endpoints, definition of endpoint, methods of data collection and analysis, discontinuation and withdrawal of treatment, number of adverse events, susceptible patient groups.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Safety	Patient Safety	C0008 (mandatory REA)
Related EUnetHTA guidelines: Safety: http://5026.fedimbo.belgium.be/outputs/methodological-guideline-rea-pharmaceuticals-safety		

General notes on using and adapting this section:
The section suggests that companies include tables from their regulatory submissions where these present the same data.

HTA CORE model reference	Question:	In short form	Adaptation notes
	For the technology, tabulate patient exposure to technology and comparator in each of the studies providing safety data.		A table is provided to facilitate completion.
	Describe the relevant endpoints, including the definition of the endpoint, methods of data collection and methods of analysis.	Y	A table is provided to facilitate completion. In the short form the company is requested only to provide a definition of the endpoint and methods of analysis.
	If any outcomes, studies or study arms are excluded from the summary of safety outcomes provide a justification for their exclusion.		A table is provided to facilitate completion.
	For the technology, tabulate the number of patients who permanently or temporarily discontinued treatment for each study providing safety data.		A table is provided to facilitate completion.
C0008	For the technology, and the comparator, tabulate the total number of adverse events, frequency of occurrence (as a %), absolute and relative risk and 95% CI reported in each of the clinical studies. Categorise the adverse events by frequency, severity and system organ class.	Y	A table is provided to facilitate completion. Example tables are provided for collecting this information. The tables include different levels of detail that depends on the extent to which agencies assess safety as well as effectiveness.

5.6 Subgroups

Uses: Pharmaceuticals and medical devices		
Description: This section provides details of subgroup analyses undertaken in the clinical trials.		
Contents: Subgroup characteristics, justifications, plausibility, analysis methods, results.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Clinical effectiveness Safety	Mortality Morbidity Function Health related quality of life Patient satisfaction Patient safety	D0001 (mandatory REA), D0005 (mandatory REA), D0006 (mandatory REA), D0011(mandatory REA), D0014, D0016 (non-mandatory REA), D0012 (mandatory REA), D0013 (mandatory REA), D0017 (non-mandatory REA) C0008 (mandatory REA) C0005 (mandatory REA)
Related EUnetHTA guidelines:		

General notes on using and adapting this section:
Adapt the text to mark if only pre-specified subgroups are requested and if certain subgroups are specifically requested e.g. age, gender, disease severity

HTA CORE model reference	Question:	In short form	Adaptation notes
	Describe which subgroup(s) were analysed in the clinical trials of the technology under assessment.		
	State which papers are relevant to the subgroup analyses.		
	Specify the methods of subgroup analysis used in the clinical trials.		
D0001, D0003, D0005, D0006, D0011, D0014, D0016, D0012, D0013, D0017, C0008, C0005	Give the results of the subgroup analyses from the clinical trials.		Companies are reminded that a subgroup may be a group of patients with a different profile of harms as well as those with a different treatment benefit.

5.7 Risk of bias study level: randomised controlled trials

Uses: Pharmaceuticals and medical devices		
Description: This section presents risk of bias at study level for randomised controlled trials e.g. there will be one assessment of bias for each study. The following section addresses the assessment of risk of bias at the outcome level for randomised studies.		
Contents: Randomisation sequence, allocation concealment, blinding, complete outcome reporting, other aspects of bias.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Clinical effectiveness Safety	Domain methodology	
Related EUnetHTA guidelines: http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Internal_Validity.pdf See also recommendations from the GRADE working group and the Cochrane Collaboration Handbook about the assessment of risk of bias http://www.gradeworkinggroup.org/publications/JCE_series.htm and http://handbook.cochrane.org/		

General notes on using and adapting this section:
Agencies who complete their own independent assessment of the evidence may not need a company to do a full critical appraisal of the evidence if this is to be repeated by the agency. Consider whether a risk of bias assessment is required for both studies of the intervention and of the comparators for the assessment process and adapt the template text accordingly.
Agencies who want to appraise a companies' network meta-analysis should request this section as well.

HTA CORE model reference	Question:	In short form	Adaptation notes
EUnetHTA methodology guidelines and HTA CORE model methodology	For each RCT identified give the adequacy of:		Companies are directed to respond: yes/no/unclear and to provide reasons for classification if an unclear or no response is given. Methods of randomisation, allocation concealment and blinding are included in the section on study characteristics.
	• Random sequence generation (was the method used to generate the allocation or randomisation sequence adequate to produce comparable groups?)		
	• Allocation concealment (was the method used to mask the sequence of allocation to the intervention adequate?)		
	• Blinding (were participants, medical personnel and statistical investigators appropriately blinded with respect to intervention assignment?)		
	• Completeness of the data for each outcome considered (was the amount, nature or handling of incomplete outcome data adequately described?)		

	• Selective outcome reporting (were all relevant pre-specified outcomes reported independently by the results?)		
	• Other sources of bias (is the trial free from other aspects that affect the risk of bias, e.g. early interruption of the study because of the benefits without an appropriate stopping rule, use of non-validated measurement instrument, incorrect statistical analysis?).		
	• Overall risk of bias		Companies are asked to respond low/high.

5.8 Risk of bias at outcome level

Uses: Pharmaceuticals and medical devices		
Description: This section is used to record the risk of bias in outcomes used in the evidence synthesis in this submission. This is bias assessed for each study outcome (clinical outcomes and safety outcomes), therefore if a study provides more than one outcome in the analysis there will be more than one assessment of bias. It is used for randomised studies.		
Contents: Blinding of outcome assessor, intention to treat (ITT) implementation, complete outcome reporting, other aspects of outcome bias.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Clinical effectiveness Safety	Domain methodology	
Related EUnetHTA guidelines: The EUnetHTA safety guideline includes quality assessment of safety outcomes. http://5026.fedimbo.belgium.be/outputs/methodological-guideline-rea-pharmaceuticals-safety See also recommendations from the GRADE working group and the Cochrane Collaboration Handbook about the assessment of risk of bias http://www.gradeworkinggroup.org/publications/JCE_series.htm and http://handbook.cochrane.org/		

General notes on using and adapting this section:
Agencies who complete their own independent assessment of the evidence may not need a company to do a full critical appraisal of the evidence if this is to be repeated by the agency. Consider whether a risk of bias assessment is required for both studies of the intervention and of the comparators for the assessment process and adapt the template text accordingly.

HTA CORE model reference	Question:	In short form	In REA submission	Adaptation notes
EUnetHTA methodology guidelines and HTA CORE model methodology	For each study outcome included in the evidence synthesis, state whether:			
	• the outcome assessor was blinded			Companies are asked to respond: yes/no/unclear. Methods of randomisation, allocation concealment and blinding are included in the study description section.
	• intention-to-treat (ITT) was appropriately implemented			
	• selective outcome reporting is unlikely			
	• the study is free from other (outcome-specific) aspects that affect the risk of bias.			
	• Overall risk of bias			Companies are asked to respond low/high.

5.9 Risk of bias: non-randomised studies

Uses: Pharmaceuticals and medical devices		
Description: This section presents risk of bias for non-randomised controlled trials. It can be completed at the level of the outcome. Therefore separate risk of bias assessment at the outcome level is not required.		
Contents: Bias due to: confounding, selection of patients, measurement of interventions, departures from intended interventions, missing data, outcome measurement, selection of reported results, comparability at baseline		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Clinical effectiveness Safety	Domain methodology	-
Related EUnetHTA guidelines: Guideline in development as part of joint action 2 on the internal validity of non-randomised studies on interventions http://www.eunethta.eu/outputs/publication-ja2-methodological-guideline-internal-validity-non-randomised-studies-nrs-interv See also recommendations from the GRADE working group and the Cochrane Collaboration Handbook about the assessment of risk of bias http://www.gradeworkinggroup.org/publications/JCE_series.htm and http://handbook.cochrane.org/		

General notes on using and adapting this section:
Agencies who complete their own independent assessment of the evidence may not need a company to do a full critical appraisal of the evidence if this is to be repeated by the agency. Consider whether risk of bias is required for both studies of the intervention and of the comparators for the assessment process and adapt the template text accordingly.

HTA CORE model reference	Question:	In short form	In REA submission	Adaptation notes
EUnetHTA methodology guidelines and HTA CORE model methodology	For each non-randomised study identified state whether there is:			
	• Bias due to confounding (is confounding of the effect of intervention likely in this study?)			Companies are asked to respond: Low/Moderate/Serious/Critical/No information.
	• Bias in selection of participants into the study (how was the treatment group determined for each patient?)			
	• Bias in the measurement of interventions (is intervention status well defined and unaffected by knowledge of the outcome or risk of the outcome?)			
	• Bias due to departures from intended interventions (was intention-to-treat (ITT) appropriately implemented?)			
	• Bias due to missing data (are outcome data or			

	intervention status reasonably complete?)			
	• Bias in measurement of outcomes (was outcome measurement objective and comparable across intervention groups or was the definition of case status (and control status if applicable) based on objective criteria?)			
	• Bias in selection of the reported results (were all relevant outcomes reported?)			
	• Comparability at baseline (were the characteristics of selected groups comparable at baseline?)			
	• Overall bias.			Companies are asked to respond low/moderate/serious/critical/no information.

5.10 Methods of evidence synthesis

Uses: Pharmaceuticals and medical devices		
Description: This section is used to record methods of evidence synthesis e.g. narrative synthesis, meta-analysis, indirect comparisons, mixed treatment comparisons or network meta-analysis.		
Contents: Type of synthesis, outcomes and comparators in synthesis, studies included in synthesis, justifications, syntheses of subgroup data, methods used for synthesis, heterogeneity, consistency, publication bias, sensitivity analyses.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Clinical effectiveness Safety	Domain methodology	-
Related EUnetHTA guidelines: Direct and indirect comparisons: http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Direct%20and%20indirect%20comparisons.pdf See also http://mdm.sagepub.com/content/33/5/679.full.pdf+html for a reviewers' checklist for the reporting of network meta-analyses.		

General notes on using and adapting this section:

Agencies accepting meta-analyses and network meta-analyses should also request information in the sections about:

- identification of the studies of the intervention and comparator,
- study descriptions for the intervention and the comparators,
- study results for the intervention and the comparators, and
- risk of bias assessment.

This is to enable agencies to assess the appropriateness and robustness of the analysis. In addition, for network meta-analysis appendices should be requested for the data that were entered into the network meta-analysis and the computer code used to run the analysis.

This section requesting the methods of evidence synthesis should be used with the next section requesting the results of evidence synthesis.

HTA CORE model reference	Question:	In short form	Adaptation notes
EUnetHTA methodology guidelines and HTA CORE model methodology	State the type of synthesis (e.g. narrative, meta-analysis, indirect or mixed treatment comparison) and justify the approach taken.		The text should be adapted by agencies who do not accept network meta-analyses. The types of synthesis are not mutually exclusive, e.g. meta-analysis may be completed before network meta-analysis.
	State the outcomes included in the synthesis and the time point for the collection of outcome data. Justify the choice of outcomes and time point.		
	State whether any syntheses of subgroup data are being presented. Justify the subgroups chosen.		
	State the comparators included in the synthesis, indicate whether any comparators have been added to the synthesis		

	(e.g. to help create a network of evidence) or excluded from the synthesis (e.g. because of an absence of data) and justify.		
	Where a quantitative approach is used, list the studies informing the synthesis showing the comparisons made by the studies. Justify any exclusions from the synthesis.		Tables are provided to facilitate completion. The first table could also be substituted with a network diagram with the studies included and the links they create included diagrammatically.
	Describe the methods used to synthesise the evidence:		
	• Meta-analysis: state methods and models used and justify these. If Bayesian methods are used, justify the priors chosen.		
	• Indirect or mixed treatment comparisons: state the statistical model, software and whether a fixed or random effects model has been used. Justify the choice of methods. If Bayesian methods are used, justify the priors chosen.		Agencies should request as appendices the computer code and tables of the actual study data included in the indirect or mixed treatment comparison.
	• Narrative review, give details of the methods used.		
	Discuss the extent to which the studies may be considered (1) homogenous as a group and (2) representative of the target population and treatments.		
	State how heterogeneity in the relative treatment effects was assessed and give evidence of the degree of heterogeneity in each of the pairwise comparisons.		
	If network meta-analysis is used, state how consistency between direct and indirect comparisons was assessed. Highlight any inconsistencies in comparisons.		For network meta-analysis only.
	State how publication bias was assessed and give evidence to justify whether or not publication bias is presumed to be present.		
	Describe the sensitivity analyses done. If conclusions are sensitive to outliers or influential studies, present sensitivity analyses.		

5.11 Results of evidence synthesis

Uses: Pharmaceuticals and medical devices		
Description: This section is used to present the results of the evidence synthesis for clinical and safety.		
Contents: Relative effects on mortality, morbidity, management, quality of life, satisfaction, patient safety.		
HTA CORE model domain	**HTA CORE model topics**	**HTA CORE model Assessment Elements**
Clinical effectiveness Safety	Mortality Morbidity Function Health related quality of life Patient satisfaction Patient safety	D0001 (mandatory REA); D0005 (mandatory REA); D0006 (mandatory REA), D0011(mandatory REA); D0014; D0016 (non-mandatory REA); D0012 (mandatory REA), D0013 (mandatory REA); D0017 (non-mandatory REA); C0008 (mandatory REA)
Related EUnetHTA guidelines: Endpoints used for relative effectiveness assessment of pharmaceuticals: clinical endpoints http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf Endpoints used for relative effectiveness assessment of pharmaceuticals: composite endpoints http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Composite%20endpoints.pdf Endpoints used in relative effectiveness assessment of pharmaceuticals: surrogate Endpoints http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Surrogate%20Endpoints.pdf Endpoints used for relative effectiveness assessment of pharmaceuticals: HRQOL and utility measures http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Health-related%20quality%20of%20life.pdf Safety: http://5026.fedimbo.belgium.be/outputs/methodological-guideline-rea-pharmaceuticals-safety See also recommendations for presentation from the GRADE working group http://www.gradeworkinggroup.org/publications/jce_series.htm		

General notes on using and adapting this section: This section provides a structured format for presenting the results of the evidence synthesis			
HTA CORE model reference	**Question:**	**In short form**	**Adaptation notes**
D0001	State the effects of the technology versus the comparator(s) on mortality.		
	State the effects of the technology versus the comparator(s) on the following aspects of morbidity:		
D0005	• Severity and frequency of symptoms and findings		
D0006	• Progression of disease		

D0011	• Body functions.		
	State the effects of the technology versus the comparator(s) on the following aspects of quality of life (QOL):		
D0012	• Generic health-related quality of life (HRQOL)		
D0013	• Disease-specific HRQOL		
D0014	• Work productivity		
D0016	• Activities of daily living.		
D0017	State the effects of the technology versus the comparator(s) on aspects of patient satisfaction.		
C0008	Highlight the difference in the risks and any differences in severity of adverse events of the technology and the comparator(s).		

5.12 Conclusions

Uses: Pharmaceuticals and medical devices		
Description: This section is used to present companies' interpretation and conclusions on the clinical effectiveness and safety of the technology derived from the synthesis of evidence and/or the summary of study results.		
Contents: Relative effects on mortality, morbidity, management, quality of life, satisfaction and patient safety.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Clinical effectiveness Safety	Mortality Morbidity Function Health related quality of life Patient satisfaction Patient safety	D0001 (mandatory REA); D0005 (mandatory REA); D0006 (mandatory REA), D0011(mandatory REA); D0014; D0016 (non-mandatory REA); D0012 (mandatory REA), D0013 (mandatory REA); D0017 (non-mandatory REA); C0001, C0008 (mandatory REA), C0002 (non-mandatory REA; mandatory for pharmaceuticals), C0004 (mandatory REA; non-mandatory for pharmaceuticals C0005 (mandatory REA), C0007 (non-mandatory REA), D0029
Related EUnetHTA guidelines: Endpoints used for relative effectiveness assessment of pharmaceuticals: clinical endpoints http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf Endpoints used for relative effectiveness assessment of pharmaceuticals: composite endpoints http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Composite%20endpoints.pdf Endpoints used in relative effectiveness assessment of pharmaceuticals: surrogate Endpoints http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Surrogate%20Endpoints.pdf Endpoints used for relative effectiveness assessment of pharmaceuticals: HRQOL and utility measures http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Health-related%20quality%20of%20life.pdf Safety: http://5026.fedimbo.belgium.be/outputs/methodological-guideline-rea-pharmaceuticals-safety		

General notes on using and adapting this section: Agencies can adapt the wording of this section to combine these 2 questions to create a single question about the benefit and harms "What are the overall benefits and harms of the technology in health outcomes?" HTA CORE model assessment element D0029.			
HTA CORE model reference	**Question:**	**In short form**	**Adaptation notes**
D0001, D0003, D0005, D0006, D0011, D0014, D0016 ,D0012, D0013, D0017	Provide a general interpretation of the evidence base considering the benefits associated with the technology relative to those of the comparators.	Y	Provide guidance on whether there are particular outcomes the company should focus on e.g. mortality, morbidity, disease progression, quality of life, satisfaction, convenience.
C0001, C0008, C0002, C0004, C0005, C0007.	Provide a general interpretation of the evidence base considering the harms associated with the technology relative to those of the comparators.	Y	Provide guidance on whether there are particular outcomes the company should focus on e.g. nature and severity of harms, dose relationship, changes in harms over time, susceptible patient

			groups, harms that can be caused by users of the technology or those who maintain it.

5.13 Strengths and limitations

Uses: Pharmaceuticals and medical devices		
Description: This section is used to record the strengths and limitations (internal and external validity) of the evidence base in relation to clinical effectiveness and safety.		
Contents: Internal validity, relevance of evidence base to scope, factors influencing reproducibility in clinical practice		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Health condition and use of the technology Description and characteristics of the technology Clinical effectiveness Safety	Domain methodology	-
Related EUnetHTA guidelines: Further information about internal validity can be found in: https://5026.fedimbo.belgium.be/outputs/methodological-guideline-rea-pharmaceuticals-internal-validity Further information about external validity can be found in: https://5026.fedimbo.belgium.be/outputs/methodological-guideline-rea-pharmaceuticals-applicability-evidence-context-rea Therapeutic Medical Devices under development		

General notes on using and adapting this section:			
HTA CORE model reference	**Question:**	**In short form**	**Adaptation notes**
EUnetHTA methodology guidelines and HTA CORE model methodology	Summarise the internal validity of the evidence base, taking into account the study quality, the validity of the endpoints used as well as the overall level of evidence. Include a statement about the consistency of the results observed in the evidence base.	Y	
	Provide a brief statement of the relevance of the evidence base to the scope of the assessment.	Y	
	Identify any factors that may influence the extent to which the study results may be applied to patients in routine clinical practice; e.g. how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of which patients are suitable for the technology.		

5.14 Safety risk management (pharmaceuticals)

Uses: Pharmaceuticals Some questions are relevant only for technologies launched.		
Description: This section is used to obtain information about how risk arising from use of the technology should be managed and changes that have been made since marketing authorisation to manage identified risks.		
Contents: Methods of optimising or limiting service to minimise risk, changes to marketing authorisation as a result of safety, other harms appearing after granting of marketing authorisation.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Safety	Safety risk management	C0061, C0062, C0063
Related EUnetHTA guidelines: Safety: http://5026.fedimbo.belgium.be/outputs/methodological-guideline-rea-pharmaceuticals-safety		

General notes on using and adapting this section:			
HTA CORE model reference	**Question:**	**In short form**	**Adaptation notes**
C0061, C0062, C0063	Comment on whether there is a need to optimise or limit the use of the technology, or to monitor the use of the technology, to minimise the potential risks to safety.		
	Describe any changes made to the marketing authorisation as a result of safety issues.		Use for health technologies already launched.
	Describe any other harms that have come to light after granting of the marketing authorisation or that have been identified outside of clinical trials (e.g. from pharmacovigilance and spontaneous reporting).		Use for health technologies already launched. Agencies may wish to consider whether they want the company to provide as an appendix the safety data that have been collected since the first authorisation.

5.14 Safety risk management (medical devices)

Uses: Medical devices Some questions are relevant only for technologies already launched.		
Description: This section is used to obtain information about how risk arising from use of the technology should be managed as well as information about manufacturer vigilance data.		
Contents: List of incidents, corrective measures, recalls, modifications, methods of optimising or limiting service to minimise risk.		
HTA CORE model domain	**HTA CORE model topic**	**HTA CORE model Assessment Elements**
Safety	Safety risk management	C0061, C0062, C0063
Related EUnetHTA guidelines: Safety: http://5026.fedimbo.belgium.be/outputs/methodological-guideline-rea-pharmaceuticals-safety Therapeutic Medical Devices under development		

General notes on using and adapting this section:			
HTA CORE model reference	**Question:**	**In short form**	**Adaptation notes**
	List the incidents to which the company has been alerted.		A table has been provided to facilitate completion.
	List the corrective measures, recalls and modifications that have taken place as a result of the incidents.		A table has been provided to facilitate completion, including standardised definitions to use.
C0061, C0062, C0063	Comment on whether there is a need to optimise or limit the use of the technology, or to monitor the use of the technology to minimise the potential risks to safety.		

