



eunethta

## **EUnetHTA JA2 WP8 DELIVERABLE**

### **HTA Core Model Version 3.0**

*for the full assessment of  
Diagnostic Technologies,  
Medical and Surgical Interventions,  
Pharmaceuticals and  
Screening Technologies*



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eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

## Joint Action on HTA 2012-2015

### HTA Core Model Version 3.0

25 Jan 2016

Was developed by  
Work Package 8 – Maintenance of HTA Core Model® infrastructure  
to support shared production and sharing of HTA information

WP 8 Lead Partner: National Institute for Health and Welfare



NATIONAL INSTITUTE  
FOR HEALTH AND WELFARE

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The HTA Core Model is a methodological framework for collaborative production and sharing of HTA information.

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This document contains the following applications of the HTA Core Model, produced by EUnetHTA Joint Action 2, Work Package 8 (WP8):

- Diagnostic technologies
- Medical and surgical interventions
- Pharmaceuticals
- Screening technologies

The application for rapid relative effectiveness of pharmaceuticals, produced by EUnetHTA Joint Action 2, WP5, is available as a separate PDF document. All HTA Core Model applications are available through [www.htacoremodel.info/BrowseModel.aspx](http://www.htacoremodel.info/BrowseModel.aspx).

Several changes have been made to the ontology, based on the feedback received during EUnetHTA Joint Action 2. The 'Social Aspects' domain has been renamed to 'Patients and Social Aspects' and its content has undergone a major revision. The contents of all other domains have been updated as well, but the changes are not equally substantial.

**IMPORTANT NOTE: This is a technical document, the purpose of which is to display all contents of the HTA Core Model in a single file. Please refer to the HTA Core Model User Guide, available through [www.htacoremodel.info/ViewHandbook.aspx](http://www.htacoremodel.info/ViewHandbook.aspx) for practical guidance on how to use the Model within HTA projects.**

The Model has been developed by an international expert group. See chapter 'Introduction - Contributors' in this document for details.

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# Introduction

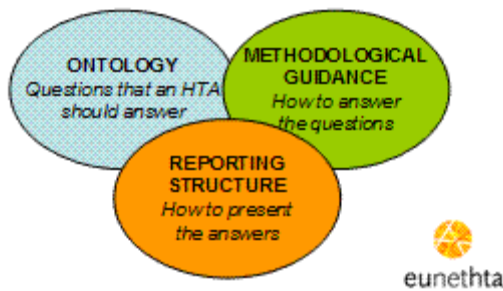
## *About the HTA Core Model<sup>®</sup> and its utilisation*

The HTA Core Model<sup>®</sup> (hereafter also ‘the Model’) is a methodological framework for collaborative production and sharing of HTA information. It consists of three main components:

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

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### The HTA Core Model



**Figure 1. Components of the HTA Core Model**

The main aim of the HTA Core Model is to enable international collaboration in producing HTA information and efficient sharing of the results so that redundant overlapping work in different countries and regions can be avoided. Normally, a health technology assessment (HTA) contains a vast amount of information. All potential content of HTAs is referred to here as ‘HTA information’. The content, focus, quality and reporting of HTAs vary significantly; this makes finding and transferring the information into local contexts difficult. The HTA Core Model addresses these problems in particular. The Model defines the content elements to be considered in an HTA and enables standardised reporting, consequently providing a common framework for the production of HTA.

Additionally, the Model can also be useful in several other tasks relevant for the development, utilisation and assessment of health technologies. Particularly the HTA ontology can be of interest to any activities where information on health technologies is produced, stored, searched and retrieved.

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The HTA Core Model divides HTA information into standardised items referred to as *assessment elements* – items of information that are relevant for the HTA. Each assessment element contains a question that one should consider including and answering within a specific assessment project. Furthermore, those elements most likely to be useful for international sharing of information are defined as *core elements*.

The HTA Core Model Online, available at [www.htacoremodel.info](http://www.htacoremodel.info), provides a computerised interface for the Model. It also contains a database of *core HTA information*, which refers to any HTA information that is produced using the Model. The database content is organized into *collections*, with each containing a number of *result cards* and other materials (e.g. an introduction and summary). The result cards contain the answers to the questions defined by the ontology.

A *core HTA* is one type of collection within the HTA Core Model Online. The purpose of each core HTA is to do the following: (1) provide answers to all relevant core elements of a specific technology; (2) consider the findings of each domain in ‘domain discussions’; and (3) summarize the most important findings. Users can also design their own collection by choosing a free selection of elements to be answered. One could, for example, consider sharing certain information from a national HTA project within other European HTA agencies by including it in the pool of core HTA information.

The HTA Core Model builds upon earlier work of EUR-ASSESS {1}, HTA Europe {2} and ECHTA/ECAHI {3, 4} projects, as well as upon other theoretical guidance referenced in relevant locations. The Model attempts to adhere to the definitions of HTA that emphasize the multidisciplinary nature of assessments, and it employs the nine domains that were originally identified in the EUR-ASSESS project (Table 1). Specific three-letter abbreviations of the domain names are commonly used in the documentation.

### **Table 1. Domains of HTA**

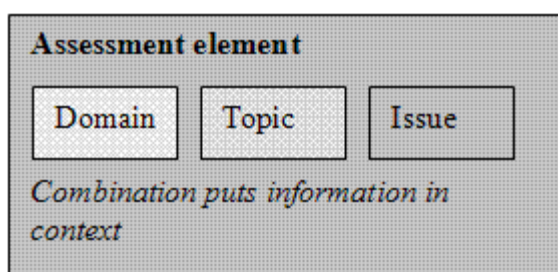
1. Health problem and current use of technology (CUR)
2. Description and technical characteristics of technology (TEC)
3. Safety (SAF)
4. Clinical effectiveness (EFF)
5. Costs and economic evaluation (ECO)
6. Ethical analysis (ETH)
7. Organisational aspects (ORG)
8. Patients and Social aspects (SOC)
9. Legal aspects (LEG)

The HTA Core Model was originally developed through *applications*, each of which focused on a specific type of technology. The first two applications, one for medical and surgical interventions {5} and the other for diagnostic technologies {6}, were created by Work Package 4 (WP4) of the EUnetHTA Project 2006-08. Furthermore, WP4 of EUnetHTA Joint Action 2010-2012 {7} developed an application for screening technologies. A fourth application to enable rapid relative effectiveness assessment (REA) of pharmaceuticals was developed by WP5 of EUnetHTA Joint Action {8}. Version 2.0 was produced within the WP8 of EUnetHTA Joint Action 2 (2012-2015) as a major overhaul of the applications on interventions, diagnostics and screening, and it was

supplemented by a new application for full assessment of pharmaceuticals. Versions 2.1 and 3.0 are also products of JA2 WP8 and contain improvements suggested by various users or identified by the developers. The application for rapid REA of pharmaceuticals will be updated separately by WP5 of Joint Action 2.

## The ontology

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



**Figure 2. An assessment element**

Assessment elements define the standardized pieces of HTA information. Each assessment element is defined more thoroughly in an *element card*, which provides further information on the element and its relation to other elements. An element card may also provide advice on how to answer the question that the element defines.

Each HTA project should evaluate the relevance of the generic questions defined by the assessment elements, while considering the technology that is the object of assessment as well as the project's aims and resources. When producing a collection of core HTA information, some collection types may carry specific requirements. During each project, relevant questions are included in the collection, translated into practical research questions and answered. When producing a core HTA, all core elements must be included in the collection. If some question is not relevant for the technology under assessment, an explanation of why it is not relevant can be included in the collection.

*Element cards* are a technical method of concisely presenting a relatively large amount of data pertaining to each assessment element. Users of the HTA Core Model Online do not need to use element cards when producing HTA information, as the online tool displays only the relevant contents of the Model in each phase of the work process. The data contained by the element cards is listed in Table 2.

**Table 2. Contents of an assessment element card**

<b>Header</b>	Unique identifier (Id) of the assessment element Issue (the generic question) Topic
<b>Application-specific properties</b>	<i>Application and Uses</i> indicate whether the element is included in the various HTA Core Model applications <i>Importance</i> defines how important it is to consider the particular issue when conducting HTA. This importance relates to the significance from the viewpoint of HTA. It is not always the same as ‘relevance’ in a particular policy context. There are three categories of importance: Critical (Should always be considered in an HTA); Important (Should be considered in most HTAs); Optional (May provide useful information) <i>Transferability</i> is an estimate about the transferability of data or other findings from one context to another. There are three categories of transferability: Complete (Data/findings are context-independent); Partially (Data/findings are not directly transferable from one setting to another. Adjustments are needed.); None (Data/findings are not transferable from one setting to another without serious difficulties.) <i>Core</i> defines whether the element being described is a core element. This is based on the element’s importance and transferability in each model application. See further details below under the heading ‘Being in or out of the core’. <i>Order</i> indicates the ordinal number of the element within a domain in different model applications. The element with no. 1 is the first element of a domain.
<b>Clarification*</b>	A more detailed description of what the issue addresses.
<b>Methodology and sources*</b>	Methodological advice on how to answer the research question(s) made of this assessment element.
<b>References</b>	Original key references used when including this issue in the HTA Core Model.
<b>Content relations*</b>	A list of assessment elements that deal with similar themes as this element.
<b>Sequential relations*</b>	A list of assessment elements likely to provide useful information when answering the questions regarding this element. This information can be used when defining projects and the order in which various research questions should be answered.
<b>Other domains</b>	Some elements are shared, i.e. included in more than one domain. This field contains a list of other domains where this element is included (if relevant).
<p>* Data relevant to all model applications in which the element is included is indicated as ‘Common to all used applications’. Data relevant for specific applications only are indicated as such, for example ‘Specific to Screening Technologies’.</p>	

## ***Being in or out of the core***

Dividing the assessment elements into core elements and non-core elements has been an attempt of the model developers to support researchers in focusing on those research questions which are most likely to be useful to share in an international context.

The method of prioritizing some elements over others (see below) has received both support and criticism from the users of the Model. Due to its controversial nature, the division of elements into two groups, as well as associated data regarding importance and transferability of assessment elements, should be viewed as an experimental feature of the Model that does not mandate the practical utilisation of the Model in any way.

Including an element into the core depends on two of its basic characteristics: its importance and transferability. If the information is fully or partly transferable, it may provide valuable input beyond its original place of origin. Transferability is low for information that is very specific to a particular context (e.g. region, country or health care system) and is most likely not useful as such in other settings. However, even non-transferable information may be useful beyond its place of origin. For example Italian incidence data on cardiovascular mortality is applicable not only to a regional HTA in Italy, but also to all Italian HTAs assessing cardiovascular technologies; similarly, Swedish data on the current use of some technology may provide researchers in another country with useful benchmark data when considering possible over- or underuse of the technology in their own country.

Importance is included as a category in order to ensure that the core is robust enough, i.e. that it contains information highly significant from the viewpoint of HTA. The importance considered here is not equal to the relevance of information to a particular policy question. It is assumed, however, that issues perceived as important from the viewpoint of HTA are often useful when making decisions about healthcare policy.

Including an element into the core is defined according to the following core matrix.

**Table 3. Core matrix**

CORE MATRIX		Importance		
		<i>1 Optional</i>	<i>2 Important</i>	<i>3 Critical</i>
Transferability	<i>3 Complete</i>	Not core	Core	Core
	<i>2 Partially</i>	Not core	Core	Core
	<i>1 None</i>	Not core	Not core	Core

It should be emphasized that the inclusion/exclusion of an element into/from the core is driven by the usability of the information across national borders or in other contexts. If an element is not part of the core, this does not make it unimportant, insignificant or not otherwise worth considering in an HTA. In the same way, important assessment elements which are, however, non-transferable are excluded from the core by definition (see Core matrix above). Such elements are likely to provide

useful or even critical information to guide decision-making and need to be addressed locally by individual HTA agencies or by other research.

In this version of the Model, the level of importance and transferability assigned to each assessment element is still based on the views of model developers, i.e. on the opinions of HTA experts. In the future, the data can be compared with practical experience from real-life HTA projects and the levels can be adjusted accordingly.

The non-core elements are not excluded from the Model completely for three reasons: 1) An element may be part of the core in some model application (e.g. for screening) while out of the core in some other application (e.g. for pharmaceuticals); 2) As explained above, the assigned values for the importance and transferability of each assessment element are estimates, based on several assumptions and the values may change over time when more practical experience of Model use is acquired. 3) Even the optional and non-transferable elements may be important to have available in some assessments and including them in the Model provides a standardised ontology also for such situations.

It should also be emphasized that the values assigned for importance and transferability, as well as the choices made in including specific importance-transferability combinations in the “core” may be highly specific to EUnetHTA and the settings in which its member organisations operate.

Consequently the division of elements to core and non-core should be applied in specific settings only if deemed useful. Keeping in mind the experimental nature of these features of the Model, individual users or organisations may choose themselves whether and how to utilise the core/non-core status of elements or the data on elements’ importance and transferability.

It is possible for different user groups to make their own lists of elements that are prioritized over others. Such an approach is used in the *Procedure Manual for rapid REAs of pharmaceuticals* (available through [www.htacoremodel.info/BrowseModel.aspx](http://www.htacoremodel.info/BrowseModel.aspx)) that provides guidance on using the HTA Core Model in specific types of projects within EUnetHTA. Some assessment elements are in this Manual marked as “mandatory” and should not be omitted in relevant projects.

## Methodological guidance

Methodological guidance in the Model is present on three levels. This introduction contains some project-level guidance in the form of ethical principles steering all HTA projects that utilise the HTA Core Model. Domain-level guidance is included in the methodology chapters of the nine respective domains, providing an overview of relevant scientific methodologies and links to further guidance on various themes available elsewhere. Assessment element –level guidance is available in individual element cards. It provides more detailed, practical assistance for answering specific research questions.

The EUnetHTA has produced a number of more detailed *EUnetHTA Guidelines* on various methodological topics. Methodological guidance within the HTA Core Model links to these guidelines in relevant sections. A full list of these guidelines is available at [www.eunethta.eu/eunethta-guidelines](http://www.eunethta.eu/eunethta-guidelines).

## Common reporting structure

Answers to the questions defined by the assessment elements are recorded as structured pieces of information, presented as question-answer-pairs. In the HTA Core Model Online these pairs are stored and can be presented as *result cards*. These are organized into collections which then form a coherent package of information, including text and other materials, as well as metadata that enables effective use of the cards in the database of core HTA information.

Currently two reporting templates have been developed for core HTA information collections, one for “core HTAs”, i.e. comprehensive assessments that contain an extensive analysis of a health technology through all nine domains and all core elements, and another for rapid assessments that focus on a limited set of domains.

For core HTAs, the information is organised as follows:

- **Collection Summary** Contains an overview of all findings in the collection. No recommendation on the use or non-use of the technology in health systems must be included in core HTA information collections. Includes a standard table summarising the consequences of using or not using the technology and the comparator(s) used in the assessment (see below).
- **Collection Methodology** Indicates the process and overall methods used in producing the collection.
- **Collection Introduction** Provides an overview of the collection, including the reasons why, and the context in which, the collection was produced.
- **Scope** A structured project scope which provides a well-defined starting point for analysis within different domains. Ensures the coherence of analysis within different domains.
- **Domain-specific sections (Each domain contains the following sections)**
  - **Introduction of domain:** Indicates the specific features of the technology that are noteworthy from the domain’s viewpoint, as well as the reasons for including the domain in the collection.
  - **Domain methodology:** Indicates the scientific methodology used within the analysis of this domain.
  - **Assessment elements of the domain** (Each element contains the following sections):
    - **Method** (optional): Used when the overall domain methodology differs from the one used in answering questions defined by the assessment element, or when the domain methodology does not provide a detailed enough description.
    - **Result:** Answer(s) to the research question(s) defined by one assessment element, with a focus on evidence or facts whenever feasible. Answers should adhere to each domain’s scientific principles and style.
    - **Comment:** (optional) While the result field typically focuses on evidence or facts, this field can be used to add researchers’ views on the result and its quality. Similar

to the discussion chapter found in journal articles, but with a focus on the question(s) included in the relevant result card.

- **Discussion:** Also similar to the discussion chapter found in journal articles, with a focus on one domain. Interpretation, significance of methodological issues encountered, and indications for further research can be included here.
- **References** All references used in the result cards and domain texts (introduction, methodology, discussion).
- **Appendices** All appendices of a domain.
- **Collection Appendices** All appendices used in the collection-level chapters (summary, methodology, introduction, scope) or within the content of more than one domain.

A summary table representing the consequences of using/not using the technology that is being assessed is available for use in the summary of the collection (Table 4).

**Table 4. Consequences**

Consequence	Using the technology under assessment	Using the comparator	Level of evidence (if applicable)	Comment

The template for rapid assessments is available through the HTA Core Model Online and the WP5 documentation.

## *HTA Core Model Version 3.0*

### Updated content

The HTA Core Model version 3.0 contains the following substantial changes to the previous version 2.1:

- The ontology has been further revised to reduce redundant overlaps across the various assessment elements. While in the version 2.1 the ontology was revised primarily for the domains CUR, TEC, SAF and EFF, the revision in 3.0 covers all domains.
- A professional English language editor has reviewed and improved most materials.
- The Social Aspects domain has been renamed to Patients and Social Aspects domain, and its content has undergone a major revision. The abbreviation SOC remains unchanged.

- Contents of all other domains have been updated.

The 'Table 1' in the first chapter of each domain ('Description') lists all topics and issues in that domain.

Changes affecting the questions in the ontology have been indicated and addressed in further detail in a separate document available through [www.htacoremodel.info/BrowseModel.aspx](http://www.htacoremodel.info/BrowseModel.aspx).

## Work process

A draft version of 2.1 was submitted for public consultation through the EUnetHTA web site ([www.eunethta.eu](http://www.eunethta.eu)) on the 15<sup>th</sup> of November 2014. Feedback gathering took place until the 7<sup>th</sup> of December 2014. The new version also received internal (EUnetHTA) feedback from WP1, WP4, WP5 and WP7 and was discussed in a joint meeting on the 20<sup>th</sup> of January 2015. Further feedback was provided by Roche Pharma through their internal review of the usefulness of the Model, and it was published on the 21<sup>st</sup> of December 2014 {9}.

The feedback from all aforementioned sources has been taken into consideration by the model developers during 2015. Due to the extensive amount of feedback, model developers needed to carefully consider all the requested changes. Some of the changes were implemented in version 2.1 (published in April 2015) and the remaining changes in the (current) version 3.0. A draft of 3.0 was published in June 2015 to show intermediate progress of work and to allow further feedback and coordination, as well as an advanced version for the English language editor, who focused on grammar, readability and consistency of content. The model developers considered also the suggestion to merge CUR and TEC domains, but decided not to do so for this version. It might bring some further clarity to the Model, but needs to be considered after obtaining further practical experience using the current updated ontology. Such a change should also be done in close cooperation with the developers of the model applications for rapid assessments.

## *HTA Core Model 2.0 and 2.1*

The version 3.0 builds heavily upon versions 2.0 and 2.1, of which the former was a more considerable overhaul of the whole Model. Those interested in the development process as a whole, can find the more detailed methodology in the documentation of the earlier versions, available through [www.htacoremodel.info/BrowseModel.aspx](http://www.htacoremodel.info/BrowseModel.aspx).

## Important definitions in the context of HTA Core Model applications

For the purposes of using and further developing the Model, the following explicit definitions and limitations regarding the various applications apply.

### *Medical and surgical interventions*

The HTA Core Model for medical and surgical interventions addresses all therapeutic acts or methods of interfering with the aetiology, symptoms, or progress of a health condition.

### *Diagnostic technologies*

Diagnostic technology is any technology or procedure that is used to confirm, exclude or classify disease, or to monitor progress of the disease or the response to therapy. {11}

The application does not include all generic questions or other content relevant for prognostic tests.

Questions related to the clinical utility and clinical validity of diagnostic tests are important and are covered by the model application. However, considering that clinical utility or validity is not required when obtaining market access for devices, the questions related to the analytical validity of diagnostic technologies are often important for the HTA community as well. The questions related to analytical validity, e.g. repeatability and other more technical test properties, are less developed in the current Model application.

### *Screening technologies*

The producers of core HTA information should be aware of how the word ‘screening’ can be attributed to a multitude of uses, and hence how 'HTA Core Model on screening technologies' is not applicable to the assessment of everything that is called screening. The primary target is the **full population screening programme** with the following components:

- It involves a test, an examination or a series of tests/examinations, AND
- It is provided either systematically to the whole target population (i.e. in a screening programme), or unsystematically to asymptomatic people, e.g. in the form of locally provided health promotion or case finding programs, AND
- It is done in order to make a statement regarding the possibility of having a certain disease or risk factor, AND
- It aims at improved prognosis, or an improvement of the management or coping with the disease (excludes technologies which aim at surveying the prevalence or spread of a certain disease, risk factor, or exposure only).

Sometimes it is necessary to assess only a certain part of the programme; e.g. the effects of replacing the conventional mammography device with a digital one in a breast cancer screening programme. In this case, a relevant subset of the HTA Core Model of screening technologies is likely applicable.

The HTA Core Model on screening technologies **is not suitable** when the aim of the HTA is assessing:

- The accuracy of a single test to determine exposure/risk factor or disease
- Effectiveness of opportunistic screening practices.

See Appendix Intro-Scr for more information on screening.

The screening application was originally pilot-tested in a project assessing the screening of abdominal aortic aneurysms {13}.

## *Ethics of HTA*

Ethical aspects of health technologies should be considered in HTAs and thus they are included in the HTA Core Model. Ethics, however, also has a broader application within the field of HTA. The assessments themselves should be designed in such a way that key ethical principles are considered and respected.

In order to safeguard against unethical use of technologies and to provide information about how they can instead be used in a beneficial way, every HTA process should be performed with consideration paid to the following ethical issues:

- The driving forces (and valued interests) behind the plan to perform the assessment at this particular stage should be identified, including the stakeholders and the whole HTA organisation.
- The morally relevant reasons for performing/not performing an HTA on the topic should be identified.
- The interests of the technology producers should be identified.
- Possible related technologies that are morally contentious should be identified.
- The interests of the content expert group should be discussed openly in order for the work to be conducted in an objective and independent way.
- The choice of endpoints in the assessment has to be carefully considered.
- The morally relevant issues related to the selection of meta-analyses and studies the HTA means to include must be identified.
- The scope of the HTA and the choice of research methods (e.g. inclusion of other assessment aspects than effectiveness in the literature searches).

These issues are discussed in further detail in the Appendix Intro-Eth.

## *Value judgments*

Multiple value judgments are made, either explicitly or implicitly, in the HTA process and in subsequent healthcare decisions. According to Strech {14-17}, value judgments occur in four instances when producing evidence (be it HTA or clinical systematic review, etc.):

- In the selection of evaluation criteria
- In the specification of evaluation criteria
- About the validity of the results
- In the weighting of results

In practice, when producing HTA information, value judgments are particularly necessary during the following phases: 'scoping', 'synthesis' and 'critical appraisal of evidence'. They are also applicable in individual domains when selecting, weighing, and reviewing available evidence – especially in the clinical effectiveness, and costs and economic evaluation domains. Making value judgments explicit can contribute to the transparency of the HTA produced and to any assessment of the overall validity of the produced HTA. Therefore, core HTA information producers should aim towards being appropriately explicit.

## **Benefit-risk balance**

Balancing benefits and risks of technology use – or benefit-risk assessment – is a common part of regulatory processes. Similar weighing of positive and negative consequences of technology use (or non-use) often takes place within HTA processes. In this version of the Model, considerations related to this have been included into some assessment elements of the clinical effectiveness, safety, costs and economic evaluation and the ethical analysis domains. However, developers have refrained from adding such considerations to the common reporting structure as a collection-level chapter – this is because value judgments associated with the weighting of results typically take place at the local (national or regional) level and are not a central part of core HTA information, which focuses primarily on evidence (which, of course, is itself likely to include the value judgments mentioned above). Instead, it was decided that the collection summary would include a table which lists the consequences of using either the technology that is being assessed or its comparator.

## Contributors

### HTA Core Model update – Version 3.0

The contributors are listed in the following table:

HTA Core Model update – Version 3.0									
	CUR-TEC-ORG			EFF-SAF-ECO			SOC-ETH-LEG		
	CUR	TEC	ORG	EFF	SAF	ECO	SOC	ETH	LEG
Primary Investigators	THL, Finland <i>Kristian Lampe</i>	NSPH, Romania <i>Daniela Valceanu &amp; Marius Ciutan</i>	THL, Finland <i>Ulla Saalasti-Koskinen</i>	UMIT, Austria <i>Petra Schnell-Inderst &amp; Gaby Sroczynski</i>	UTA, Estonia <i>Rainer Reile</i>	THL, Finland <i>Neill Booth</i>	CFK, Denmark <i>Lisbeth Ørtenblad</i>	SBU, Sweden <i>Sophie Werkö &amp; Emelie Heintz</i>	Summaryx Ltd, subcontracted by THL, Finland <i>Iris Pasternack</i>
Investigators	NSPH, Romania <i>Cristian Vladescu &amp; Daniela Valceanu</i>		CFK, Denmark <i>Lotte Groth Jensen</i>	SBU, Sweden <i>Sanna Axelsson</i>  NSPH, Romania <i>Silvia Gabriela Scintee &amp; Marius Ciutan</i>  UMIT, Austria <i>Uwe Siebert</i>	THL, Finland <i>Marjukka Mäkelä</i>	FIMEA, Finland <i>Ulla Härkönen</i>  THL, Finland <i>Taru Haula</i>  KCE, Belgium <i>Irina Cleemput</i>  UMIT, Austria <i>Beate Jahn</i>	HTAi/PCIG* <i>Karen Facey &amp; Alessandra Lo Scalzo</i>  THL, Finland <i>Niina Kovanen</i>  NSPH, Romania <i>Silvia Gabriela Scintee &amp; Marius Ciutan</i>  UTA, Estonia <i>Rainer Reile</i>	CVZ, Netherlands <i>Payam Abrishami</i>  SBU, Sweden <i>Mikael Nilsson</i>  THL, Finland <i>Maija Hytönen</i>	<i>Only minor changes to version 2.1 were implemented, hence no domain team.</i>

	CUR-TEC-ORG			EFF-SAF-ECO			SOC-ETH-LEG		
	CUR	TEC	ORG	EFF	SAF	ECO	SOC	ETH	LEG
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\* The Patient and Citizen Involvement Interest Group of the Health Technology Assessment International (HTAi).

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Some changes in the ontology are based on feedback from other Work Packages, see details below (Version 2.1).

## HTA Core Model update – Version 2.1

### Legal domain

Primary investigator: Hanna Korpela, Summaryx Ltd (subcontracted by THL, Finland)

Investigators: Iris Pasternack, Summaryx Ltd (subcontracted by THL, Finland) , Ingrid Wilbacher, HVB (Austria)

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### Ontology Update

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ECO Neill Booth, THL (Finland)

ETH Sophie Werkö & Emelie Heintz, SBU (Sweden)

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The ontology was updated after discussions with several representatives from Work Packages 4, 5, 7 and 8. We acknowledge in particular the following persons as members of the ontology revision working group: Sarah Kleijnen, ZIN (Netherlands); Anna Nachtnebel, LBI-HTA (Austria); Luciana Ballini, ASSR Regione Emilia-Romagna (Italy); Lidia Becla, ZIN (Netherlands); Julia Chamova, DHMA (Denmark); Mirella Corio, AGENAS (Italy); Zoe Garrett, NICE (United Kingdom); Mirjana Huic, AAZ (Croatia); Finn Kristensen, DHMA (Denmark); Alessandra Lo Scalzo, AGENAS (Italy); Julia Mayer, LBI-HTA (Austria); Antonio Migliore, AGENAS (Italy); Maria Rosaria Perrini, AGENAS (Italy); Simone Warren, ZIN (Netherlands).

**Technical revision of table nr 1s in domain descriptions**

Sari Bombino, THL (Finland)

**HTA Core Model update – Version 2.0**

The contributors are listed in the following table:

HTA Core Model update – Version 2.0									
	CUR-TEC-ORG			EFF-SAF-ECO			SOC-ETH-LEG		
	CUR	TEC	ORG	EFF	SAF	ECO	SOC	ETH	LEG
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Investigators	NSPH, Romania <i>Cristian Vladescu &amp; Nona Chiriac</i>	UTA, Estonia <i>Rainer Reile</i>	CFK, Denmark <i>Lotte Groth Jensen</i>	SBU, Sweden <i>Sanna Axelsson</i>  NSPH, Romania <i>Silvia Gabriela Scintee &amp; Marius Ciutan</i>  UMIT, Austria <i>Uwe Siebert</i>	THL, Finland <i>Marjukka Mäkelä</i>	THL, Finland <i>Taru Haula</i>  KCE, Belgium <i>Irina Cleemput</i>  UMIT, Austria <i>Beate Jahn(until May 2013 &amp; Nikolai Mühlberger)</i>	THL, Finland <i>Niina Kovanen</i>  NSPH, Romania <i>Silvia Gabriela Scintee &amp; Marius Ciutan</i>  UTA, Estonia <i>Rainer Reile</i>	CVZ, Netherlands <i>Payam Abrishami</i>  SBU, Sweden <i>Mikael Nilsson</i>  THL, Finland <i>Maija Hytönen</i>	Not updated

	CUR-TEC-ORG			EFF-SAF-ECO			SOC-ETH-LEG		
	CUR	TEC	ORG	EFF	SAF	ECO	SOC	ETH	LEG
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Internal Reviewers  <b>WHOLE CLUSTER</b>	Finland, THL and FIMEA  Russia, NCHTA			Austria, UMIT  Finland, THL and FIMEA  Romania, NSPH  Russia, NCHTA			Austria, UMIT  Denmark, CFK  Finland, THL  Russia, NCHTA		

### Earlier versions

The current work builds upon the earlier versions of the HTA Core Model. The many contributors of the earlier versions can be found in the Screening Model 1.0 (PDF document, page 15), available at [www.htacoremodel.info/BrowseModel.aspx](http://www.htacoremodel.info/BrowseModel.aspx).

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# Health Problem and Current Use of the Technology (CUR)

## *Description*

### What is this domain about

This domain describes the target conditions, target groups, epidemiology and the availability and patterns of use of the technology in question. Furthermore, the domain addresses the burden – both on individuals and on the society – caused by the health problem, the alternatives to the technology in question, as well as the regulatory status of the technology and the requirements for its use. Some of the topics considered relevant for this domain have generally been called ‘Background Information’ in previous European projects or recommendations for conducting assessments. {1-3}

Health Problem and Current Use of the Technology (CUR) covers the qualitative description of the **target condition**, including the underlying mechanism (pathophysiology), natural history (i.e. course of disease), available screening and diagnostic methods, prognosis, and epidemiology (incidence, prevalence), as well as the underlying risk factors for acquiring the condition as well as available treatments. A description of subgroups or special indications should be included especially in the case when the technology does not target the whole population.

**Current management** patterns of the condition should be described, including the technology as such and its alternatives, as well as recommended policies for determining the target population. It should also be specified whether the technology is intended to replace or supplement another technology in the management chain. Anticipated problems in the use, e.g., inappropriate extension of indications (off-label use), participation rate or compliance, overdiagnosis and misuse are to be discussed, as are the alternatives to the technology and the agreed-upon policies regarding the choice of patients or target group for treatment.

Regulatory information on the marketing authorisation or CE marking (if relevant), as well as on the reimbursement status is also included in this domain, as such information describes the formal position of the technology within health care system(s).

Information for this domain is drawn from recent HTAs, surveys, epidemiological research, clinical guidelines, device registers, routine statistics, and administrative databases. Furthermore, health care providers, the industry and patients can provide useful (possibly qualitative) information. In general, the information within this domain is not always fully transferable. The transferability depends on whether the analysis used aggregate figures for Europe or detailed incidence data per country. The answers to questions defined in this domain can be used, as such (or after an update), in several different collections of core HTA information. For instance, an answer describing the incidence and prevalence of the target condition, e.g., coronary artery disease, is most likely a useful piece of information for all core HTA information collections dealing with the same disease.

**Table 1: Topics and issues in this domain**

<b>Topic</b>	<b>Issue</b>	<b>Assessment element ID</b>
Target Population	What is the target population in this assessment?	A0007
Target Population	How many people belong to the target population?	A0023
Target Condition	What is the disease or health condition in the scope of this assessment?	A0002
Target Condition	What are the known risk factors for the disease or health condition?	A0003
Target Condition	What is the natural course of the disease or health condition?	A0004
Target Condition	What are the symptoms and the burden of disease or health condition for the patient?	A0005
Target Condition	What are the consequences of the disease or health condition for the society?	A0006
Target Condition	What aspects of the consequences/burden of disease are targeted by the technology?	A0009
Current Management of the Condition	What are the other typical or common alternatives to the current technology?	A0018
Current Management of the Condition	How is the disease or health condition currently diagnosed according to published guidelines and in practice?	A0024
Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?	A0025
Utilisation	For which health conditions and populations, and for what purposes is the technology used?	A0001

Utilisation	How much are the technologies utilised?	A0011
Utilisation	What kind of variations in use are there across countries/regions/settings?	A0012
Utilisation	Who decides which people are eligible for the technology and on what basis?	G0009
Utilisation	Is the technology a new, innovative mode of care, an add-on to, or modification of a standard mode of care, or a replacement of a standard mode of care?	F0001
Regulatory Status	For which indications has the technology received marketing authorisation or CE marking?	A0020
Regulatory Status	What is the reimbursement status of the technology?	A0021

## Why is this domain important

The information produced in this domain provides baseline knowledge which becomes necessary when the results from other assessment domains are put into context in a particular geographical, target population, or organisational setting. Clearly defined health problem(s) and target population(s) assist in defining appropriate use of the technology.

During the CUR analysis, one might also discover the current management practice of a health condition to actually differ from evidence-based guidelines. In such situations, improving compliance to the guidelines regarding an existing technology might be more appropriate than introducing a new technology that may be more costly, and not necessarily more effective, than the existing technology. Consequently, the analysis within this domain aims at providing the ‘big picture’ regarding the setting where the technology is supposed to be used.

Health technologies are often not used for a single purpose. An HTA report often considers a single technology for a single purpose, e.g., ultrasound for diagnosing gallstones. CUR analysis, however, should provide a wider view on the other possible uses of the same technology, as the introduction of a technology for single use may lead it actually becoming used for more than one purpose (e.g. for more than one diagnosis). The analysis in this domain can help both HTA experts and decision-makers to better understand all relevant implications of applying or implementing a health technology.

National decision-makers are interested in knowing the extent to which a technology is or can be utilised in their own country, and in knowing about regional variation. On the other hand, international benchmarking may have a great impact on the decision-making process {4,5}; it may be particularly important in cases where the estimation of the harm-benefit-costs equation is inconclusive. It could prove important to become aware of the variation in management patterns

and current use of the technology in different countries, as this may reflect country-specific epidemiology and priorities, but can also be an indication of regional or national under- or overuse of the technology. In Europe, it is rare to see great variation in approval status of technologies; therefore it may be of interest to compare the technology's status to non-European countries.

Finally, answers to questions defined within this domain provide an important input for addressing questions in other domains (see below).

## Relations to other domains

Issues in this domain should be considered at an early stage of a core HTA information project, as they may help with refining the research questions and formulating the methodological approach of, e.g., Clinical Effectiveness (EFF), Costs and Economic Evaluation (ECO) and Organisational Aspects (ORG) domains. The life cycle of the technology, its regulatory (approval and coverage) status and manufacturer information are of joint interest to other domains (Description and Technical Characteristics of the Technology (TEC), ORG, Patients and Social Aspects (SOC), Ethical Analysis (ETH), and Legal Aspects (LEG) domains).

The answers to CUR domain questions, together with TEC and ORG ones, may render the original scope of an HTA project partially outdated or target matters of secondary importance. Consequently, it is recommended that project groups reconsider the scope of their project once preliminary results of the CUR, TEC and ORG domains become available.

Some issues in this domain will inevitably overlap with issues in EFF and ECO (e.g. issues of consequences and alternative interventions), ORG (e.g. utilisation issues), TEC (e.g. life-cycle), SOC (coverage and access issues), LEG and ETH domains, as well as with the Safety (SAF) domain (e.g. overdiagnosis, false positive and false negative test results). It is important to coordinate the work regarding these issues, and to determine how to deal with potential overlaps within a particular core HTA information project, so that redundant work is avoided.

## Diagnostics-specific content

For assessing diagnostic technologies, it is crucial to understand the role of the technology in the entire healthcare pathway, including diagnostics and treatment, and also in relation to existing technologies.

Current options for diagnostics and therapy should be described, particularly the reference standard and how good the standard is in classifying the condition. All other information relevant for diagnostics, and its meaning for treatment decisions, should also be included.

The report should additionally include the effect of available treatments on the course and prognosis of the health condition, and it should describe the background information for estimating benefits and harms, e.g., the consequences of a correct or wrong diagnosis.

## Screening-specific content

A technology is usually proposed for screening after a long utilisation in clinical diagnostic use. This means that assessing a screening technology usually entails assessing the features of the technology in a new context of application. When a technology is used in screening, the assessment should account for the whole management chain, from the screening test, through the subsequent diagnostic tests, to treatments. It is therefore important to distinguish whether the proposed assessment topic includes a new screening technology that only slightly modifies the existing screening pathway, or whether it is an assessment of a completely new screening pathway. Regulatory processes rarely distinguish between uses of a technology in a clinical or a screening setting.

Knowledge on the following aspects is essential for constructing decision-analytic models for screening technologies:

1. Natural course of the health problem
2. Diagnosis of the health problem
3. Effect of available treatments on the course and prognosis
4. Burden of disease, incidence, mortality, survival
5. Current guidelines and existing screening flow charts
6. Effects of the screening technology on the epidemiology (incidence, prevalence, overdiagnosis) of the health problem

## *Methodology*

### Process for answering research questions

Although the *HTA Core Model* calls all questions deriving from the generic issues ‘research questions’, it is important to keep in mind that the questions and answering methodologies of this domain are in many ways different than in several other domains. Instead of trying to discover the ‘value’ of the technology - as is the case, e.g., in the EFF and ECO domains - the analysis in this domain aims at providing many of the other domains, and the whole collection of HTA information, a pragmatic and practical set of background information. The information should be gathered and compiled in an adequately reliable manner that matches the intended extent of analysis within the other domains and the type of collection. Extensive collections, such as core HTAs, most likely benefit from a robust set of information in this domain, whereas a rapid assessment may need less information.

In several cases, methodologies familiar from clinical or HTA research are not suitable for finding proper up-to-date answers for questions of this domain. Consequently, it may be much faster and more efficient to collect a proper background set of information through an international survey among HTA agencies, health ministries or health service providers, rather than to perform extensive

literature searches to conclude that ‘evidence was not available’ – an answer that is not at all helpful in this domain.

The researchers working on the CUR domain should consider their basic approach very early on in the project, as several other domains depend on the answers of this domain. The same applies to the TEC and ORG domains. A joint survey early on in the project should be considered as a pragmatic approach to finding answers to key questions of these three domains. In addition, other domains should contribute to these survey questions so that they provide useful information for all domains

An example of such a survey is available in the core HTA on abdominal aortic aneurysm screening at <https://mekat.thl.fi/htacore/DownloadAttachment.aspx?id=106.COL%20Appendix%201>.

If the researchers of this domain decide to make a full systematic literature review to answer one or more questions in this domain, they should also consult the EUnetHTA Guideline [Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness](http://www.eunethta.eu/eunethta-guidelines), available at <http://www.eunethta.eu/eunethta-guidelines>. Although focusing on effectiveness, the guideline may provide useful advice for work within other domains as well.

## Gathering information

### *Where to find information*

The source of information will depend on the location of a technology within its product life cycle. Review articles and textbooks can be helpful when searching for information about the history and characteristics of an established technology. The information concerning the technology may be obtained from its manufacturers, from clinical experts using the technology, but also from literature (i.e. descriptive publications). For prototypes and innovative technologies, published peer reviewed literature may be limited. It may need to be supplemented with grey literature (includes non-peer reviewed and non-published literature, as well as confidential commercial information) as well as with anecdotal information from general web-searches. There are some issues, e.g., the coverage status of a technology (inclusion in the benefit catalogue, levels of co-payment, etc.), where information is not easy to retrieve. Identification of adequate and usable information sources requires local knowledge of the healthcare system {1}. This data can be obtained through a survey early on in the project.

Whenever the technology is subject to some form of regulation, the regulatory documents are also important sources of information for this domain.

### Databases and search strategies

Some important databases and other possibly useful sources of information for the analysis in this domain are listed below. The list is extensive and researchers within each HTA project should carefully consider which sources best match the needs of their project. It is also recommended to use the *Summarised Research in Information Retrieval for HTA* (SuRe Info, available at <http://vortal.htai.org/?q=sure-info>), which provides research-based information relating to the information retrieval aspects of producing health technology assessment.

## **Bibliographic databases on published literature**

- Health sciences:
  - MEDLINE (published by the United States National Library of Medicine) / Pubmed <http://www.ncbi.nlm.nih.gov/pubmed>,
  - EMBASE (Excerpta Medica published by Elsevier) (<http://www.embase.com>),
  - Cochrane Library ([www.cochranelibrary.com](http://www.cochranelibrary.com))
  - CRD Databases
    - DARE (Centre for Reviews and Dissemination / Database of Abstracts of Reviews of Effects)
    - HTA (Health Technology Assessment)
    - NHS EED (National Institute for Health Research / Economic Evaluation Database)
  - Cinahl (Cumulative Index to Nursing and Allied Health Literature)
  - PsycInfo (literature in behavioral sciences and mental health)
- Social Science databases:
  - Sociological Abstracts, Social Services Abstracts,
  - Social Care on line / Caredata and SocINDEX,
  - ASSIA (Applied Social Sciences Index and Abstracts)
- Administrative studies:
  - General science publishers' databases such as Emerald Library,
  - Science Direct and Ebsco Academic Search Elite,
  - Pub Med Central (PMC) and Bio Med Central (BMC),
  - ProQuest Health Management
- Educational database:
  - ERIC (Education Resources Information Center)

## **Other databases**

- GIN (Guideline International Network) at <http://www.g-i-n.net/>
- Experience of organisations e.g. NHS Technology Adoption Centre <http://www.technologyadoptionhub.nhs.uk/>
- The EUnetHTA pool of structured HTA information at <http://www.corehta.info> will be a pertinent source of information on e.g. disease incidence

- HTAi Vortal includes information for conducting HTA (<http://www.htai.org>)
- The Joanna Briggs Institute Library at <http://www.joannabriggslibrary.org/jbilibrary/>
- Ongoing research databases, e.g.
  - EUnetHTA POP database at <http://eunetha.dimdi.de/PopDB/>
  - ClinicalTrials.gov at <http://www.clinicaltrials.gov/>
  - Prospero (International prospective register of systematic reviews) at <http://www.crd.york.ac.uk/PROSPERO/>
- Horizon scanning databases and web sites, e.g. EuroScan at [www.euroscan.org.uk](http://www.euroscan.org.uk) and BIOSIS Previews at <http://thomsonreuters.com/en/products-services/scholarly-scientific-research/scholarly-search-and-discovery/biosis-previews.html>
- Institute of Health Economics (IHE) ‘Health technology assessment on the net’ report (<http://www.ahfmr.ab.ca>) can provide a useful starting point (see also other sources in Appendix 1).
- Databases of international organisations, e.g. the WHO, OECD
- Regulatory bodies’ databases
- Grey literature:
  - Dissertational Abstracts, conference proceedings (Web of Science database);
  - Scirus (Reports of Hospital Studies and Doctoral Thesis),
  - OAIster (including open access collections)

### **Registers and statistics**

- Technology and procedure registers (in Appendix 1)
- Disease registers (in Appendix 1)
- Birth defect registries
- National screening registries
- Routinely collected statistics and administrative data (e.g. DRG, discharge databases, reimbursement claims databases)
- Pharmaceutical registers (Rote Liste, Vidal, DrugDex)

## Websites

- Scientific specialist associations' web sites
- Clinicians' web sites
- Patient associations' web sites
- Manufacturer's web sites
- Marketing authorisation and other regulatory institutions' web sites (in Appendix 1).
  - The SPC (Summary of Product Characteristics) includes information on the marketing authorisation status of a pharmaceutical [http://en.wikipedia.org/wiki/Summary\\_of\\_Product\\_Characteristics](http://en.wikipedia.org/wiki/Summary_of_Product_Characteristics)
  - EPARs (European Medicines Agency / European Public Assessment Reports)
- National health services' web sites
- Regional/local governments' health departments' web sites
- Benefits and sickness funds' web sites
- Technology developers' and manufacturers' web sites
- Various sources through using internet search engines

## Other sources

- Grey literature (e.g. Working papers from research groups or committees, white papers, or preprints)
- Conference proceedings
- Market research reports
- Manufacturers' handbooks and direct contacts
- Industry
- Expert opinions: Contacts or interviews with appropriate experts and agencies
- National and regional guidelines
- National and regional norms and regulations

## **Own primary research**

There could be different reasons why own research is needed; for example, if no studies were found in the literature search, and if there is a specific need for information of one's own country which is not available in the literature.

Some aspects to take into account when considering own research:

- Own qualitative research might be the only way to assess real practice use and misuse.
- Apart from actual trials, the following may provide useful information:
  - Discussions with experts or officials
  - Expert surveys or interviews
  - Research using administrative databases
  - Register-based research

If the resources available for the assessment project does not allow carrying out own primary research, it can be useful to consult health care professionals or other content experts.

## ***What kind of information is required?***

### **Study types, design, outcome measures**

There is no single methodological approach which can be applied to all issues in this domain (See Table 2). The epidemiology of the target health condition and its consequences are usually described in terms of prevalence and incidence (e.g. mortality, disability, sick leave, retirement).

**Table 2. Types of information required in this domain**

Research question	Study type	Quality assessment	Systematic data retrieval needed?	Synthesis
Disease mechanisms	Descriptive	No established way to assess the quality of narrative reviews and text books.	No. Updating existing information is sufficient.	Narrative
Natural course of condition	Observational	STROBE check list {7}	No. Updating existing context relevant information is sufficient.	Narrative
Prevalence and incidence of the condition	Observational	STROBE check list {7}	No. Updating existing context relevant information is sufficient.	Data may be meta-analysed, but often there is no opportunity to do that.
Risk factors and consequences	Observational	Newcastle-Ottawa scale {8}	Yes	Meta-analysis per subgroups if possible.
Prognosis	Prognostic	Newcastle-Ottawa scale {8}	Yes	Data may be meta-analysed
Technology utilisation	Narrative reviews, surveys, observational and qualitative research, register analysis  Market research reports	Relevant at least for quantitative studies.	Not necessarily, in particular in Google or other non-scientific sources.	Narrative
Current practise in the management of the condition, practise variation	Guidelines, consensus statements, observational and qualitative research	Not needed	Not necessarily, information from internet or other non-scientific sources may be useful.	Narrative

## Screening specific content

It is difficult to obtain information on misuse or overuse of a screening technology, or on the spontaneous diffusion of using a test on a healthy population before the implementation of a screening programme. Consequently, this information needs to be collected from indirect sources. A case report which describes the routine use of a screening test, in all cases who have been admitted for a certain disease or health problem in a certain hospital, provides reliable information on the use of the screening technology, although the clinical results of this study would not be reliable.

## Tools for critical appraisals

The validity of the information may differ considerably, depending on the source and type of information requested (see Table 2).

Quality assessment of retrieved information may be difficult, as there is often no standard way of doing it, and 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 source and type of information requested (quantitative or qualitative; registers, administrative data, etc.)..

For example, it might be difficult to find up-to-date information on the approval status of a technology by reviewing published literature. Even if there are scientific publications on the issue (e.g. policy studies) they are likely to rapidly become outdated. Information obtained from websites or through telephone query of relevant authorisation and reimbursement agencies, or from the local HTA agencies, is likely to be more reliable and practical.

The Canadian CADTH has reviewed quality assessment tools and provides useful insights into the topic and details beyond what is included in this chapter {9}. Relevant guidance about critical appraisal of quantitative and qualitative studies is available in the Cochrane Handbook for Systematic Reviews of Interventions in part 2, Chapter 8 (Assessing risk of bias in included studies) [www.cochrane-handbook.org](http://www.cochrane-handbook.org).

Appropriate methods for appraising the available evidence should also be selected with consideration to the level of detail and precision one wishes to achieve in providing CUR information. As discussed earlier, these depend on the aims of the assessment and the collection type.

## *Critical Appraisal of Quantitative and Qualitative Evidence*

Within quantitative reviews, there is a range of study designs that may be incorporated. A common approach is to state a preferred hierarchy of types of studies: Experimental e.g. randomised controlled trials (RCTs); Quasi experimental e.g. non-randomised controlled trials; Observational (Correlational) – e.g. cohort, case control studies; Observational (Descriptive) – e.g. case series and case study; and Expert opinion. By stating also the level of evidence, the quality of evidence would be more appropriately assessed. An example of such an approach is the JBI Levels of Evidence

classification, available at <http://joannabriggs.org/jbi-approach.html#tabbed-nav=Levels-of-Evidence>.

Although this kind of hierarchical view on different types of studies may be useful for some assessment elements of this domain, the overall approach cannot be applied in the same manner as for example within the Clinical Effectiveness domain. Some study types, such as randomised clinical trials, may rank high in the evidence hierarchy, but at the same time they may be less useful for some questions within this domain.

## ***Quality assessment of trials***

The RCT (Randomised Controlled Trials) and quasi-RCT represent some of the most frequent research studies where quantitative data on results of applying a certain health technology can be found. Quality of this information should be assessed on aspects such as: random assignment of patients, blinded allocation of patients, blinded evaluation of outcomes, similar control and treatment groups, confounders, outcomes measurement, statistical analysis etc. Relevant guidance is in the Cochrane handbook (Part 2, 8.4 Introduction to sources of bias in clinical trials), [www.cochrane-handbook.org](http://www.cochrane-handbook.org), and in Joanna Briggs Institute's Reviewer's Manual, 2014{10}.

## ***Quality assessment of observational studies***

There are several checklists or scales on critical appraisal of observational studies but no consensus about using those. In choosing the checklist, it has to be taken into account how easy the scale is to use and how long it takes to complete each instrument. Useful scales include the Newcastle Ottawa Scale {8} and the checklist of STROBE on reporting observational studies {7}. A now somewhat outdated analysis was published by the AHRQ in 2002 {11}.

## ***Guidelines***

The AGREE has produced an instrument for assessing quality of clinical practice guidelines {12}. Grading the quality of evidence and strength of recommendations could be done by the GRADE system {13}.

## ***Quality assessment of epidemiologic studies***

Different fields in epidemiology have different levels of validity. One way to assess the validity of findings is the ratio of false-positives (claimed effects that are not correct) to false-negatives (studies which fail to support a true effect).

There are several checklists or scales available for critical appraisal of observational studies, but no consensus about using those. In choosing the checklist, one has to take into account how easy the scale is to use and how long it takes to complete each instrument. The most appropriate scales are Newcastle Ottawa Scale {8}\*, and checklist of STROBE\*\* on reporting observational studies {7}.

The EUnetHTA guideline for classifying evidence and assessing risk of bias for non-randomised studies recommends the ACROBAT-NRSI (A Cochrane Risk of Bias Assessment Tool) as primary

RoB tool for the assessment of non-randomised studies: [Internal validity of non-randomised studies \(NRS\) on interventions](#) available at <http://www.eunethta.eu/eunethta-guidelines>

*\*Newcastle Ottawa scale may not be appropriate in the quality assessment of studies examining disease prevalence or burden of disease. It is more appropriate for studies assessing the link between diseases and risk factors.*

*\*\*STROBE check list can be used as a check list for study quality, although it is an instrument meant for assessing the quality of reporting.*

## **Cohort/Case-controllede studies**

Case-control or Cohort studies can be used to identify if the benefits observed in randomised trials translate into effectiveness across broader populations in clinical settings and provide information on adverse events and risks. Relevant guidance is available in Joanna Briggs Institute's Reviewer's Manual, 2014, particularly Appendices V and VI {10}.

**Descriptive/Case series:** See Joanna Briggs Institute's Reviewer's Manual, 2014, Appendices V and VI {10}.

## ***Quality assessment of manufacturer data***

The information provided by manufacturers might be limited due to issues of confidentiality and marketing. This kind of source can be useful in answering questions concerning the requirements for use of the technology, the development status or forthcoming innovations of the technology. Manufacturers may also provide information about on-going research and on scientific literature not yet published. Scientific information provided by manufacturers needs to be evaluated for validity and applicability. 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.

## ***Quality assessment of primary data***

If there is not enough time to perform a primary study, health care professionals and content experts or other stakeholders can be consulted for their opinion. However, one needs to be aware that the amount of knowledge or the respondents' views may be limited, as it reflects the willingness of the participants to listen and speak. Even when speaking, the participant's information output is influenced by the positions and power relations of the professionals and patients, knowledge asymmetry, patient's dependency on the doctor's good will, and time constraints. Stakeholders may represent the patient's perspective, but the evaluator should be critical to any political agenda.

## ***Quality assessment of text or expert opinion***

While establishing validity, it is not possible to focus on limiting bias in the appraisal of quantitative studies, especially when dealing with text and opinion. In appraisal of text, the opinions being raised are vetted, the credibility of the source investigated, the motives for the opinion examined, and the global context in terms of alternate or complementary views is considered. The validity in this context therefore relates to what is being said, the source, his/her credibility and logic, and consideration of the overt and covert motives at play.

## ***Quality assessment of registers, statistics and routinely collected data***

### **Registers**

When one or more quality-assured registers exist, as is the case for example for many organized screening programs or medical implants, the information can be highly reliable.

The relevance and quality of registers should be appraised carefully, considering the following questions:

- How representative is the register? (European, national, regional, local?)
- What kind of information has been coded?
- What are the inclusion/exclusion criteria for the data entered?
- What is the quality of information?
- How complete is the coverage?

Data access is an important aspect when working with registers. It may be impossible for institutions other than the ones managing the register to analyse the raw data. However, some registers conduct customized analyses.

### **Statistics and routinely collected data**

Routinely collected administrative data (e.g. DRGs, discharge databases, reimbursement claims databases) can be useful, when available. For example sickness funds collect large amounts of information which could be used to analyse the utilisation of a technology. By definition, this data has been collected for purposes other than research and they cannot be used to answer scientific questions without previous processing. An analysis of this kind of data might be very time-consuming, since data needs to be 'prepared' before analysis, and hence the data may not be feasible for use within an HTA project. The use of routinely collected statistics has several limitations. The reliability of the diagnosis varies and it is usually 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. There are several national and international sources of statistics which can be used to assess the incidence, prevalence, mortality, or burden of disease. These statistics are usually in aggregated form and increasingly available online.

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. Researchers of this domain should be aware of the *Policy for HTA Core Model and core HTA information*(<http://www.corehta.info/PoliciesAndTerms.aspx>) that defines specific rules for using non-public data, available through the HTA Core Model Online.

## ***Critical Appraisal of Qualitative Evidence***

A variety of checklists and tools are available for assessing qualitative studies. These tools use a series of criteria that can be scored and the decision to include a study can be made based on whether it meets a pre-determined proportion of all criteria, or certain criteria. Some tools use weighted scores to evaluate different criteria. An example of a checklist for critical appraisal of qualitative research is available within the CASP (Critical Appraisal Skills Programme) Checklists at <http://www.casp-uk.net>.

Appraisal should consider appropriateness of research method(s), sampling, data collection and analysis. Although there are several available quality assessment instruments, disagreement still exists about which criteria is appropriate for the critical appraisal of qualitative research, and whether quality assessment should be done at all.

For example, within a Cochrane Intervention review, a critical appraisal of qualitative studies is considered an essential step. According to Cochrane guidance, critical appraisal involves (1) filtering against minimum criteria, involving adequacy of reporting detail on the data sampling, collection and analysis; (2) technical rigour of the study elements indicating methodological soundness and (3) paradigmatic sufficiency, referring to researchers' responsiveness to data and theoretical consistency. When choosing an assessment instrument, the review team needs to consider how appropriate their choice is in the context of their review, and to be aware that whether or not a study meets the standard might depend on the instrument used. {3}

## **Analysing and synthesising evidence**

There are several issues defined in the HTA Core Model, in this domain particularly, where systematic data retrieval is not necessary (see Table 1). Unsystematic information gathering from books, surveys, introduction sections of reviews and articles, registers and the internet (until saturation is reached) may be enough. However, one should be aware of the possibility for selection bias, which is due to e.g. insufficient or selective inclusion of information sources and data, and duly reflect the possible limitations in the domain's discussion chapter.

When using systematic data retrieval, the approach to data extraction must be appropriate with regard to the review question, the type of review and the available evidence. The data extraction needs to be systematic and transparent. The design of these forms should be undertaken carefully, as it can be a subjective process {7}. The amount of information to be extracted should be directly related to the questions posed and it must balance detail with usefulness (overly inclusive/minimalist data extraction form).

In reviews of qualitative studies, data extraction is typically a more iterative process. Review authors may move between reading primary papers, data extraction and synthesis/interpretation in several cycles as key themes and questions emerge from the synthesis. {16}

Key components of data extraction (especially of quantitative studies) include: identifying features of the study (title, authors, journal, publication details); population characteristics and care setting; methodological quality; interventions; outcomes: length of follow-up: drops-outs: missing data; data of the results: effect measures, and notes.

A different form may be necessary if there are findings from qualitative studies. The Cochrane handbook has aggregated different kinds of extraction forms of qualitative studies {16}. Relevant guidance is available also through the Joanna Briggs Institutes' Reviewer's Manual {10} and the SUMARI (System for the Unified Management, Assessment and Review of Information), available at <http://joannabriggs.org/sumari.html>). SUMARI is designed to assist researchers and practitioners in fields such as health, social sciences and humanities to appraise and synthesis evidence of feasibility, appropriateness, meaningfulness and effectiveness; and to conduct economic evaluations of activities and interventions. It is composed of several modules which e.g. facilitates critical appraisal, data extraction and meta-aggregation of the findings of qualitative studies.

### **Inclusion and exclusion criteria: principles and tools**

The inclusion or exclusion criteria should be clearly defined *a priori*. The eligibility criteria used should specify the patients, interventions or exposures and outcomes of interest. In many cases the type of the study design will also be a key component of the eligibility criteria.

### ***Biases, confounding factors, level of evidence***

Triangulation is a way to reduce bias in research, and thus should be recommended when assessing CUR issues. Triangulation compares the results from two or more different methods of data collection (for example, interview and observation) or two or more data sources (for example, interviews with members of different interest groups). The researcher looks for patterns of convergence to develop or corroborate an overall interpretation. Triangulation can be seen as a way of ensuring comprehensiveness and encouraging a more reflexive analysis of data than as a pure test of validity. {17}

## *Evidence tables*

Until now, the HTA Core Model has not contained any standard tables for summarising the evidence supporting the answers to research questions. Provision of table templates will be explored in collaboration with Work Packages 4 and 5 of the EUnetHTA Joint Action 2.

The following resources provide useful insights into presenting data in tabular format:

- The Cochrane Handbook for Systematic Reviewers of Interventions, <http://www.cochrane.org/training/cochrane-handbook> and <http://handbook.cochrane.org>
  - particularly chapter 11.5 ‘Summary of findings tables ‘
- Guidelines International Network: Evidence Tables Working Group <http://www.g-i-n.net/activities/etwg>
- Sign 50: A Guideline Developer’s Handbook <http://www.sign.ac.uk/guidelines/fulltext/50/index.html> , example at <http://www.sign.ac.uk/guidelines/fulltext/50/compevidence.html>
- NICE: The Guidelines Manual 2012, appendices J-K, <http://publications.nice.org.uk/the-guidelines-manual-appendices-jk-pmg6c>
- HTA 101: V. Appraising the evidence, <http://www.nlm.nih.gov/nichsr/hta101/ta10107.html>
- GRADE: The Grading of Recommendations Assessment, Development and Evaluation <http://www.gradeworkinggroup.org/index.htm>

## *Meta-analysis*

Meta-analysis is rarely used in the TEC domain because most studies are qualitative or otherwise not suitable for meta-analysis.

## *Qualitative synthesis*

Synthesising qualitative evidence entails a process of combining evidence from individual qualitative studies in order to create new understanding. This is done by comparing and analysing concepts and findings from different sources of evidence with a focus on the same topic of interest. The synthesis can be an aggregative or interpretive process which requires authors to identify and extract evidence, categorise the evidence, and combine categories so as to develop synthesized findings. It is important to understand why people feel or behave in certain ways rather than just to make a description of it. {18}

There is range of methods available for synthesising diverse forms of evidence, for example meta-ethnography, grounded theory, thematic synthesis, narrative synthesis, realist synthesis, content analysis. Some of the methods maintain the qualitative form of the evidence such as meta-ethnography and some involve converting qualitative findings into a quantitative form such as content analysis. {15}

Synthesis methods are classified in different ways, and it has been argued whether it is acceptable to conduct syntheses of qualitative evidence at all, and if it is acceptable to synthesize qualitative studies derived from different traditions. {15, 19-21}

Qualitative and quantitative findings could be synthesized in two ways: multilevel synthesis (separate and combined synthesis) and parallel (separate and juxtaposed synthesis) {18}. Quantitative and qualitative studies can be synthesized together; one example is a systematic review on teenage pregnancy and social disadvantage {22}.

## Reporting and interpreting

Transparency in information retrieval is crucial when reporting core HTA information; for each issue, one should explicitly state the sources and methods of information retrieval, whether they are systematic or not, and what the quality assessment criteria was (also when missing).

A reader of core HTA information might be interested to learn the incidence of the condition and the extent of use of the technology in other countries, particularly when there is no information available from one's own country. Therefore, both European and national-level data may be of importance, and can thus be reported. Tables, graphs and figures make for abundant numerical information, e.g. trends in epidemiology, more digestible.

An overview of the guidelines synthesising the main recommendations for management practises would be illustrative.

## Assessment elements

A0007 Assessment element card						
Issue: What is the target population in this assessment?						
Topic: Target Population						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	None	Yes	1
	Medical and Surgical Interventions (3.0)	Yes	Critical	None	Yes	1
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	1
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	1
Clarification	<p><b>Common to all used applications</b></p> <p>Relevant for all assessments: Both safety and effectiveness depend largely on the subpopulation towards which the intervention is targeted. The technology may be used on all patients with the condition, or only on those in the early stages, or at a specific level of severity, or on those at moderate risk of having the condition.</p> <p>Personalised medicine divides the target population into even smaller units when targeting the intervention onto specific subgroups, based on e.g. genetic profile.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Use the target population defined in the scope of the project for assessment, and consider adding further details and description of who defined the selected subgroups, and why.</p> <p>Point out, e.g., whether certain populations should be excluded from the analysis</p> <p>Sources: HTAs, guidelines, reviews, developers/manufacturers. Method: A descriptive summary.</p>					
References	<p><b>Common to all used applications</b></p> <p>Burls et al. 2000 {1}, Busse et al. 2002 {2}, Liberati et al. 1997 {3}, Imaz-Iglesia et al. 1999 {23}, Kristensen et.al 2007 {24}</p>					
Content relations						
Sequential relations						

A0023 Assessment element card						
Issue: How many people belong to the target population?						
Topic: Target Population						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	None	Yes	2
	Medical and Surgical Interventions (3.0)	Yes	Critical	None	Yes	2
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	2
	Screening Technologies (3.0)	Yes	Critical	None	Yes	2
Clarification	<p><b>Common to all used applications</b></p> <p>This information can be used to provide an idea of the resource requirements for implementing the technology. Estimates of likely relevant increases or decreases in the size of the target population in the future should also be included.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Sources: text books, HTAs, national registries, statistics, systematic reviews. Method: A descriptive summary.</p>					
References	<p><b>Common to all used applications</b></p> <p>Burks et al. 2000 {1}, Busse et al. 2002 {2}, Liberati et al. 1997 {3}, Imaz-Iglesia et al. 1999 {23}, Kristensen et.al 2007 {24}</p>					
Content relations						
Sequential relations						

A0002 Assessment element card						
Issue: What is the disease or health condition in the scope of this assessment?						
Topic: Target Condition						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Complete	Yes	3
	Medical and Surgical Interventions (3.0)	Yes	Critical	Complete	Yes	3
	Pharmaceuticals (3.0)	Yes	Critical	Complete	Yes	3
	Screening Technologies (3.0)	Yes	Critical	Complete	Yes	3
Clarification	<p><b>Common to all used applications</b></p> <p>Indicate the target condition used in the project scope and consider providing a more comprehensive description of it.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Use the target condition and ICD codes defined in the scope of the project, and consider possibly adding details such as the description of anatomical site, disease aetiology and pathophysiology, types of disease or classification according to origin, severity, stages, or risk level, and different manifestations of the condition. The following properties of the target condition are defined in separate assessment elements and should not be repeated here: risk factors (A0003), natural course (A0004), symptoms (A0005), and burden of disease for the society (A0006).</p> <p>Sources: text books, HTAs, guidelines, epidemiological reviews or studies, WHO documents, disease registers. Method: A descriptive summary.</p>					
References	<p><b>Common to all used applications</b></p> <p>Burls et al. 2000 {1}, Busse et al. 2002 {2}, Liberati et al. 1997 {3}, Imaz-Iglesia et al. 1999 {23}, Kristensen et.al 2007 {24}</p>					
Content relations						
Sequential relations						

A0003 Assessment element card						
Issue: What are the known risk factors for the disease or health condition?						
Topic: Target Condition						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	4
	Medical and Surgical Interventions (3.0)	Yes	Important	Partial	Yes	4
	Pharmaceuticals (3.0)	Yes	Important	Partial	Yes	4
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	4
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Describing risk factors is especially important when the factors 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 being assessed. The risk factors for acquiring the condition, and the risk factors for relapses or a worsening of the condition should be reported here separately. The prevalence of various risk factors might differ depending on various geographic areas and sub-populations.</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Sources: text books, HTAs, guidelines, epidemiological reviews or studies. Method: Systematic review is generally not required. A descriptive summary is sufficient.</p>					
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Burls et al. 2000 {1}, Busse et al. 2002 {2}, Liberati et al. 1997 {3}, Imaz-Iglesia et al. 1999 {23}, Kristensen et.al 2007 {24}</p>					
<b>Content relations</b>						
<b>Sequential relations</b>						

A0004 Assessment element card						
Issue: What is the natural course of the disease or health condition?						
Topic: Target Condition						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Complete	Yes	5
	Medical and Surgical Interventions (3.0)	Yes	Critical	Complete	Yes	5
	Pharmaceuticals (3.0)	Yes	Critical	Complete	Yes	5
	Screening Technologies (3.0)	Yes	Critical	Complete	Yes	5
Clarification	<p><b>Common to all used applications</b></p> <p>This assessment element should provide information on the prognosis and course of the condition when left untreated. This information is relevant for appraising the overall value of the technology. A technology targeted at curing a life-threatening condition – for example, a bypass surgery for severe coronary artery disease – has a different significance than a technology intended to alleviate the symptoms of a self-limiting condition, such as medications to alleviate the symptoms of common cold.</p> <p>Understanding the natural course of a disease may also guide the assessment of the predicted value or effectiveness of the technology, as technologies may work differently at a disease's different stages or grades of severity; there may also be a relationship between earlier intervention and a better prognosis. This element should also provide information on the time delay between the onset of disease and the symptoms or other findings which eventually trigger the need for diagnostics and care.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Sources: text books, HTAs, guidelines, epidemiological reviews or studies. Method: A descriptive summary.</p>					
References	<p><b>Common to all used applications</b></p> <p>Burls et al. 2000 {1}, Busse et al. 2002 {2}, Liberati et al. 1997 {3}, Imaz-Iglesia et al. 1999 {23}, Kristensen et.al 2007 {24}</p>					
Content relations						
Sequential relations						

A0005 Assessment element card						
Issue: What are the symptoms and the burden of disease or health condition for the patient?						
Topic: Target Condition						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Complete	Yes	6
	Medical and Surgical Interventions (3.0)	Yes	Critical	Complete	Yes	6
	Pharmaceuticals (3.0)	Yes	Critical	Complete	Yes	6
	Screening Technologies (3.0)	Yes	Critical	Complete	Yes	6
Clarification	<p><b>Common to all used applications</b></p> <p>Describe the patient's relevant symptoms before intervention with the technology, their severity, their urgency 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. For example, back pain is rarely caused by a life-threatening disease, but it can still very negatively affect patients' quality of life and ability to work.</p> <p>This issue is especially relevant when the patient or individual is expected to undergo a substantial change in pain, disability, psychosocial issues, or other determinants of quality of life.</p> <p>Knowing the severity and/or urgency level of the condition the technology is directed to is relevant in the ethical analysis of the technology. Information about the severity level is also important to decision-makers when making decisions about whether or not to implement a technology.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Sources: text books, HTAs, quality of life studies, qualitative patient perception studies. Method: A descriptive summary.</p>					
References	<p><b>Common to all used applications</b></p> <p>Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24} from the CUR domain</p>					
Content relations						
Sequential relations						
Other domains	Also in: Ethical analysis					

A0006 Assessment element card						
Issue: What are the consequences of the disease or health condition for the society?						
Topic: Target Condition						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	7
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	7
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	7
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	7
Clarification	<p><b>Common to all used applications</b></p> <p>Describe consequences and burden of the disease or health condition, by providing information on prevalence or incidence of the disease being prevented/treated with the technology.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Methods to use may include disease-specific mortality and disability, life years lost and/or disability-adjusted life years (DALYs), quality of life (QALYs).</p> <p>Sources: text books, HTAs, registries and national statistics, WHO incidence, mortality and survival databases. <a href="http://www.who.int/cancer/resources/incidences/en/">http://www.who.int/cancer/resources/incidences/en/</a> Method: A descriptive summary</p>					
References	<p><b>Common to all used applications</b></p> <p>Burls et al. 2000 {1}, Busse et al. 2002 {2}, Liberati et al. 1997 {3}, Imaz-Iglesia et al. 1999 {23}, Kristensen et.al 2007 {24}</p>					
Content relations						
Sequential relations						

A0009 Assessment element card						
Issue: What aspects of the consequences / burden of disease are targeted by the technology?						
Topic: Target Condition						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Complete	Yes	8
	Medical and Surgical Interventions (3.0)	Yes	Critical	Complete	Yes	8
	Pharmaceuticals (3.0)	Yes	Critical	Complete	Yes	8
	Screening Technologies (3.0)	Yes	Critical	Complete	Yes	8
Clarification	<p><b>Common to all used applications</b></p> <p>The technology can affect only some aspects (e.g. mortality) and leave other aspects (e.g. quality of life) unaffected.</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>The application of the diagnostic technology may target only one aspect of the burden of disease, e.g. disability, but not mortality. Or, on the other hand, it can target mortality but not symptoms.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>Screening may increase disease incidence due to early diagnosis and overdiagnosis.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Deductive models (based on the natural history of the disease, test target and treatment target; epidemiological studies (if sufficient testing has been done).</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>B0002</p>					
Sequential relations						

A0018 Assessment element card						
Issue: What are the other typical or common alternatives to the current technology?						
Topic: Current Management of the Condition						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	9
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	9
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	9
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	9
Clarification	<p><b>Common to all used applications</b></p> <p>Provide an overview of alternatives to using the technology under assessment. The focus should primarily be on those alternatives used within professional health care delivery. Consider also including technologies that people may commonly seek or use, even if these would not commonly be provided in professional health care (e.g., technologies for self-testing or self-treatment, or alternative medicine).</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Clinical guidelines, recommendations, systematic reviews</p>					
References	<p><b>Common to all used applications</b></p> <p>Burls et al. 2000 {1}, Busse et al. 2002 {2}, Liberati et al. 1997 {3}, Imaz-Iglesia et al. 1999 {23}, Kristensen et.al 2007 {24}</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>B0001; A0025</p>					
Sequential relations						

A0024 Assessment element card						
Issue: How is the disease or health condition currently diagnosed according to published guidelines and in practice?						
Topic: Current Management of the Condition						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	10
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	10
	Pharmaceuticals (3.0)	Yes	Important	Partial	Yes	10
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	10
Clarification	<p><b>Common to all used applications</b></p> <p>The effectiveness of an intervention may vary among differently diagnosed populations. A sensitive test tends to have low specificity, resulting in some people, who do not have the condition, to be 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.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Sources: Clinical guidelines and published utilisation reviews; in the absence of these, clinical experts survey. See Appendix 1. Method: Systematic review of clinical guidelines. Quality appraisal of guidelines can be done using e.g. AGREE II Instrument. For practice mapping, a pragmatic review or listing of available information is sufficient. Flowcharts are illustrative in reporting diagnostic pathways.</p>					
References	<p><b>Common to all used applications</b></p> <p>Burls et al. 2000 {1}, Busse et al. 2002 {2}, Liberati et al. 1997 {3}, Imaz-Iglesia et al. 1999 {23}, Kristensen et.al 2007 {24}</p>					
Content relations						
Sequential relations						

A0025 Assessment element card						
Issue: How is the disease or health condition currently managed according to published guidelines and in practice?						
Topic: Current Management of the Condition						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	11
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	11
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	11
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	11
Clarification	<p><b>Common to all used applications</b></p> <p>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. When considering alternatives, note that element A0018 focuses on the alternatives and you can refer to it here.</p> <p>Are there differences in the treatment of diseases at their various stages? Identify practice variations resulting from differences in the forms, stages or severity of the disease. This may be useful in understanding the proper place of technology in the health care delivery process.</p> <p>Different stages of the disease may call for different therapeutic procedures (for example, aortic insufficiency is first treated with medication, but at a certain point of cardiac structural changes an operation is preferred).</p> <p>Identification of practice variations may imply differences in the quality of health care. Deviation from evidence-based guidelines may suggest over/under-use of the technology.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Provide an overview of treatment alternatives, including also the technology/ies in this assessment. Likewise, diagnostic or monitoring methods used for various diseases may vary depending on the stage of disease.</p> <p>Clinical guidelines, recommendations and published utilisation reviews; in the absence of these clinical experts survey. See Appendix 1. Method: Systematic review of clinical guidelines. Quality appraisal of guidelines can be done using e.g. AGREE II Instrument. For practice mapping, a pragmatic review or listing of available information is sufficient. Flowcharts are illustrative in reporting management pathways.</p>					
References	<p><b>Common to all used applications</b></p> <p>Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24}</p>					

<b>Content relations</b>	<b>Common to all used applications</b>  A0018; G0008, G0001
<b>Sequential relations</b>	

A0001 Assessment element card						
Issue: For which health conditions and populations, and for what purposes is the technology used?						
Topic: Utilisation						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Complete	Yes	12
	Medical and Surgical Interventions (3.0)	Yes	Critical	Complete	Yes	12
	Pharmaceuticals (3.0)	Yes	Critical	Complete	Yes	12
	Screening Technologies (3.0)	Yes	Critical	Complete	Yes	12
Clarification	<p><b>Common to all used applications</b></p> <p>Include all relevant conditions and populations for which the technology has been proposed. This question is especially relevant when there are (1) multiple potential target conditions and populations for which the technology is used, or (2) multiple intended uses, both those (officially) indicated as well as others. There may also be differing views about the appropriate use of the technology that are essential to highlight.</p> <p>Describe the following:</p> <ol style="list-style-type: none"> <li>1. Differences in the use of the technology for various indications, and how it might act differently in different patient groups. Point out e.g., if certain populations should be excluded from using the technology, or if they require, e.g., a different dosage. Certain technologies may be primarily indicated for second-line use, but are also used for first-line treatment.</li> <li>2. Specific group(s) of patients on which the technology is used within the present assessment should be provided.</li> <li>3. Aims of the technology (in terms of benefits to the target population).</li> </ol>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Method: A descriptive summary.</p> <p>Sources: HTAs, guidelines, reviews, clinician consultation, developers/manufacturers.</p>					
References	<p><b>Common to all used applications</b></p> <p>Burls et al. 2000 {1}, Busse et al. 2002 {2}, Liberati et al. 1997 {3}, Imaz-Iglesia et al. 1999 {23}, Kristensen et.al 2007 {24}</p>					
Content relations						
Sequential relations						

A0011 Assessment element card						
Issue: How much are the technologies utilised?						
Topic: Utilisation						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	None	Yes	13
	Medical and Surgical Interventions (3.0)	Yes	Important	None	No	13
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	13
	Screening Technologies (3.0)	Yes	Critical	None	Yes	13
Clarification	<p><b>Common to all used applications</b></p> <p>Provide national estimates for current and future utilisation rates, in the indication under assessment, for both the technology under assessment and its comparators. Variations in utilisation reflect market access, sales figures, actual usage on the hospital level, and adherence to the use of the technology by both professionals and patients. Data on current and previous utilisation reflects the phase that the technology is in (experimental, emerging, established or obsolete). This also has implications for the availability of evidence and the level of uncertainties.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>What is the current rate of screening adherence?</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>National statistics, surveys, technology and procedure registers, disease management studies, utilisation studies, manufacturer sales data</p>					
References	<p><b>Common to all used applications</b></p> <p>Burls et al. 2000 {1}, Busse et al. 2002 {2}, Liberati et al. 1997 {3}, Imaz-Iglesia et al. 1999 {23}, Kristensen et.al 2007 {24}</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>G0009, G0010</p>					
Sequential relations						

A0012 Assessment element card						
Issue: What kind of variations in use are there across countries/regions/settings?						
Topic: Utilisation						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	14
	Medical and Surgical Interventions (3.0)	Yes	Important	Partial	Yes	14
	Pharmaceuticals (3.0)	Yes	Important	Partial	Yes	14
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	14
Clarification	<p><b>Common to all used applications</b></p> <p>This information can be useful for decision-makers in understanding regional variations in their own country, as well as understanding the situation in comparison to other countries.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>National statistics, surveys, disease management studies, manufacturer sales data, utilisation reviews, audits, studies on praxis-variation. Own primary analysis of: Disease register, procedure register, device register, administrative data (DRG, discharge databases, reimbursement claims database).</p>					
References	<p><b>Common to all used applications</b></p> <p>Burls et al. 2000 {1}, Busse et al. 2002 {2}, Liberati et al. 1997 {3}, Imaz-Iglesia et al. 1999 {23}, Kristensen et.al 2007 {24}</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>G0009, G0010, G0007, G0008</p>					
Sequential relations						

G0009 Assessment element card

Issue: Who decides which people are eligible for the technology and on what basis?

Topic: Utilisation

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	15
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	15
	Pharmaceuticals (3.0)	Yes	Important	Partial	Yes	15
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	15

Clarification

**Common to all used applications**

Provide information on the key actors who decide on the use of the technology. Do most important decisions take place on the national level (e.g. population screening) or are they, for example, made by individual professionals (e.g. surgical method for a specific disease)? How is the decision made – are there some documented criteria?

Information about the possible variations on the decision level and decision criteria has ethical implications.

This issue may be especially important in the context of rare diseases.

This issue is related to the issue of work processes (G0001).

**Specific to Pharmaceuticals (3.0)**

Companion diagnostics (tests or measurements) assist physicians in making treatment decisions for their patients by elucidating the efficacy and/or safety of a specific pharmaceutical or a class of pharmaceuticals for a targeted patient group or sub-groups. Specify and explain how companion diagnostics should be used to identify eligible patients.

Specify the criteria for higher risk groups of patients such as the elderly and children.

**Specific to Screening Technologies (3.0)**

Decisions about people eligible for screening are made in the beginning of the screening. Usually, the decisions have been made nationally or regionally (in municipalities) but also locally (by employers). In systematic screening, the screening unit does not make decisions about who is eligible for screening. The management of positive test results needs systems to guarantee proper follow-up and, sometimes, case specific evaluation. In this topic responsibilities should be identified.

<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Literature search, guidelines, documents of hospitals, own research: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory).</p>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>KristensenFB et al. 2007 {24} from the CUR domain</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>A0011, A0012; B0004, B0016; D0021; I0012; H0012, F0012; G0001</p>
<b>Sequential relations</b>	
<b>Other domains</b>	<p>Also in: Organisational aspects</p>

F0001 Assessment element card						
Issue: Is the technology a new, innovative mode of care, an add-on to or modification of a standard mode of care or replacement of a standard mode of care?						
Topic: Utilisation						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	16
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	16
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	16
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	16
Clarification	<p><b>Common to all used applications</b></p> <p>Explain how the possible use/non-use of the technology would affect the current treatment process and practices. How substantial is the change in current practices?</p> <p>Notice that the technology may be in a different phase of utilisation for different health conditions or purposes of use.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Horizon scanning databases, ongoing research databases, information from manufacturers.</p>					
References	<p><b>Common to all used applications</b></p> <p>Mitcham 2004 {25}</p>					
Content relations						
Sequential relations						

A0020 Assessment element card						
Issue: For which indications has the technology received marketing authorisation or CE marking?						
Topic: Regulatory Status						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Complete	Yes	17
	Medical and Surgical Interventions (3.0)	Yes	Critical	Complete	Yes	17
	Pharmaceuticals (3.0)	Yes	Critical	Complete	Yes	17
	Screening Technologies (3.0)	Yes	Critical	Complete	Yes	17
Clarification	<p><b>Common to all used applications</b></p> <p>There are both international and national market authorisation systems. There are established systems for pharmaceuticals, but less so for devices and procedures. An overview of the authorisation systems status with regard to key processes, e.g. CE marking or EMA/FDA approval, is recommended. Information on national data and an analysis of possible discrepancies can also be highly useful.</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>Imaging devices may require approval. Substances needed for obtaining images (e.g. radiotracers) may also require additional approval. In some cases, the approval for primary screening is different to that for clinical use (FDA recently licensed tests explicitly for screening), but approval is in most cases obtained for diagnostic use and the test is proposed for screening without any other formal approval.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>Imaging devices may require approval. Substances needed for obtaining images (e.g. radiotracers) may also require additional approval. In some cases, the approval for primary screening is different to that for clinical use (FDA recently licensed tests explicitly for screening), but approval is in most cases obtained for diagnostic use and the test is proposed for screening without any other formal approval.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>CE-Approval, EMA, FDA, national authorities. Manufacturers should be contacted in order to identify which steps have they taken/ are they planning to take concerning market approval.</p>					
References	<p><b>Common to all used applications</b></p> <p>Burls et al. 2000 {1}, Busse et al. 2002 {2}, Liberati et al. 1997 {3}, Imaz-Iglesia et al. 1999 {23}, Kristensen et.al 2007 {24} from the CUR domain</p>					

<b>Content relations</b>	<b>Common to all used applications</b>  I0015; B0002
<b>Sequential relations</b>	
<b>Other domains</b>	Also in: Description and technical characteristics of technology

A0021 Assessment element card						
Issue: What is the reimbursement status of the technology?						
Topic: Regulatory Status						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Complete	Yes	18
	Medical and Surgical Interventions (3.0)	Yes	Important	Complete	Yes	18
	Pharmaceuticals (3.0)	Yes	Important	Complete	Yes	18
	Screening Technologies (3.0)	Yes	Important	Complete	Yes	18
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>List information on national reimbursement status from different countries for the technology as well as the comparators, including key dates and anticipated licensing timeframe. Notice that reimbursement status may differ for different purposes, e.g., treatment vs. prevention. Information on full coverage, co-payments, coverage under special circumstances/conditional coverage is useful.</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p><a href="#">Appendix 1 of REA model</a>: List of websites of national agencies with information on reimbursement  <a href="#">EVIDENT database</a>.</p>					
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Burls et al. 2000 {1}, Busse et al. 2002 {2}, Liberati et al. 1997 {3}, Imaz-Iglesia et al. 1999 {23}, Kristensen et.al 2007 {24} from the CUR domain</p>					
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>I0012; B0002</p>					
<b>Sequential relations</b>						
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# Description and technical characteristics of technology (TEC)

## *Description*

### **What is this domain about?**

The information given in this domain describes the technology (or a sequence of technologies) and its technical characteristics, i.e. when it was developed and introduced, for what purpose(s); who will use the technology, in what manner, for what condition(s), and at what level of health care. Material requirements for the premises, equipment and staff are described, as are any specific training and information requirements. The regulatory status of the technology should be listed, where applicable.

The issues in this domain need to be described in sufficient detail to differentiate the technology from its comparators. Terms and concepts should be used in a manner that allows those unfamiliar with the technology to get an overall understanding of how it functions and how it can be used. It is important to distinguish between scientifically proven versus suspected mechanisms of action. Important terms should be defined, and a glossary or a 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.

The TEC domain contains 16 issues. The issues are related to the four main topics: (1) training and information needed to use the technology; (2) features of the technology; (3) investments and tools required to use the technology and (4) regulatory status. Table 1 below shows the topics and issues specific to this domain.

**Table 1. Topics and issues in the TEC domain**

<b>Topic</b>	<b>Issue</b>	<b>Assessment element ID</b>
Features of the technology	What is this technology and the comparator(s)?	B0001
Features of the technology	What is the claimed benefit of the technology in relation to the comparator(s)?	B0002
Features of the technology	What is the phase of development and implementation of the technology and the comparator(s)?	B0003
Features of the technology	Who administers the technology and the comparator(s) and in what context and level of care are they provided?	B0004
Features of the technology	Are reference values or cut-off points clearly established?	B0018
Regulatory Status	For which indications has the technology received marketing authorisation or CE marking?	A0020
Regulatory Status	What is the reimbursement status of the technology?	A0021
Investments and tools required to use the technology	What material investments are needed to use the technology?	B0007
Investments and tools required to use the technology	What kind of special premises are needed to use the technology and the comparator(s)?	B0008
Investments and tools required to use the technology	What equipment and supplies are needed to use the technology and the comparator(s)?	B0009
Investments and tools required to use the technology	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator(s)?	B0010

Training and information needed to use the technology	What kinds of requirements in terms of qualification and quality assurance processes are needed for the use or maintenance of the technology?	B0012
Training and information needed to use the technology	What kinds of skills and training characteristics and information are needed for the personnel/caregivers using this technology?	B0013
Training and information needed to use the technology	What kind of training resources and information should be provided to the patient who uses the technology, or for his family?	B0014
Training and information needed to use the technology	What information about the technology should be provided to patients outside the target group and to the general public?	B0015
Other	Who manufactures the technology?	A0022

## Why is this domain important?

A careful description of the technical characteristics and special requirements of the technology, and the rationale for its use may help with translating policy questions into research questions in other domains. Different generations or versions of a technology may have different indications, performance characteristics and applicability. A good description of the technology is particularly important in fast developing fields where even minor changes or improvements in a technology can have variable effects on the measures of benefit.

## Relations to other domains

Taking into account that the health technology is the topic of this evaluation, it can be said that the TEC domain is related to all other domains: Health Problem and Current Use of the Technology (CUR), Safety (SAF), Clinical Effectiveness (EFF), Costs and Economic Evaluation (ECO), Organisational Aspects (ORG), Ethical Analysis (ETH), Patients and Social Aspects (SOC), and Legal Aspects (LEG) domains. In practice there is a considerable overlap with CUR, ORG and LEG. The authors of the TEC domain should cooperate with the authors of those domains to avoid duplication of work.

# *Methodology*

## **Process for answering research questions**

Although the HTA Core Model calls all questions deriving from the generic issues ‘research questions’, it is important to keep in mind that the questions and answering methodologies of this domain are in many ways different than in several other domains. Instead of trying to discover the ‘value’ of the technology - as is the case, e.g., in the EFF and ECO domains - the analysis in this domain aims at providing many of the other domains, and the whole collection of HTA information, a pragmatic and practical set of background information. The information should be gathered and compiled in an adequately reliable manner

In several cases, methodologies familiar from clinical or HTA research are not suitable for finding proper up-to-date . Consequently, it may be much faster and more efficient to collect a proper background set of information through an international survey among HTA agencies, health ministries or health service providers, rather than to perform extensive literature searches to conclude that ‘evidence was not available’ – an answer that is not at all helpful in this domain.

The researchers working on the TEC domain should consider their basic approach very early on in the project, as several other domains depend on the answers of this domain. The same applies to the CUR and ORG domains. A joint survey early on in the project should be considered as a pragmatic approach to finding answers to key questions of these three domains. In addition, other domains should contribute to these survey questions so that they provide useful information for all domains.

If the researchers of this domain decide to make a full systematic literature review to answer one or more questions in this domain, they should also consult the EUnetHTA Guideline *Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness*, available at <http://www.eunetha.eu/outputs/eunetha-methodological-guideline-process-information-retrieval-systematic-reviews-and-health>. Although focusing on effectiveness, the guideline may provide useful advice for work within other domains as well.

## **Gathering information**

### *Where to find information?*

The source of information will depend on the location of a technology within its product life cycle. Review articles and textbooks can be helpful when searching for information about the history and characteristics of an established technology. The information concerning the technology may be obtained from its manufacturers, from clinical experts using the technology, but also from literature (i.e. descriptive publications). For prototypes and innovative technologies, published peer reviewed literature may be limited. It may need to be supplemented with grey literature (includes non-peer reviewed and non-published literature, as well as confidential commercial information) as well as with anecdotal information from general web-searches. There are some issues, e.g., the coverage status of a technology (inclusion in the benefit catalogue, levels of co-payment, etc.), where information is not easy to retrieve. Identification of adequate and usable information

sources requires local knowledge of the healthcare system{ 1 }. This data can be obtained through a survey early on in the project. Whenever the research group considers using confidential information, e.g., from manufacturers, they should take into account the relevant principles defined in the *Policy for HTA Core Model and core HTA information*.

## Databases and search strategies

Review articles and textbooks can be helpful when searching for information about the history and characteristics of the technology. Published literature may be obtained by searching bibliographic databases such as MEDLINE (published by the United States National Library of Medicine), Pubmed (<http://www.ncbi.nlm.nih.gov/pubmed/>), EMBASE (Excerpta Medica published by Elsevier, <https://www.embase.com>), the Cochrane Library (<http://www.thecochranelibrary.com>) and the Centre for Reviews and Dissemination (CRD) and possibly HTA and/or clinical practice guideline search engines. Establishing regular notifications for new results using the alert function on these databases will facilitate easy updating of the literature review to ensure that it is up to date at the time of completing the HTA. Electronic searches can be supplemented by hand-searching the reference lists of key papers.

### Useful other sources and links

Grey literature (e.g., working papers from research groups or committees, white papers, or preprints), hand-searching of reference lists, as well as conference proceedings may be identified by searching the websites of HTA and related agencies, professional associations. Contacting manufacturers, clinicians, nurses, paramedics and patients and reading Internet discussion forums may also be valuable.

Key information may also be extracted from the life sciences database BIOSIS (<http://thomsonreuters.com/en/products-services/scholarly-scientific-research/scholarly-search-and-discovery/biosis-previews.html>), which includes patents, journals, conferences, books, review articles, etc. While deciding which of these sources are most relevant for the search will largely depend on the technology in question, compilations of potentially relevant sources of information, such as the HTAi IRG Vortal (<http://www.htai.org>) and Institute of Health Economics (IHE) 'Health technology assessment on the net' report (<http://www.ahfmr.ab.ca>) can provide a useful starting points [see also other sources in [111] in Appendix 1].

If the technology has obtained regulatory approval, the information that has been submitted as part of the approval process could be used as a source of data on the description and technical characteristics of the technology. This may be available from major EU or US regulatory bodies as well as from regulatory bodies in those countries where the technology has been approved for use (see [109] in Appendix 1). Further information (e.g., description of the technology, expected performances, and intended use) can be obtained from the manufacturer's website, or in the case of confidential information, by directly requesting it from the manufacturer.

There may also be relevant user information on web sites of clinicians, nurses, paramedics and patients. Published information may be supplemented with contacts or interviews with appropriate experts and agencies. Regardless of the source, all data should be subject to the same requirements for scientific rigour and transparency.

Some important databases and other possibly useful sources of information for the analysis in this domain are listed below. The list is extensive and researchers within each HTA project should carefully consider which sources best match the needs of their project. It is also recommended to use the *Summarised Research in Information Retrieval for HTA* (SuRe Info, available

at <http://vortal.htai.org/?q=sure-info>), which provides research-based information relating to the information retrieval aspects of producing health technology assessment.

**List of bibliographic databases on published literature:**

- MEDLINE (published by the United States National Library of Medicine),
- Pubmed (<http://www.ncbi.nlm.nih.gov/pubmed/>),
- EMBASE (Excerpta Medica published by Elsevier) (<https://www.embase.com/>),
- Cochrane Library (<http://www.thecochranelibrary.com/view/0/index.html>)
- CRD DARE (Centre for Reviews and Dissemination / Database of Abstracts of Reviews of Effects)
- NHS EED (National Institute for Health Research / Economic Evaluation Database)
- Cinahl (Cumulative Index to Nursing and Allied Health Literature)
- PsycInfo (literature in behavioral sciences and mental health)
- Social Science databases: Sociological Abstracts, Social Services Abstracts, Social Care on line / Caredata and SocINDEX, ASSIA (Applied Social Sciences Index and Abstracts)
- Administrative studies: General science publishers' databases such as Emerald Library, Science Direct and Ebsco Academic Search Elite, Pub Med Central (PMC) and Bio Med Central (BMC), ProQuest Health Management
- Educational database: ERIC (Education Recourses Information Center)
- GIN (Guideline International Network)
- Databases of international organisations, e.g. the WHO, OECD
- Ongoing research databases, e.g. EUnetHTA POP database at <http://eunethta.dimdi.de/PopDB/> and ClinicalTrials.gov at <http://www.clinicaltrials.gov/>
- Horizon scanning databases and web sites, e.g. EuroScan at [www.euroscan.org.uk/](http://www.euroscan.org.uk/)
- The EUnetHTA pool of structured HTA information will be a pertinent source of information on e.g. disease incidence
- BIOSIS Preview <http://thomsonreuters.com/en/products-services/scholarly-scientific-research/scholarly-search-and-discovery/biosis-previews.html>
  - includes patents, journals, conferences, books, review articles etc.
- Regulatory bodies' databases
- Grey literature:
  - Dissertational Abstracts, conference proceedings (Web of Science database);
  - Scirus (Reports of Hospital Studies and Doctoral Thesis),

- OAIster (including open access collections)

**Registers and statistics:**

- Technology and procedure registers ( see further information in [100] of Appendix 1)
- Disease registers (see further information in [105] of Appendix 1)
- Birth defect registries
- National screening registries
- Routinely collected statistics and administrative data (e.g. DRG, discharge databases, reimbursement claims databases)
- Pharmaceutical registers (Rote Liste, Vidal, DrugDex)

**Web sites:**

- Scientific specialist association web sites
- Clinician web sites
- Patient association web sites
- Manufacturer web sites
- Marketing authorisation and other regulatory institutions' web sites (see further information in [109] of Appendix 1).
  - The SPC (Summary of Product Characteristics) includes information on the marketing authorisation status of a pharmaceutical [http://en.wikipedia.org/wiki/Summary\\_of\\_Product\\_Characteristics](http://en.wikipedia.org/wiki/Summary_of_Product_Characteristics)
  - EPARs (European Medicines Agency / European Public Assessment Reports)
  - National health services' web sites
  - Regional/local governments' health departments' web sites
  - Benefits and sickness funds' web sites
  - Technology developers' and manufacturers' web sites
  - Various sources through using internet search engines

**Other sources:**

- Hand-searching the reference lists of key papers
- Grey literature (e.g., working papers from research groups or committees, white papers, or preprints)
- Conference proceedings

- Market research reports
- Manufacturers' handbooks and direct contacts
- Expert opinions: Contacts or interviews with appropriate experts and agencies
- HTAi IRG Vortal (<http://www.htai.org>)
  - includes information for conducting HTA
  - Experience of organisations e.g. NHS Technology Adoption Centre <http://www.technologyadoptionhub.nhs.uk/>
  - Institute of Health Economics (IHE) 'Health technology assessment on the net' report (<http://www.ahfmr.ab.ca>) can provide a useful starting point (see also other sources in [111] in Appendix 1).
  - National and regional guidelines
  - National and regional norms and regulations

## ***Own primary research***

There could be different reasons why own research is needed; for example, if no studies were found in the literature search, and if there is a specific need for information of one's own country which is not available in the literature.

Some aspects to take into account when considering own research:

- Own qualitative research might be the only way to assess real practice use and misuse.
- Apart from actual trials, the following may provide useful information:
  - Discussions with experts or officials
  - Expert surveys or interviews
  - Research using administrative databases
  - register-based research

If the resources available for the assessment project do not allow carrying out own primary research, it can be useful to consult healthcare professionals or other content experts in a less formal manner.

The information collected should give an exhaustive overview of answers to the issues in the domain.

## Tools for critical appraisals

A technology assessment nearly always requires a systematic review of the existing scientific literature, and will often have to be supplemented with an analysis of data from other primary information or data sources. The two approaches lead to results of different reliability and validity and it is primarily the HTA question that determines the choice of the most appropriate method {2}.

Quality assessment of retrieved information may be difficult, as there is often no standard way of doing it, and 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 source and type of information requested (quantitative or qualitative; registers, administrative data, etc.).

The specificity and uniqueness of a certain health technology could generate very little information, and with the addition of novelty, the researchers are usually faced with a lack of evidence. For example, it might be difficult to find up-to-date information on the approval status of a technology by reviewing published literature. Even if there are scientific publications on the issue (e.g. policy studies) they are likely to rapidly become outdated. Information obtained from websites or through telephone query of relevant authorisation and reimbursement agencies, or from the local HTA agencies, is likely to be more reliable and practical.

### *Quality assessment of manufacturer data*

The information provided by manufacturers might be limited due to issues of confidentiality and marketing. This kind of source can be useful in answering questions concerning the requirements for use of the technology, the development status or forthcoming innovations of the technology. Manufacturers may also provide information about on-going research and on scientific literature not yet published. Scientific information provided by manufacturers needs to be evaluated for validity and applicability. 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.

### *Quality assessment of expert opinions*

If there is not enough time to perform a primary study, health care professionals and content experts or other stakeholders can be consulted for their opinion. However, one needs to be aware that the amount of knowledge or the respondents' views may be limited, as it reflects the willingness of the participants to listen and speak. Even when speaking, the participant's information output is influenced by the positions and power relations of the professionals and patients, knowledge asymmetry, patient's dependency on the doctor's good will, and time constraints. Stakeholders may represent the patient's perspective, but the evaluator should be critical to any political agenda.

While establishing validity, it is not possible to focus on limiting bias in the appraisal of quantitative studies, especially when dealing with text and opinion. In appraisal of text, one needs to consider the opinions being raised are vetted, the credibility of the source investigated, the motives for the opinion examined, and the global context in terms of alternate or complementary views. The

validity in this context therefore relates to what is being said, the source, his/her credibility and logic, and consideration of the overt and covert motives at play.

## ***Quality assessment of registers, statistics and routinely collected data***

**Registers:** When one or more quality-assured registers exist, as is the case for example for many organized screening programs or medical implants, the information can be highly reliable.

The relevance and quality of registers should be appraised carefully, considering the following questions:

- How representative is the register? (European, national, regional, local?)
- What kind of information has been coded?
- What are the inclusion/exclusion criteria for the data entered?
- What is the quality of information?
- How complete is the coverage?

Data access is an important aspect when working with registers. It may be impossible for institutions other than the ones managing the register to analyse the raw data. However, some registers conduct customized analyses.

**Statistics and routinely collected data:** Routinely collected administrative data (e.g. DRGs, discharge databases, reimbursement claims databases) can be useful, when available. For example sickness funds collect large amounts of information which could be used to analyse the utilisation of a technology. By definition, this data has been collected for purposes other than research and they cannot be used to answer scientific questions without previous processing. An analysis of this kind of data might be very time-consuming, since data needs to be ‘prepared’ before analysis, and hence the data may not be feasible for use within an HTA project. The use of routinely collected statistics has several limitations. The reliability of the diagnosis varies and it is usually not possible to differentiate between different stages of the disease. Even the validity of the coding of death causes may be variable, and in some countries it is known to be very limited. There are several national and international sources of statistics which can be used to assess the incidence, prevalence, mortality, or burden of disease. These statistics are usually in aggregated form and increasingly available online.

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. Researchers of this domain should be aware of the *Policy for HTA Core Model and core HTA information* that defines specific rules for using non-public data.

## ***Critical Appraisal of Qualitative Evidence***

A variety of checklists and tools to assess qualitative studies is available. These tools use a series of criteria that can be scored and the decision to include a study can be made based on whether it meets a pre-determined proportion of all criteria, or certain criteria. Some tools use weighted scores to evaluate different criteria.

Appraisal should consider appropriateness of research method(s), sampling, data collection and analysis. Although there are several available quality assessment instruments, disagreement still exists about which criteria is appropriate for the critical appraisal of qualitative research, and whether quality assessment should be done at all.

For example, within a Cochrane Intervention review, a critical appraisal of qualitative studies is considered an essential step. According to Cochrane guidance, critical appraisal involves (1) filtering against minimum criteria, involving adequacy of reporting detail on the data sampling, collection and analysis; (2) technical rigour of the study elements indicating methodological soundness and (3) paradigmatic sufficiency, referring to researchers' responsiveness to data and theoretical consistency. When choosing an assessment instrument, the review team needs to consider how appropriate their choice is in the context of their review, and to be aware that whether or not a study meets the standard might depend on the instrument used. {3}

## **Analysing and synthesising evidence**

### ***Data extraction***

There are several issues defined in the *HTA Core Model*, particularly in this domain, where systematic data retrieval is not necessary. Unsystematic gathering of information may instead be enough.

A higher level of evidence provides decision-makers with sufficient confidence in the relevance and reliability of findings. When describing the technical characteristics of a technology, several biases may exist in relation to the selection of information, the quality of information, or the co-founding factors.

### ***Qualitative synthesis***

In general, the characteristic of a technology can be obtained from a few sources. The description of the comparator could instead be part of a huge research work and in this case, a synthesis of the evidence is useful.

Qualitative and quantitative findings could be synthesised in two ways: multilevel synthesis (separate and combined synthesis) and parallel synthesis (separate and juxtaposed synthesis) {4}. Furthermore, quantitative and qualitative studies can be synthesised together; one example is a systematic review on teenage pregnancy and social disadvantage {5}.

Qualitative synthesis is a process of combining evidence from individual qualitative studies in order to create new understanding. This is done by comparing and analysing concepts and findings from

different sources of evidence, with a focus on the same topic of interest. It can be an aggregative or interpretive process, which requires authors to identify and extract evidence, categorise it, and combine categories so as to develop synthesised findings. It is important to understand why people feel or behave in a certain way and not to just make a description of these events {4}.

There is a range of methods available for synthesising diverse forms of evidence; for example, meta-ethnography, grounded theory, thematic synthesis, narrative synthesis, realist synthesis, content analysis. Some of the methods, such as meta-ethnography, maintain the qualitative form of the evidence, while others, such as content analysis, involve converting qualitative findings into a quantitative form {6}.

Synthesis methods are classified in different ways, and it has been argued whether it is acceptable to conduct syntheses of qualitative evidence at all, as well as whether it is acceptable to synthesise qualitative studies derived from different traditions. {6, 7, 8}

## Reporting and interpreting

Transparency in information retrieval is crucial when reporting core HTA information; it should be explicitly stated what the sources and methods of retrieval were, whether they were systematic or not, and what quality assessment criteria were (also when missing).

The issues in the TEC domain need to be described in sufficient detail to differentiate the technology from its comparators. Terms and concepts should be used in a manner which allows those unfamiliar with the technology to get an overall understanding of how it functions and how it can be used. It is also important to distinguish between scientifically proven versus suspected mechanisms of action. Important terms should be defined, and a glossary or a 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.

The users of HTA require sufficient information on the design and function of the technology to understand the technology's mode of action, its technical requirements and possible problems and alternatives, its staffing requirements, its applicability range, its variants, and its possible direct risks. For medical devices, it may be helpful to include drawings or schematics for the technology that illustrate the components, dimensions and materials of construction of the device.

For diagnostic and monitoring technologies (laboratory tests, imaging, questionnaires etc.), it is important to include sufficient information about the technical precision of the technology. This information, which is different from the accuracy data presented in the clinical effectiveness domain, should be reported in this domain.

For management processes (such as screening programs) the position and interaction of the technology within the broader healthcare sequence should be described. This also may require listing alternative technologies.

## Assessment elements

B0001 Assessment element card						
Issue: What is this technology and the comparator(s)?						
Topic: Features of the technology						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	1
	Medical and Surgical Interventions (3.0)	Yes	Critical	Complete	Yes	1
	Pharmaceuticals (3.0)	Yes	Critical	Complete	Yes	1
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	1
Clarification	<p><b>Common to all used applications</b></p> <p>This is relevant for all assessments. Use the descriptions of the technology and comparator(s) defined in that scope and elaborate them in more detail. The technology may include a single device, a questionnaire, imaging or a sequence of technologies. The HTA may address one or several similar technologies.</p> <p>Separately describe the technology and the comparator. The description should include the type of device, technique, procedure or therapy; its biological rationale and mechanism of action; there should also be a description of how the technology differs from its predecessors, and of the various current modifications or different manufacturers' products, especially if the dissimilarities affect performance.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Manufacturers' sites, published literature including reviews, textbooks, introduction sections of research articles, effectiveness studies, clinical experts, studies in basic science, HTA-reports.</p>					
References	<p><b>Common to all used applications</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p>					

<b>Content relations</b>	<b>Common to all used applications</b> A0022, A0018; F0001
<b>Sequential relations</b>	

B0002 Assessment element card						
Issue: What is the claimed benefit of the technology in relation to the comparators?						
Topic: Features of the technology						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Complete	Yes	2
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	2
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	2
	Screening Technologies (3.0)	Yes	Important	Complete	Yes	2
Clarification	<p><b>Common to all used applications</b></p> <p>This issue is especially relevant for new technologies with uncertain expectations and claims of benefit.</p> <p>Describe the following aspects:</p> <ul style="list-style-type: none"> <li>• How is it expected to be an improvement over previous/existing technologies used for the same health problem? What are the claimed objectives? (e.g. increased safety, health benefit, accuracy or patient compliance)</li> <li>• Is the technology intended to replace or to supplement existing technologies.</li> <li>• Is the technology licensed as a mono-intervention, or in addition to current interventions (which should be specified)</li> <li>• Are there stopping rules for use of the technology?</li> <li>• Is there evidence that the technology works (or is used) outside its current indication area, or produces incidental findings that can have consequences relevant to effectiveness, safety, organisational, social and ethical domains?</li> </ul> <p>This information may explain the choice of comparator(s) and outcomes for the assessment and helps in appraising the overall results.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Manufacturers' sites, HTAs, effectiveness studies, clinical experts, published literature including reviews, introduction sections of research articles, grey literature, hand-searches and conference proceedings, consulting clinical professionals, lay journals and websites.</p>					

<b>References</b>	<p><b>Common to all used applications</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>A0001, A0009; C0008</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>A0018, D1019</p>
<b>Sequential relations</b>	

B0003 Assessment element card

Issue: What is the phase of development and implementation of the technology and the comparator(s)?

Topic: Features of the technology

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	3
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	3
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	3
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	3
<p><b>Clarification</b></p>	<p><b>Common to all used applications</b></p> <p>Most technologies will be introduced at approximately the same time in several countries. This information is relevant for the assessment of technologies that are at an earlier stage in their development, as during that time the evidence base may change rapidly. It is also important to establish whether new versions of the technology, which include substantial improvements, are expected in the near future. It is useful for end users to know if new versions or adaptations of the technology are expected in the near future.</p> <p>Describe the following aspects:</p> <ul style="list-style-type: none"> <li>• Is the technology an innovation?</li> <li>• When was it developed?</li> <li>• 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?</li> <li>• When was the technology introduced into healthcare?</li> <li>• Is the technology an already established one, but now used in a different way, for instance for a new indication?</li> <li>• Is it experimental, emerging, established in use or obsolete (implementation level)?</li> <li>• Is the technology field changing rapidly?</li> <li>• How does this technology differ from its predecessors (other technologies used for similar purposes)?</li> <li>• Are there new aspects that may need to be considered when applying it?</li> <li>• 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 EFF, SAF, ORG, SOC and ETH?</li> </ul>					
<p><b>Methodology and sources</b></p>	<p><b>Common to all used applications</b></p> <p>Manufacturers' sites and effectiveness studies, HTAs, guidelines, published literature including reviews, textbooks, introduction sections of research articles, grey literature, hand-searches and conference proceedings.</p>					

<b>References</b>	<p><b>Common to all used applications</b></p> <p>Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24}</p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>A0020, A0021, A0011, A0019, A0020; F0001</p>
<b>Sequential relations</b>	

B0004 Assessment element card

Issue: Who administers the technology and the comparators and in what context and level of care are they provided?

**Topic: Features of the technology**

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	4
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	4
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	4
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	4
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Describe the following aspects:</p> <ul style="list-style-type: none"> <li>• Which professionals (nurses, doctors, and other professionals) apply and make decisions about starting or stopping the use of the technology?</li> <li>• Do the patients themselves, or their caregivers, administer the technology?</li> <li>• Who can select the patients, make referrals, decide to initiate the use of the technology, or interpret the outcome?</li> <li>• Are there certain criteria (skills, function, training requirements) for the patients or professionals who will administer the technology?</li> </ul> <p>Describe the level of care in which the technology is used: self-care, primary care, secondary and/or tertiary care; furthermore, If used in secondary or tertiary care, describe whether it is intended to be used in the outpatient or inpatient setting.</p> <p>The technology's role in the management pathway can be a replacement, an add-on, or for triage</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Clinical guidelines, professionals' consensus statements, HTAs, manufacturers' websites, introduction sections of research articles, interviews with clinical professionals or patients.</p> <p>Manufacturer, effectiveness studies, clinical experts, legislation. National or local judgement, as well as grey literature, hand-searches and conference proceedings can be also used.</p>					

<b>References</b>	<p><b>Common to all used applications</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>A0012, A0025; G0001, G0005</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>D1007</p>
<b>Sequential relations</b>	

B0018 Assessment element card						
Issue: Are reference values or cut-off points clearly established?						
Topic: Features of the technology						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	5
	Medical and Surgical Interventions (3.0)	Yes	Important	Partial	Yes	5
	Pharmaceuticals (3.0)	No				
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	5
Clarification	<p><b>Common to all used applications</b></p> <p>Are conflicting/varying definitions of an abnormal finding likely to affect the interpretation of the results? (If so, please describe them.)</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Manufacturers' sites, published literature including reviews, textbooks, handbooks, introduction sections of research articles, interviews with specialists, as well as grey literature, hand-searches and conference proceedings.</p>					
References	<p><b>Common to all used applications</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p>					
Content relations						
Sequential relations						

A0020 Assessment element card

Issue: For which indications has the technology received marketing authorisation or CE marking?

Topic: Regulatory Status

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Complete	Yes	6
	Medical and Surgical Interventions (3.0)	Yes	Critical	Complete	Yes	6
	Pharmaceuticals (3.0)	Yes	Critical	Complete	Yes	5
	Screening Technologies (3.0)	Yes	Critical	Complete	Yes	6
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>There are both international and national market authorisation systems. There are established systems for pharmaceuticals, but less so for devices and procedures. An overview of the authorisation systems status with regard to key processes, e.g. CE marking or EMA/FDA approval, is recommended. Information on national data and an analysis of possible discrepancies can also be highly useful.</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>Imaging devices may require approval. Substances needed for obtaining images (e.g. radiotracers) may also require additional approval. In some cases, the approval for primary screening is different to that for clinical use (FDA recently licensed tests explicitly for screening), but approval is in most cases obtained for diagnostic use and the test is proposed for screening without any other formal approval.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>Imaging devices may require approval. Substances needed for obtaining images (e.g. radiotracers) may also require additional approval. In some cases, the approval for primary screening is different to that for clinical use (FDA recently licensed tests explicitly for screening), but approval is in most cases obtained for diagnostic use and the test is proposed for screening without any other formal approval.</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>CE-Approval, EMA, FDA, national authorities. Manufacturers should be contacted in order to identify which steps have they taken/ are they planning to take concerning market approval.</p>					

<b>References</b>	<b>Common to all used applications</b>  Burls et al. 2000 {1}, Busse et al. 2002 {2}, Liberati et al. 1997 {3}, Imaz-Iglesia et al. 1999 {23}, Kristensen et.al 2007 {24} from the CUR domain
<b>Content relations</b>	<b>Common to all used applications</b>  I0015; B0002
<b>Sequential relations</b>	
<b>Other domains</b>	Also in: Health Problem and Current Use of the Technology

A0021 Assessment element card						
Issue: What is the reimbursement status of the technology?						
Topic: Regulatory Status						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Complete	Yes	7
	Medical and Surgical Interventions (3.0)	Yes	Important	Complete	Yes	7
	Pharmaceuticals (3.0)	Yes	Important	Complete	Yes	6
	Screening Technologies (3.0)	Yes	Important	Complete	Yes	7
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>List information on national reimbursement status from different countries for the technology as well as the comparators, including key dates and anticipated licensing timeframe. Notice that reimbursement status may differ for different purposes, e.g., treatment vs. prevention. Information on full coverage, co-payments, coverage under special circumstances/conditional coverage is useful.</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p><a href="#">Appendix 1 of REA model</a>: List of websites of national agencies with information on reimbursement  <a href="#">EVIDENT database</a>.</p>					
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Burls et al. 2000 {1}, Busse et al. 2002 {2}, Liberati et al. 1997 {3}, Imaz-Iglesia et al. 1999 {23}, Kristensen et.al 2007 {24} from the CUR domain</p>					
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>I0012; B0002</p>					
<b>Sequential relations</b>						
<b>Other domains</b>	Also in: Health Problem and Current Use of the Technology					

B0007 Assessment element card						
Issue: What material investments are needed to use the technology?						
Topic: Investments and tools required to use the technology						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	8
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	8
	Pharmaceuticals (3.0)	Yes	Important	Partial	Yes	7
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	8
Clarification	<p><b>Common to all used applications</b></p> <p>These can include devices, machinery, computer programs, etc. – those parts of the technology that need to be purchased (and often installed) by an organisation in order for the technology to be used. Includes the need for back-up investment to cover malfunctions in use.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Manufacturers' sites, published literature including reviews, textbooks, handbooks, introduction sections of research articles, interviews with specialists, clinical experts, user information. National or local judgement, as well as grey literature, hand-searches and conference proceedings.</p>					
References	<p><b>Common to all used applications</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p>					

<b>Content relations</b>	<b>Common to all used applications</b>  E0001, E0002; G0006, G0003  <b>Specific to Screening Technologies (3.0)</b>  E0001, E0002, G0006
<b>Sequential relations</b>	

B0008 Assessment element card						
Issue: What kind of special premises are needed to use the technology and the comparator(s)?						
Topic: Investments and tools required to use the technology						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	9
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	9
	Pharmaceuticals (3.0)	Yes	Critical	Complete	Yes	8
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	9
Clarification	<p><b>Common to all used applications</b></p> <p>Many technologies require purpose-built premises, such as radiation-secured areas, Faraday cages, dressing rooms for the patient, or specific premises for storage and reconstitution of chemotherapy pharmaceuticals equipped with fume cupboards.</p> <p>Typical premises in primary or secondary care may differ markedly from country to country.</p> <p>Clearly describe the necessary facilities, rather than just using general statements (e.g. to be used in hospitals only).</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>User information from manufacturer and market approval authority. HTAs, applicability studies, interviews with clinical experts and hospital managers.</p> <p>National or local judgement can be also used.</p>					
References	<p><b>Common to all used applications</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p>					

<b>Content relations</b>	
<b>Sequential relations</b>	

B0009 Assessment element card						
Issue: What equipment and supplies are needed to use the technology and the comparator?						
Topic: Investments and tools required to use the technology						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	10
	Medical and Surgical Interventions (3.0)	Yes	Critical	Complete	Yes	10
	Pharmaceuticals (3.0)	Yes	Critical	Complete	Yes	9
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	10
Clarification	<p><b>Common to all used applications</b></p> <p>Describe all required disposable items necessary for using the technology, such as: syringes, needles, pharmaceuticals and contrast agents, fluids, bandages and tests for identifying patients eligible for treatment.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Information from manufacturer, HTAs, applicability studies, interviews with clinical professionals and hospital manager, user information.</p> <p>National or local judgement can be also used.</p>					
References	<p><b>Common to all used applications</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>E0001, E0002; G0006</p>					
Sequential relations						

B0010 Assessment element card						
Issue: What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?						
Topic: Investments and tools required to use the technology						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	11
	Medical and Surgical Interventions (3.0)	Yes	Critical	None	Yes	11
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	10
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	11
Clarification	<p><b>Common to all used applications</b></p> <p>Describe the data that needs to be collected about the care process, professionals involved, patients and their health outcomes. These include, e.g., clinical indications, specified populations, prescriber information, inpatient or outpatient use, test results, review period, and health outcomes. In case of new technologies, consult EVIDENT database.</p> <p>Describe the general importance of having a registry for monitoring the use of this particular technology and the comparator is also needed. 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? National examples should be provided.</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>Refer to SPC and EPAR.</p> <p>Registries are sometimes connected with the risk sharing scheme that innovative pharmaceuticals require in some countries. Notice also the requirements of pharmacovigilance monitoring.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Sources: Local authorities and legislation, administrative staff, clinical professionals, HTAs, National or local judgement.</p>					
References	<p><b>Common to all used applications</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002 {1}; Kristensen FB et al. 2007 {10}; Draborg E et al. 2005 {35} from the SAF domain</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>Busse R et al. 2002 {1}</p>					

<b>Content relations</b>	<b>Common to all used applications</b> G0008, G0003
<b>Sequential relations</b>	
<b>Other domains</b>	Also in: Safety

B0012 Assessment element card

Issue: What kind of requirements in terms of qualification and quality assurance processes are needed for the use or maintenance of the technology?

Topic: Training and information needed to use the technology

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	12
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	12
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	11
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	12
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Differentiate between the users who are (1) applying the technology (could be different from those interpreting results); (2) interpreting the results and making clinical decisions and (3) taking care of service and maintenance.</p> <p>Describe the type of training materials (writing and/or translation, other adaptation) needed, and the characteristics of the personal training (individual and/or group sessions, number and length of sessions, number and qualifications of trainers)? Are regular or frequent standardisation or quality checks required (e.g. CME points)?</p> <p>Provide an estimate of the extent to which the training and quality assurance measures may affect the efficacy and safety of the technology.</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Manufacturers' sites, approving authority, published literature including handbooks, textbooks, reviews, HTA-reports, interviews with specialists and clinical experts, as well as grey literature, hand-searches and conference proceedings.</p> <p>Research studies and national or local judgment can be used.</p>					

<b>References</b>	<p><b>Common to all used applications</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>G0003; C0020, C0062, C0063; E0001, E0002; G0006</p>
<b>Sequential relations</b>	

B0013 Assessment element card

Issue: What kinds of skills and training characteristics and information are needed for the personnel/caregivers using this technology?

Topic: Training and information needed to use the technology

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	13
	Medical and Surgical Interventions (3.0)	Yes	Important	None	No	13
	Pharmaceuticals (3.0)	Yes	Important	None	No	12
	Screening Technologies (3.0)	Yes	Important	None	No	13
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Describe the type of training materials (writing and/or translation, other adaptation) and the characteristics of the personal training (individual and/or group sessions, number and length of sessions, number and qualifications of trainers).</p> <p>If the technology requires a specific skill that is developed while using the technology over a period of time (learning curve), an estimate should be provided of the number of patients a professional needs to treat (as a basis or per year) in order to reach an acceptable minimum standard. Provide an estimate of the extent to which the training and quality assurance measures may affect the efficacy and safety of the technology.</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Manufacturer, effectiveness studies, observational studies, applicability studies, clinical experts, user information, HTA-reports. National or local judgement.</p>					
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p>					

<b>Content relations</b>	<b>Common to all used applications</b> G0003; C0020, C0062, C0063; I0008; F0006
<b>Sequential relations</b>	

B0014 Assessment element card						
Issue: What kind of training resources and information should be provided to the patient who uses the technology, or for his family?						
Topic: Training and information needed to use the technology						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	14
	Medical and Surgical Interventions (3.0)	Yes	Critical	None	Yes	14
	Pharmaceuticals (3.0)	Yes	Optional	None	No	13
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	14
Clarification	<p><b>Common to all used applications</b></p> <p>Describe the type of training materials that should be provided (writing and/or translation, other adaptation), by whom they should be provided, and the characteristics of the personal training (individual and/or group sessions, number and length of sessions, number and qualifications of trainers) and if an informed consent regarding this type of training participation is required.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Manufacturer data, effectiveness studies, observational studies, applicability studies, clinical experts, user information, patient organisations, HTA-reports.</p> <p>National or local judgement</p>					
References	<p><b>Common to all used applications</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>C0008, C0003, C0005, C0007, C0062; F0004, F0006; G0004; H0003, H0007, H0008; I0002</p>					
Sequential relations						

B0015 Assessment element card						
Issue: What information about the technology should be provided to patients outside the target group and to the general public?						
Topic: Training and information needed to use the technology						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	15
	Medical and Surgical Interventions (3.0)	Yes	Critical	None	Yes	15
	Pharmaceuticals (3.0)	Yes	Optional	None	No	14
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	15
Clarification	<p><b>Common to all used applications</b></p> <p>Describe what type of information materials that should be provided (writing and/or translation, other adaptation), and whether informed consent for this type of training participation is required.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Manufacturer data, effectiveness studies, observational studies, applicability studies, clinical experts, user information, patient organisations, HTA-reports, discussion forums in web, as well as grey literature, hand-searches and conference proceedings.</p> <p>National or local judgement</p>					
References	<p><b>Common to all used applications</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>F0005, F0011; G0004; H0002, H0007, H0008; I0002, I0008</p>					
Sequential relations						

A0022 Assessment element card						
Issue: Who manufactures the technology?						
Topic: Other						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	16
	Medical and Surgical Interventions (3.0)	Yes	Important	Partial	Yes	16
	Pharmaceuticals (3.0)	Yes	Important	Partial	Yes	15
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	16
Clarification	<p><b>Common to all used applications</b></p> <p>Please provide information on national, European and international level about the manufacturer of this technology.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Manufacturers' information, clinical guidelines, legislation, HTAs, approving authority</p> <p>National or local judgement.</p>					
References	<p><b>Common to all used applications</b></p> <p>Liberati A. et al. 1997 {3}; Busse R. et al. 2002 {2}; Kristensen FB et al. 2001; Draborg E et al. 2005</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (3.0)</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005</p>					
Content relations						
Sequential relations	<p><b>Common to all used applications</b></p> <p>I0037</p>					

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# Safety (SAF)

## *Description*

### **What is this domain about?**

Safety is an umbrella term for any unwanted or harmful effects caused by using a health technology. An HTA should include an assessment of safety both in order to benefit individual patients and to inform policy makers {1}. Safety information, balanced with data on effectiveness, forms the basis for further assessments of the technology with regard to, e.g., costs and organisational aspects.

The diversity of various types of health technology draws with itself many different types of safety issues; due to this, legitimate differences can occur in the way one can undertake an assessment of safety. The authors of a core HTA should cover those safety issues that are important to patients, or otherwise likely to be important in guiding the decisions of health care providers and policy makers.

**Table 1: Topics and issues in this domain**

Topic	Issue	Assessment element ID
Patient safety	How safe is the technology in relation to the comparator(s)?	C0008
Patient safety	Are the harms related to dosage or frequency of applying the technology?	C0002
Patient safety	How does the frequency or severity of harms change over time or in different settings?	C0004
Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	C0005
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?	C0006
Patient safety	Are the technology and comparator(s) associated with user-dependent harms?	C0007
Occupational safety	What kind of occupational harms can occur when using the technology?	C0020
Environmental safety	What kind of risks for the public and the environment may occur when using the technology?	C0040
Safety risk management	How can one reduce safety risks for patients (including technology-, user-, and patient-dependent aspects)?	C0062
Safety risk management	How can one reduce safety risks for professionals (including technology-, user-, and patient-dependent aspects)?	C0063
Safety risk management	How can one reduce safety risks for the environment (including technology-, user-, and patient-dependent aspects)?	C0064
Safety risk management	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator(s)?	B0010

The following categories of harm may help identify and classify assessment elements for the Safety domain.

- A technology may cause **direct** harm: mortality, morbidity or disability due to radiation, toxicity, immunogenicity, idiosyncrasy, hypersensitivity, invasiveness, etc.; or it can harm **indirectly** due to e.g. insufficient training or experience, lack of equipment maintenance, or inappropriate patient selection.
- Indirect harms can further be grouped into **operator or setting dependent** and **patient dependent** harms. The former can be modified by changing practices or improving user knowledge, skills and behaviour. The latter may indicate vulnerable patient groups that require special protection.
- Harms are often classified according to their **fatality** or **intensity** into mild, moderate, and serious or severe {2}. ‘**Serious**’ refers to adverse effects that have significant medical consequences: they can for example lead to death, permanent disability, or prolonged hospitalisation. In contrast, ‘**severe**’ refers to the intensity of a particular adverse effect. A non-serious adverse effect, such as headache, may be severe in intensity (as opposed to mild or moderate).
- Harms can occur not only in **patients** or individuals using the technology. Their **family** and close ones, **foetus**, other patients, health care **professionals**, **public**, and the **environment** can also be affected.
- **Risk** is an estimate of the probability of the harm.
- Harms can be classified according to their **dose-relatedness** or **time-relatedness**. Increasing amount of exposure to technology (larger dose or longer time) can increase the risk of an adverse effect.
- Harms can be previously **known** or **unexpected**. Control of known harms can be attempted by, e.g., using specific monitoring tests to identify vulnerable patients or limiting the dose or time of exposure. Unexpected harm should be considered especially when expanding the use of a technology and in particular when launched outside a study context {2}.
- The **causality** of harm, i.e. the likelihood that the intervention is causative of an observed adverse event, is frequently evaluated.

For the *HTA Core Model*-suggested definitions for safety-related terms, see the guideline ‘Endpoints used in REA of pharmaceuticals – Safety’ {3}.

It is important that HTA assessors use consistent and precise terminology to avoid confusion and misleading conclusions. For this purpose, the *Medical Dictionary for Regulatory Activities* (MedDRA), developed by the International Conference on Harmonisation, could be a useful instrument. {4} MedDRA includes medical signs, symptoms, syndromes and diagnoses as well as social conditions, surgical and medical procedures and laboratory and clinical investigations. It comprises five levels: lowest level terms (LLTs); preferred terms (PTs); high level terms (HLT); and high level group terms (HLGTs). It is organised into 26 system organ classes (SOCs). The use of MedDRA for recording and reporting adverse effects/reactions data on marketed medicines is mandatory in the European Union. MedDRA is available free of charge to regulatory authorities and to certain non-profit-making organisations and on payment of an annual subscription to other users. {6}

Besides MedDRA-coded adverse events, it may be useful to also analyse endpoints which measure harms not based on this terminology. These concern explicitly pre-planned endpoints which are recorded according to pre-planned definitions (e.g. different evaluations of bleeding events: major bleeding, minor bleeding, etc.). For observational studies in claims databases and electronic health records, other terminology may be used for AE assessment (ICD-9, ICD-10, READ).

Additionally, the *HTA Core Model* recommends the use of terminology developed in the National Cancer Informatics Program (NCIP) Open-Development Initiative at the National Institutes of Health in the USA. This includes the *NCI Common Terminology Criteria for Adverse Events* (CTCAE) v.4 and the WHO system-organ class categories {7}. Some researchers observe that standard ‘preferred terms’ can distort descriptions in the original reports of adverse events and blur distinctions between them, as the terminology has not been well standardised {8}.

## Why is this domain important?

Safety information is essential for being able to form a balanced view of the overall diagnostic or therapeutic value of a technology. Reliable information on harms is challenging to gather and find; it is therefore particularly important to share it on the European level.

Assessment of safety issues should always be considered, but it is especially necessary in any of the following cases {9}:

- The technology presents any risk of serious harm or a high risk of milder harms.
- The technology is used in large populations.
- The benefit-harm-balance is close to even.
- Several technologies with similar effectiveness can be used for the condition, and they have different safety profiles.
- The false positive rate of a diagnostic or screening test is high and patients may be subjected to unnecessary, potentially harmful investigations or treatments.
- Adverse effects or poor tolerability threaten the acceptability and use of the technology.

## Relations to other domains

Work in the Safety domain should be carefully coordinated with the Clinical Effectiveness (EFF) domain. Benefit-harm-balance is an essential issue in EFF. It is worthwhile to discuss how to avoid duplicate work in finding information for that. The Safety domain may require information from Health Problem and Current Use of the Technology (CUR), Description and Technical Characteristics of the Technology (TEC), and Ethical Analysis (ETH) domains. Information provided by SAF is of relevance to at least the Organisational Aspects (ORG), Costs and Economic Evaluation (ECO), ETH domains, and possibly also to the Legal Aspects (LEG) domain.

Other domains, especially EFF, may identify and cover safety-related information. A rapid HTA process can include an integrated literature search for both efficacy and safety information, although this approach may overlook study designs that provide more extensive safety information.

## Screening-specific content

Since screening technologies are used for large numbers of healthy persons, the tolerance threshold for harms should be very low {10}. Indirect harms specific to screening technologies are:

- False positive results, which may cause stress and anxiety and lead to unnecessary, possibly harmful, further investigations or treatments.
- False negative results of a screening test may have potential to delay the detection of illness. A false negative result may have medical, psychological, economic, or legal consequences.
- A true negative test result may reduce normal alertness to symptoms of disease and lead to a false sense of security.
- Overdiagnosis and overtreatment can be a problem if screening tends to find and lead to treatment of conditions that have a good prognosis, even when not treated. The same occurs if screening detects other conditions than the one it aims to detect.

## Pharmaceutical-specific content

The safety issues specific to pharmaceutical technologies (drug safety, patient safety, adverse drug reactions, patient susceptibility, pharmaceutical safety) should be considered while working on the safety domain {11}. For further details, see the guideline ‘Endpoints used in REA of pharmaceuticals – Safety’ {3}.

## *Methodology*

### Gathering information

#### *Where to find information?*

Primary sources of published information are the medical reference databases: The Cochrane Library, Medline, EMBASE, etc. The SuRe Info database (Summarized Research in Information Retrieval for HTA, <http://vortal.htai.org/?q=sure-info>) is a web resource that provides research-based information relating to the information retrieval aspects of producing systematic reviews and health technology assessments, including domain-specific searching advice. In addition, the following sources or enquiries may be helpful:

- National or international safety monitoring systems of adverse events which may be managed by a national statutory body or by a supra-national body; Risk Management Programs and systematic safety research; particular attention to label warnings and open questions in pharmacovigilance is needed

- Disease or technology monitoring registries of patients receiving treatment, which may be organised at an international, national or regional level and is managed by a government agency, professional body or the manufacturer.
- Pharmacovigilance data analysis and pharmacovigilance systems or spontaneous adverse event databases, such as:
  - The Uppsala Monitoring Centre spontaneous reporting database (<http://www.who-umc.org>) and the Vigibase Services, maintained by Uppsala Monitoring Centre, responsible for the management of the WHO Programme for International Drug Monitoring
  - The EMA collects adverse reactions reports on medicines licensed across the EU through the EudraVigilance database. Reports are received from EU regulatory agencies and pharmaceuticals companies.
  - Adverse Event Reporting System (AERS), the database supported by the FDA's post-marketing safety surveillance program for approved drugs. The MedWatch website, on which the FDA collects information about adverse reactions.
- Manufacturers' product data sheets or applications for a product license if available. European Public Assessment Reports of pharmaceuticals. Risk Management Plans for pharmaceuticals.
- Manufacturers' periodic safety update reports (PSUR), a pharmacovigilance tool; collecting information from a variety of different sources (spontaneous reports from different countries, clinical trials, registries).
- Specific enquiries to manufacturers (e.g., industry submissions, product information), regulators, professional bodies or patient group perspectives may help identify additional sources of information.

When information is scarce, it may be necessary to look for grey literature (drug monographs, bulletins, or conference proceedings); to do reference checking of retrieved literature, or hand searching of selected journals; or to ask experts in the area. Inclusion of unpublished studies can provide additional adverse effects information and more precise risk estimates. However, there is insufficient evidence to indicate whether inclusion of unpublished studies has a major influence on the pooled risk estimates in meta-analyses of adverse effects {12}. In some cases, routine statistics from hospital, primary care, or health system funders may be available and provide suitable information. Furthermore, information from patient associations may provide valuable patient experiences especially in emerging technologies {13}.

The sources of information that have been used should be clearly stated.

## **Databases and search strategies**

Searches may not detect all relevant studies because indexing terms for adverse effects are not always assigned in original studies, and the authors do not mention adverse effects in the title or abstract. To improve the sensitivity of the search, terms for specific adverse effects have to be defined separately for search strategies in each respective database {14}. New, previously unrecognised adverse effects remain therefore easily undetected {15}. The search should consider

including several study types, as systematic reviews of adverse effects have often used inadequate searches to identify studies {16}.

The following approaches can be used to complement the search strategy with key elements derived from study population and the technology in question:

- Index terms (thesaurus terms, e.g., MeSH in Medline)
  - For specific adverse effects: ‘haemorrhage’, ‘pain’, ‘nausea’, ‘lethargy’, ‘fatigue’, etc.
  - For harm in general: ‘Adverse Effects’ (subheading), ‘safety’, ‘toxicity’, ‘drug toxicity’, ‘complications’, etc.
- Subheadings or qualifiers either attached to technology name indexing terms or ‘floated’, i.e. searched without being attached to an indexing term
- Text words (terms used by the original authors in title and abstract), also taking into account different conventions in spelling and variations in the endings of the terms.
  - For specific adverse effects: ‘pain’, ‘nausea’, ‘anxiety’, ‘tiredness’, ‘lethargy’, ‘malaise’, etc.
  - For harm in general: ‘side effect’, ‘safety’, ‘adverse effect/event/reaction’, ‘complication’, ‘poisoning’, etc.
- Index terms and text words to capture certain study designs, such as cohort studies or case reports.

The search strategies for each database and study inclusion criteria should be clearly reported. This applies also to information retrieved elsewhere.

## ***What kind of information is required?***

A systematic approach is required in the assessment of safety (harms). Core HTA authors, who are not aware of any specific safety problem, usually start with a broad overview of the whole range of adverse effects associated with the use of the technology. They may be confronted with an unstructured mix of lists and texts covering many diverse outcomes due to a lack of consistency in reporting harms. A predefined classification of adverse effects could help the authors in approaching the data {9}.

In relative safety assessment, the main objectives of HTA assessors should be the following:

- To identify the adverse effects
- To quantify the adverse effects in terms of frequency, incidence, severity and seriousness

To compare the safety profile of a pharmaceutical with its comparator(s). The aim is not necessarily to cover all known and previously unrecognised harms of a technology. Rather, core HTA producers should focus their review and predefine the safety issues and outcome measures they wish to address in their assessment {2}. The producers should also define the demographic characteristics of the population in which the technology is to be used; these can be used for later comparisons against populations in which safety data has been identified.

Core HTA authors may choose to narrow their research down into some of the following areas:

- The five to ten most frequent adverse effects
- All adverse effects that either the patient or the clinician considers to be serious (pose a threat to patients' life or functioning)
- The most common adverse effects that lead the patient to stop using the intervention
- By category, for example:
  - Diagnosed by clinician (e.g. gastrointestinal haemorrhage)
  - Diagnosed by lab results (e.g. hypokalaemia)
  - Patient-reported symptoms (e.g. pain).
  - Biomarkers that may be early indicators of possible adverse effects (for example, abnormal liver enzymes); offering a means of collecting relevant information even from short-term studies.

This is not a comprehensive list, but the use of any of the above strategies should help authors approach the adverse effects analysis in a systematic, manageable and clinically useful fashion {2}.

## **Study types, designs, and outcome measures**

A broad range of study types may be considered for identifying harms relevant for the assessment, as they bring different and complementary information. Namely, randomised controlled trials, observational studies and case reports provide evidence on the types and frequencies of harms. Randomised trials are methodologically the 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 {11, 17}.

Rare adverse effects are not usually detected in randomised trials, and not even relatively frequent harms with a longer latency period can be easily quantified. 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 cases of cancer) can be estimated based on analogies and assumptions from epidemiological studies.

Besides published research, it is also possible to use routinely collected data or register data. Even though these databases are often generic and may not contain enough information, their advantages lie in their larger size or coverage over long periods of time {1}. This can be especially relevant in the assessment of, e.g., public preventive programs.

Spontaneous reporting of adverse drug reactions is a standard method in identifying safety signals for marketed drugs. Its primary purpose is to provide early warnings of adverse drug reactions not recognised prior to marketing. Once a signal has been identified, other methods will be used to quantify the potential risk in order to avoid unnecessary alarms.

Harms are sometimes summarised into quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs). Here QALY approaches refer to using a non-disease specific outcome measure, which incorporates both quality and duration of life, to represent the years of healthy life lived. DALYs are defined as years of healthy life lost. DALYs and QALYs are complementary

concepts, and both approaches multiply the number of years by the quality of those years. In order to reflect the burden of disease, QALYs use ‘utility weights’ of health states, whereas DALYs use ‘disability weights’ for handicaps. QALYs and DALYs simultaneously capture both positive and negative changes in morbidity and mortality associated with treatment-related benefits and harms, and translate outcomes from different diseases into a comparable common metric that is useful for subsequent quantitative benefit–harm balance analysis. {18, 19, 20}.

Results from trials are usually presented as information on the frequency of occurrence, relative risk (RR), risk difference (RD), odds ratio (OR), or number needed to harm (NNH) which is the inverse of absolute risk increase. Estimates of risk from case-control studies are presented in exposure odds ratios of cases compared with controls. Analysing data based on NNH can be dangerous, since this measure can be very sensitive if the risk difference is close to zero (i.e. an OR or RR close to 1) {21}. For meta-analyses, risk ratio (RR) is the most common summary statistic, followed by the Peto odds ratio. Risk difference (RD) is rarely used in meta-analyses although it is the most interpretable statistic and is particularly appropriate when examining rare event data {22}.

## **Search issues specific for screening technologies**

Suggested index terms:

- Primary Prevention [Mesh] or Mass Screening [Mesh] or Public Health Practice [Mesh]. Medicalization, false positive, false negative, overdiagnosis, over-treatment
- Drug monographs
- Bulletins
- Conference proceedings
- Reference checking
- Hand searching
- Personal communication
- Manufacturers Periodic Safety Update Reports (PSURs)
- National or international safety monitoring systems (databases) of adverse events which may be managed by a national statutory body or by a supra-national body
- Disease or technology registries of patients receiving treatment which may be organised at an international, national or regional level and managed by a government agency, professional body or the manufacturer

- In some cases routine statistics from hospital, primary care or health system funders may be available and provide suitable information
  - Specific enquiries to manufacturers (e.g. industry submissions, product information), regulators or professional bodies
  - Information from patient associations may provide valuable patient experiences especially in emerging technologies {13}.
  - Internet discussion forums may provide valuable, but probably unreliable, additional information.

## Useful other sources of information

Inclusion of unpublished studies can provide additional information on adverse effects, as well as more precise risk estimates. However, there is insufficient evidence to indicate whether inclusion of unpublished studies has a major influence on the pooled risk estimates in meta-analyses of adverse effects {12}.

## Tools for critical appraisal

There is often a trade-off between the comprehensiveness and the quality of harms data to be included in an assessment. Including evidence that is likely to be biased, even if no better evidence exists, may lead to biased conclusions. All included data should therefore be critically appraised. There is a lack of a relevant quality assessment tools for risk analysis {9}. Any available tool should be used with caution. Comparing evidence from randomised trials and observational studies is useful.

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

The authors of a core HTA should consider at least the following aspects:

- Were the methods used for detecting adverse effects reported? (Prospective or routine monitoring, spontaneous reporting, or patient checklists/questionnaires/diaries)
- How rigorous were these methods?
- Was the follow-up sufficiently long to assess the risk of serious longer-term safety issues?
- How complete is the reporting? Did the investigators report all serious or common harms? Did the report give numerical data by group? Were there differences between studies in how the severity or seriousness were assessed, or in the definition of a signs or symptoms, which could explain part of the observed heterogeneity?
- Were any patients excluded from the harms analysis?

Different methods of monitoring harms yield different results, which makes comparisons between studies meaningless. Active surveillance and use of checklists yield higher harm frequencies than

passive or less focused methods {9}. Case reports of suspected adverse events are widely published in scientific journals, but not many of these reports have been subsequently investigated or confirmed to be valid {23}. Some spontaneous reporting systems are inevitably erroneous {9}.

Original studies may report only some outcome categories even though they measured several; the intervention groups may be combined (e.g. X participants withdrew from the study); or statements may be unclear or too generic (e.g. no unexpected adverse effects were seen). One should be aware of poor reporting styles for harms-related data {24}, such as:

- Vague statements are present, e.g., ‘the drug was generally well tolerated’.
- No separate safety data for each study arm are given, or only summed numbers of all adverse events are presented.
- Severity or seriousness of adverse events is not given.
- Vague frequency rate of harm is presented; e.g., ‘> 3 % of patients’.
- Adverse events are reported only by means or medians instead of extreme values.
- The relative timing of the adverse events has been handled improperly.
- A distinction has not been made between patients with one adverse event and those with multiple adverse events.
- Statements on harm are provided with p values without giving exact count of events.
- Data on harms is not provided for all study participants but only for ‘completers’.

It is recommended to have two assessors. The assessors’ background should be reported, as should the way in which they resolved disagreements. Results of the quality assessment of the original studies should be presented in a table, or otherwise graphically. Individual quality items should be investigated as a potential source of heterogeneity.

Methods used in assessing bias should be clearly described, and the risk of bias should be reported, both regarding the information sources and the data collection method.. It should also be clearly explained how information on the risk of bias is used in the report. Detailed recommendations on how to assess the risk of bias and the quality of data on harms are included in section 2.4 of the guideline *Endpoints used in REA of pharmaceuticals – Safety* {3}

## ***Trials***

Adverse events are reported in varying and sometimes poor ways in randomised trials {17} and in systematic reviews of trials {14}. The definition of a particular harm may vary between studies, as may definitions of severity. Harms can be measured in different ways and with the use of different thresholds. Nevertheless, one guideline which supports better reporting of harms in randomised trials is an extension of the CONSORT Statement (Consolidated Standards for reporting Trials) {24}.

Basic requirements for the data are the following: (1) it should be presented numerically (there should at least be the frequency of serious events per study arm); (2) the severity of adverse effects should be stated; and (3) data should be given separately for each type of adverse effect {25}.

Analysis of zero events ('no serious adverse effects were seen') needs careful consideration. Before concluding that no adverse effect occurred, reviewers should consider the quality of methods used to detect adverse effects in the original studies, how many patients were studied, and for how long {9}.

Even in cases where adverse events have been examined and reported adequately, there is often insufficient evidence for drawing conclusions, since most trials are tailored towards optimising efficacy estimates {21}. It should be noted that no mention of harms in the original study does not necessarily mean that no harms occurred. Authors must choose whether to exclude a study from the harms analysis or, exceptionally, to include it assuming that the incidence was zero {9}.

Interpretation of withdrawal or drop-out data as surrogate measures for safety or tolerability should be approached with caution. Reasons for withdrawal can be numerous and varying, from mild side effects to serious toxicity, lack of efficacy or non-medical issues {24}. Patients or investigators in a trial may be more (or less) willing than usual to continue when side effects occur {9}.

## ***Observational studies***

Trials usually report small, fragmented pieces of evidence on harms that are not primary outcomes, whereas observational studies are primarily devoted to assessing specific harms. Nested case control studies, full cohort analyses, and survival analysis methodologies are, on the other hand, study designs used for harms assessment. When looking for major sources of bias in observational studies, these include: confounding by factors associated with both treatment and outcome; differential recall of exposure; and differential detection of outcomes {25}. Some tools for assessing observational studies are the STROBE checklist of items to be addressed in reports of observational studies {26} or the Newcastle Ottawa scale, available at [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.htm](http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm). The strengths and weaknesses of different study designs that can be included in a systematic review of harms are discussed by Jefferson and Demicheli {27}.

## **Diagnostics-specific content**

Aspects against which a diagnostic accuracy study's quality can be assessed include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and mutual blinding of results from experimental and reference tests {28}.

There are different tools for assessing the quality of diagnostic accuracy studies. The *Cochrane handbook for Systematic Reviews of Diagnostic Test Accuracy* {28} recommends the QUADAS tool.

## **Screening-specific content**

Quality assessment of diagnostic accuracy studies is subjective and hampered by poor reporting. Incorporating quality in the overall assessment is difficult due to limited number of studies. Relationships between quality items and bias are not as straightforward as they are in the case of interventions. Screening studies be additionally confounded by lead time bias, length time bias, and overdiagnosis.

## **Analysing and synthesising evidence**

The aim is not necessarily to cover all known and previously unrecognised harms of a technology. Rather, core HTA producers should focus their review and predefine the safety issues and outcome measures they wish to work with in their assessment {2}. The producers should also define the demographic characteristics of the population in which the technology is to be used; these can be used for later comparisons against populations in which safety data has been identified.

### ***Biases, confounding factors, level of evidence***

Harms are frequently insufficiently reported {17}. Poorly reporting the safety of the original research can lead to misinterpretations and to inadequate conclusion about the technology under assessment.

Reported harm frequencies may differ greatly by study type. A study comparing the harms reported in randomised as opposed to observational studies found that observational studies yield lower estimates of absolute risk of harm {30}.

Randomised trials frequently have restrictive inclusion and exclusion criteria, which can result in harm being underestimated. Furthermore, trials may exclude harm-sensitive subgroups because of ethical concerns, or include them in insufficient numbers. Measurements of late-onset harms (e.g. number of radiation-induced cases of cancer) are also seldom seen in publications. Frequency of rare harms is always an estimate, based on analogies and presumptions from epidemiological research. Adverse effects data is usually equally well-reported in studies funded by the industry. However, interpretations and conclusions by industry-funded authors may be biased {16}.

### ***Evidence tables***

An evidence table could contain the following information for each included type of harm:

- Description of harm
- Frequency or probability of harm in intervention and control groups
- Fatality (mild, moderate, severe, life-threatening, death)
- Intensity (mild, moderate, severe)
- Other classifications: self-reported/objective measure, immediate/delayed etc.
- Study type or source of information: (trial, systematic review, prospective cohort study; manufacturer report, register data, etc.)
- Quality of information (e.g. how the data was collected)
- Comments on generalisability of the evidence
- Reference or other source

## ***Meta-analysis***

Safety events are usually rare (incidence <5 %). Hence, safety estimates would require large sample sizes in trials to detect differences between patient groups. For rare event data, and when trials are balanced, exact methods in meta-analyses seem to be superior to the asymptotic Mantel-Haenzel method and to the Peto method {31}.

Since asymptotic approximations in dichotomous data require a non-zero event rate, most reviewers add 0.5 to each cell instead of zero. However, this approach is inappropriate if the event is rare. Exact methods do not provide a point estimate in a situation where no events are observed in one arm, which is intuitively acceptable too. The majority of systematic reviews use asymptotic approximations even though they are known to be imprecise with rare events.

## ***Qualitative synthesis of evidence***

At this stage, authors of a core HTA should check that the extracted data is relevant to the research questions, and that analyses and syntheses of the data are answering these. The available evidence is not always as useful as one might hope, and authors should be explicit about how well the evidence answers the original research question.

In many circumstances, it is not possible to calculate frequencies, and information about harms is then best presented in a qualitative or descriptive manner. It is not possible to combine data derived from different study designs, different populations or acquired with different data collection methods. Anticipated adverse effects can be reported congruently, whereas unanticipated harms detected during a trial might be reported in markedly different ways by different investigators {30}

## **Reporting and interpreting**

The interpretation of evidence should clearly state qualitative and quantitative limitations of the sources, searches, data, and methods used for the analysis. When summarising data, it may be helpful to present it using tables, as they are clear and transparent. {1}. Information sources should be clearly stated.

When discussing the safety of a technology, it should be described how the harms were caused. Namely, harm may be device-dependent, or related to how the technology is applied. Occurrence of adverse effects may also be operator- or setting-dependent (e.g. learning curve). The timing and severity of adverse effects as well as risk differences among different groups of patients should also be considered {9}.

The safety of a technology should always be assessed in balance with its benefits, even if the patient populations used in the benefit analysis differ from the ones in the harm analysis {9}. Once a possible relationship between a technology and a harm is suspected, causality assessment can be made using established algorithms {2} – e.g., for pharmaceuticals, those published by the WHO Collaborating Centre for International Drug Monitoring. The best way to assess causality of an adverse event is by conducting an RCT. The above mentioned algorithms are therefore an option if RCTs cannot be performed. In RCTs presenting adverse event rates, non-statistically significant differences are associated with low statistical power. A high probability of type II error may lead to erroneous inferences {24}.

Whenever possible, the overall effect of harms needs to be quantified, and information on the frequency of occurrence, relative risk or number needed to harm (NNH or NNTH) provided. A small absolute risk is still clinically important if an adverse effect is serious or severe, or if the absolute benefit from the intervention is small {30}. Finally, about it is necessary to comment on the generalisability of the findings to the population in which HTA results will be applied {2}.

Estimates of risk are in case-control studies presented as the exposure odds ratio of cases compared to controls. The unintuitive odds ratios can be used to calculate the number needed to harm (number of patients needed to be treated for one additional patient to experience an adverse event) {32}. In cases where adverse events are incorporated in utility values or quality of life measures, the source of quantification should be accessible.

## Assessment elements

C0008 Assessment element card						
Issue: How safe is the technology in relation to the comparator(s)?						
Topic: Patient safety						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	1
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	1
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	1
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	1
Clarification	<p><b>Common to all used applications</b></p> <p>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(s). For harms that are common to both the technology and the comparator(s), provide information on which has the higher risk of the particular harm. Aspects of individual patients, populations, service delivery &amp; cost-effectiveness should be considered.</p> <p>User-dependent harms are described in C0007. Harms are identified in placebo-controlled trials, observational studies, and in registries. It is important to refer to the source and report identified harms separately. Report harms per indication or target population. Categorise the identified harms according to their severity and frequency. The seriousness of harm is typically graded based on events that pose a threat to a patient's life or functioning. Frequency of each harm's occurrence is usually presented in comparison with placebo or no treatment, as percentages or risk ratios. Finally, the harms should be grouped by their severity and frequency, and ordered in such a way that the severe and/or frequent harms are presented first. If there are many different harms reported in the literature, focus on reporting the most serious and the most frequent ones.</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>Consider the important identified and potential adverse events/reactions presented in the Risk Management Plan of the pharmaceutical (RMP), as well as the important identified and potential interactions with other medicinal products, foods and other substances, and the important pharmacological class effects.</p> <p>Pay special attention to drug interactions. Information in the label warnings and PSUR should be evaluated using literature and registration data.</p> <p>Distinguish between absolute and relative contra-indications of the pharmaceutical use for particular patient groups co-medications. Co-medication should be understood in its largest way: not only medically prescribed pharmaceuticals but also over-the-counter pharmaceuticals such as non-steroidal anti-inflammatory pharmaceuticals, and herbal remedies.</p> <p>In addition, pay attention to the possibility of medication errors. Errors may be classified</p>					

	<p>into near-miss events, no-harm events, and sentinel events. Cases of accidental overdose may be described in the EPAR, but errors may also be related to the route of administration, storage conditions, reconstitution aspects, dosage, too long/too short treatment durations, mistaking two pharmaceuticals which look alike, or difficulties reading handwriting which lead to mistakes made by a patient or a professional.</p> <p>For further information see <a href="http://www.eunetha.eu/eunetha-guidelines">Methodological guideline for REA of pharmaceuticals: Safety</a> available at <a href="http://www.eunetha.eu/eunetha-guidelines">http://www.eunetha.eu/eunetha-guidelines</a></p>
<p><b>Methodology and sources</b></p>	<p><b>Common to all used applications</b></p> <p>Placebo controlled trials, observational research, FDA database, safety monitoring databases, observational research, registers, statistics registers, statistics, research articles, manufacturers' product data sheets.</p> <p>Other HTA reports or systematic reviews of main comparators.</p> <p>Method: Systematic review. Results should be presented by risk level (i.e. the product of severity and frequency of harm).</p>
<p><b>References</b></p>	<p><b>Common to all used applications</b></p> <p>Busse R et al. 2002 {1}; Ioannidis JP et al. 2004 {24}; Loke YK et al. 2007 {9}; Ioannidis JP et al. 2001 {11}; Loke YK et al. 2006 {23}; MacMahon S et al. 2001{25}; Papanikolaou PN et al. 2006 {30}; Golder S, Loke YK 2010 {33 }</p>
<p><b>Content relations</b></p>	<p><b>Common to all used applications</b></p> <p>B0001, A0018; D0009, D0003; A0001, A0007</p>
<p><b>Sequential relations</b></p>	<p><b>Common to all used applications</b></p> <p>B0001; A0018, A0001, A0007</p>

C0002 Assessment element card						
Issue: Are the harms related to dosage or frequency of applying the technology?						
Topic: Patient safety						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Complete	Yes	2
	Medical and Surgical Interventions (3.0)	Yes	Critical	Complete	Yes	2
	Pharmaceuticals (3.0)	Yes	Critical	Complete	Yes	2
	Screening Technologies (3.0)	Yes	Critical	Complete	Yes	2
Clarification	<p><b>Common to all used applications</b></p> <p>Include information on whether safe use of the technology is sensitive to even small changes in dosage, 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.</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>For further information see <a href="http://www.eunetha.eu/eunetha-guidelines">Methodological guideline for REA of pharmaceuticals: Safety</a> available at <a href="http://www.eunetha.eu/eunetha-guidelines">http://www.eunetha.eu/eunetha-guidelines</a></p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Phase 1 studies for pharmaceuticals, other research articles, HTAs, manufacturers' product data sheets, safety monitoring databases. Method: Systematic review.</p>					
References	<p><b>Common to all used applications</b></p> <p>Loke YK et al. 2008 {2}, Edwards IR et al. 2003 {6}</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>A0025; B0001</p>					
Sequential relations	<p><b>Common to all used applications</b></p> <p>A0025; B0001</p>					

C0004 Assessment element card						
Issue: How does the frequency or severity of harms change over time or in different settings?						
Topic: Patient safety						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	3
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	3
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	3
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	3
Clarification	<p><b>Common to all used applications</b></p> <p>This issue is especially relevant for new or evolving technologies where there are considerable uncertainties in the evidence of safety, and in technologies with steep learning curves. Describe how the safety profile of the technology varies between different generations, approved versions or products, and whether there is evidence that harms increase or decrease in different organisational settings.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Sources: HTAs, efficacy and safety research articles, articles on learning curve, manufacturers' information. Method: Descriptive summary.</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>D0001, D0008, D0009; B0004, B0001</p>					
Sequential relations	<p><b>Common to all used applications</b></p> <p>B0004, B0001</p>					

C0005 Assessment element card						
Issue: What are the susceptible patient groups that are more likely to be harmed through the use of the technology?						
Topic: Patient safety						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Complete	Yes	4
	Medical and Surgical Interventions (3.0)	Yes	Important	Complete	Yes	4
	Pharmaceuticals (3.0)	Yes	Critical	Complete	Yes	4
	Screening Technologies (3.0)	Yes	Critical	Complete	Yes	4
Clarification	<p><b>Common to all used applications</b></p> <p>Typically, these are people with comorbidities and co-medication, pregnancy, intolerances, or specific genetic profiles, elderly people, children and immunosuppressed patients. Report any relevant contra-indications or interactions with other technologies.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>HTAs, guidelines, market access authorities, manufacturers' product information, label warnings, safety monitoring databases. Method: Descriptive summary.</p>					
References	<p><b>Common to all used applications</b></p> <p>Loke YK et al. 2008 {2}, Edwards IR et al. 2003 {6}</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>D0008, D0009; B0016, B0001</p>					
Sequential relations	<p><b>Common to all used applications</b></p> <p>B0016, B0001</p>					

C0006 Assessment element card

Issue: What are the consequences of false positive, false negative and incidental findings generated by using the technology from the viewpoint of patient safety?

Topic: Patient safety

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	5
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	5
	Pharmaceuticals (3.0)	No				
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	5
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Describe the consequences of false positive, false negative and incidental findings generated by using the technology.</p> <p>False negative test results (Type II error) incorrectly identify sick people 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.</p> <p>False positive test results (Type I error) incorrectly identify healthy people as sick with the possible consequence of overtreatment. 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 overdiagnosis and overtreatment.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>In screening programmes, one should separately consider the false negative screening test results and the subsequent false negative diagnostic test results</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Research articles, manufacturers' product data sheets, safety monitoring databases</p>					
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Welch G et al 2011 {34} from the SAF domain.</p>					
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>D0028, D0027, D0009; B0001; E0001; F0001; G0001, G0100</p>					

<b>Sequential relations</b>	<b>Common to all used applications</b> B0001
<b>Other domains</b>	Also in: Clinical Effectiveness

C0007 Assessment element card

Issue: Are the technology and comparator(s) associated with user-dependent harms?

Topic: Patient safety

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	6
	Medical and Surgical Interventions (3.0)	Yes	Important	Partial	Yes	6
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	5
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	6
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Describe the current knowledge on 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 device malfunctioning 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? Is there a risk of addiction? Describe what is known about the learning curve, intra- or inter-observer variation in the interpretation of outcomes, errors or other user-dependent concerns in the quality of care.</p> <p>For further information see Endpoint used in REA of pharmaceuticals – Safety.</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Sources: Studies on effectiveness, safety and health services research; manufacturers' product data sheets, safety monitoring databases, label warnings. Method: Systematic review</p>					
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Loke YK et al. 2008 {2}, Edwards IR et al. 2003 {6}</p>					
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>B0006, B0001</p>					
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>B0006, B0001</p>					

C0020 Assessment element card						
Issue: What kind of occupational harms can occur when using the technology?						
Topic: Occupational safety						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Complete	Yes	7
	Medical and Surgical Interventions (3.0)	Yes	Important	Complete	Yes	7
	Pharmaceuticals (3.0)	Yes	Important	Complete	Yes	6
	Screening Technologies (3.0)	Yes	Important	Complete	Yes	7
Clarification	<p><b>Common to all used applications</b></p> <p>Consider whether there are possible harms to professionals applying the technology: working positions, radiation or infection risks, etc.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Research articles, manufacturers' product data sheets, safety monitoring databases</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>B0012, B0013</p>					
Sequential relations	<p><b>Common to all used applications</b></p> <p>B0012, B0013</p>					

C0040 Assessment element card						
Issue: What kind of risks for public and environment may occur when using the technology?						
Topic: Environmental safety						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Optional	Partial	No	8
	Medical and Surgical Interventions (3.0)	Yes	Optional	Partial	No	8
	Pharmaceuticals (3.0)	Yes	Optional	Partial	No	7
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	8
Clarification	<p><b>Common to all used applications</b></p> <p>Several chemical substances or their toxic metabolites are potentially harmful in ecological environments; some of the most recent concerns are related to endocrine modulators and disruptors and nanoparticles. The statistical risk of radiation at the public level should also be described here.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Method: Systematic review.</p> <p>Research articles, manufacturers' product data sheets, safety monitoring databases</p>					
References						
Content relations						
Sequential relations						

C0062 Assessment element card						
Issue: How can one reduce safety risks for patients (including technology-, user-, and patient-dependent aspects)?						
Topic: Safety risk management						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Complete	Yes	9
	Medical and Surgical Interventions (3.0)	Yes	Important	Partial	Yes	9
	Pharmaceuticals (3.0)	Yes	Important	Partial	Yes	8
	Screening Technologies (3.0)	Yes	Critical	Complete	Yes	9
Clarification	<p><b>Common to all used applications</b></p> <p>Describe whether there is a requirement for specific training, use of a protocol or available guideline which may reduce the occurrence or severity of the harm.</p> <p>Information on what kind of risk communication is needed for patients, citizens and decision-makers can be included.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Research articles, manufacturers' product data sheets, safety monitoring databases</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>F0006; B0012, B0014, B0015</p>					
Sequential relations						

C0063 Assessment element card						
Issue: How can one reduce safety risks for professionals (including technology-, user-, and patient-dependent aspects)?						
Topic: Safety risk management						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	10
	Medical and Surgical Interventions (3.0)	Yes	Important	Partial	Yes	10
	Pharmaceuticals (3.0)	Yes	Important	Partial	Yes	9
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	10
Clarification	<p><b>Common to all used applications</b></p> <p>Report possible requirements for specific training, use of a protocol, or available guidelines which may reduce the occurrence or severity of the harm?</p> <p>Information on what kind of risk communication is needed for patients, citizens and decision-makers can be included.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Research in occupational health and safety research literature</p>					
References						
Content relations						
Sequential relations						

C0064 Assessment element card						
Issue: How can one reduce safety risks for environment (including technology-, user-, and patient-dependent aspects)						
Topic: Safety risk management						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	11
	Medical and Surgical Interventions (3.0)	Yes	Important	Partial	Yes	11
	Pharmaceuticals (3.0)	Yes	Important	Partial	Yes	10
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	11
Clarification	<p><b>Common to all used applications</b></p> <p>Report possible requirements for specific training, use of a protocol, or available guidelines which may reduce the occurrence or severity of the harm?</p> <p>Information on what kind of risk communication is needed for patients, citizens and decision-makers can be included.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Research articles, manufacturers' product data sheets.</p>					
References						
Content relations						
Sequential relations						

B0010 Assessment element card						
Issue: What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?						
Topic: Safety risk management						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	12
	Medical and Surgical Interventions (3.0)	Yes	Critical	None	Yes	12
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	11
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	12
Clarification	<p><b>Common to all used applications</b></p> <p>Describe the data that needs to be collected about the care process, professionals involved, patients and their health outcomes. These include, e.g., clinical indications, specified populations, prescriber information, inpatient or outpatient use, test results, review period, and health outcomes. In case of new technologies, consult EVIDENT database.</p> <p>Describe the general importance of having a registry for monitoring the use of this particular technology and the comparator is also needed. 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? National examples should be provided.</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>Refer to SPC and EPAR.</p> <p>Registries are sometimes connected with the risk sharing scheme that innovative pharmaceuticals require in some countries. Notice also the requirements of pharmacovigilance monitoring.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Sources: Local authorities and legislation, administrative staff, clinical professionals, HTAs, National or local judgement.</p>					
References	<p><b>Common to all used applications</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002 {1}; Kristensen FB et al. 2007 {10}; Draborg E et al. 2005 {35} from the SAF domain</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>Busse R et al. 2002 {1}</p>					

<b>Content relations</b>	<b>Common to all used applications</b>  G0008, G0003
<b>Sequential relations</b>	
<b>Other domains</b>	Also in: Description and technical characteristics of technology

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# Clinical Effectiveness (EFF)

## *Description*

### What is this domain about?

The effectiveness domain in a health technology assessment considers two questions: Can this technology work, and does this technology work in practice? This assessment commonly uses two definitions: {1, 2}

- Efficacy is the extent to which a technology does more good than harm under ideal circumstances (e.g. within the protocol of a randomised controlled trial [RCT]).
- Effectiveness assesses whether a technology does more good than harm when provided under usual circumstances of health care practice (e.g. by a physician in a community hospital treating outpatients) ({1}, (adapted from the International Network of Agencies for Health Technology Assessment [INAHTA] glossary)). The research questions defined within this domain aim at answering these questions, with emphasis on the second question.

Commonly, the focus of the evaluation of clinical effectiveness is to determine the magnitude of health benefits and harms or, in other words, of the net benefit (benefits minus harms) that are caused by a technology. The evaluation also focuses on determining the certainty of the evidence ({3}). As the harms are addressed in the core model in a separate domain (Safety - SAF) this domain focuses on the assessment of the health benefits and the benefit-harm-balance. In order to provide evidence of a causal relationship between intervention and health outcomes, the generally accepted standard is an appropriately designed and conducted randomised controlled trial (RCT), even without a need for a deeper biological theory as to why the intervention works or does not work {4} .

Comparative clinical effectiveness research compares two or more alternative methods for preventing, diagnosing, treating and monitoring a clinical condition, or for improving the delivery of care. The two key elements of the research are that effective interventions should be directly compared and studied in patients who are typical in day-to-day health care settings{5}.

The assessment of health benefits should primarily consider patient-relevant outcomes such as mortality, morbidity, and quality of life.

**Table 1: Topics and issues in this domain**

Topic	Issue	Assessment element ID
Mortality	What is the expected beneficial effect of the technology on mortality?	D0001
Morbidity	How does the technology modify the effectiveness of subsequent interventions?	D0026
Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?	D0005
Morbidity	How does the technology modify the magnitude and frequency of morbidity?	D0032
Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	D0006
Function	What is the effect of the technology on patients' body functions?	D0011
Function	What is the effect of the technology on work ability?	D0014
Function	What is the effect of the technology on return to previous living conditions?	D0015
Function	How does the use of the technology affect activities of daily living?	D0016
Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	D0012
Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	D0013
Quality of life	Does the knowledge of the test result affect the patient's non-health-related quality of life?	D0030
Patient satisfaction	Were patients satisfied with the technology?	D0017

Test-treatment chain	Is there an effective treatment for the condition the test is detecting?	D0024
Test accuracy	What is the accuracy of the test against reference standard?	D1001
Test accuracy	How does the test compare to other optional tests in terms of accuracy measures?	D1002
Test accuracy	What is the reference standard and how likely is it to classify the target condition correctly?	D1003
Test accuracy	What are the requirements for accuracy in the context where the technology will be used?	D1004
Test accuracy	What is the optimal threshold value in this context?	D1005
Test accuracy	Does the test reliably rule in or rule out the target condition?	D1006
Test accuracy	How does test accuracy vary in different settings?	D1007
Test accuracy	What is known about the intra- and inter-observer variation in test interpretation?	D1008
Test accuracy	Is there evidence that the replacing test is more specific or safer than the old one?	D1019
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?	C0006
Change-in-management	Does use of the test lead to improved detection of the condition?	D0020
Change-in-management	How does use of the test change physicians' management decisions?	D0021
Change-in-management	Does the test detect other potential health conditions that can impact the subsequent management decisions?	D0022

Change-in-management	How does the technology modify the need for hospitalisation?	D0010
Benefit-harm balance	What are the overall benefits and harms of the technology in health outcomes?	D0029

## Why is this domain important?

In health policy, most actors primarily require information on the effectiveness and safety of a technology. These can include the insurer, agency or government providing care, as well as users, citizens and consumers. It is generally of no interest to examine other aspects, such as the costs of a technology if the technology is not at all effective. However, if the technology is relatively less effective than other technologies, and is sufficiently inexpensive, the assessment of other aspects may be relevant.

## Relations to other domains

- The Clinical Effectiveness (EFF) domain requires information from the **Health Problem and Current Use of the Technology (CUR)** domain, as well as from the **Safety (SAF)** domain in order to specify the appropriate populations, interventions, comparisons and outcomes for the research questions.
- There is a possibility of overlapping with **SAF**, so co-operation is needed in the protocol phase.
- The **Costs and Economic Evaluation (ECO)** domain requires information from EFF in order to determine the incremental health benefit part of the incremental cost-effectiveness ratio
- Depending on the technology, the **Ethical Analysis (ETH)** domain may be important for setting the framework for effectiveness analysis. For example, how patient-relevant outcomes for which value judgments may be important are defined. {6}
- Effectiveness may sometimes strongly depend on aspects from the **Organisational Aspects (ORG)** domain.
- Effectiveness may also be related to the **Legal Aspects (LEG)** domain, e.g. when there is legal support for a public health programme (mandatory vaccination or mass screening)

## Pharmaceutical-specific content

From a legal viewpoint, following the European transparency guideline (Transparency Directive 89/105/EEC<sup>[1]</sup>), countries have the legal obligation to do an assessment within a certain time period (90/180 days). In these cases, a 'rapid' assessment is preferred in order to meet these strict timelines. Assessments of pharmaceuticals should take their marketing authorisation status into account (e.g. <http://www.ema.europa.eu>), hence the assessment should be performed within the marketing authorisation status of a pharmaceutical. The assessment should usually not evaluate and thus support off-label use.

At the moment specific issues about orphan drugs are not considered in the EFF domain.

[1] The Transparency Directive 89/105/EEC is a harmonised legal instrument to guarantee the transparency of pricing and reimbursement measures. Part of the Transparency Directive is a strict timeframe of 90 days from receipt of application (90 days for pricing and 90 days for reimbursement, this in total 180 days).

## Methodology

### Guidelines for conducting a rapid relative effectiveness assessment

WP5 of Joint Action 1 has developed guidelines on nine specific methodological issues. The recommendations provided in these guidelines should be considered when conducting a rapid REA with the [Model for Rapid REA](#). (In general, these guidelines can also be considered for use for other technologies, but technology-specific characteristics have to be taken into account.) Throughout the model text, specific guidelines are referred to when appropriate.

[WP5 guidelines](#) on methodological issues for the Model for Rapid REA:

- Endpoints used for REA of pharmaceuticals
- Clinical endpoints
- Composite endpoints
- Surrogate endpoints
- Safety
- Health-related quality of life
- Criteria for the choice of the most appropriate comparator(s)
- Direct and indirect comparison
- Internal validity of randomised controlled trials

- Applicability of evidence in the context of a relative effectiveness assessment

WP7 methodological guidelines:

- Internal validity of non-randomised studies (NRS) on interventions
- Meta-analysis of diagnostic test accuracy studies
- Methods of health economic evaluations
- Therapeutic medical devices
- Process of information retrieval for systematic reviews and HTAs on clinical effectiveness
- Personalised medicine and co-dependent technologies (methodological reflection paper)

The first step in performing the evaluation of the clinical effectiveness of a technology is specifying the research question by using the PICO (Population, Intervention; Comparison, Outcome) scheme. The choice of target population, comparisons and outcomes usually has a strong influence on the results on clinical effectiveness. How to do a systematic search of clinical effectiveness, safety and cost-effectiveness is described elsewhere {7}, {8} The clinical effectiveness results are especially sensitive to flaws in the literature search and study selection when the outcomes of interest are quantitatively pooled in a meta-analysis. Results may be substantially biased if relevant studies are not found (e. g. because they are not published or not properly selected).

## Screening-specific content

Starting with the publication of Wilson and Jungner in 1968, different lists of criteria have been developed which state the conditions under which the introduction of a screening programme might be useful. {9} Many of these criteria directly relate to the clinical effectiveness of the screening test, diagnostic workup and treatment, and they stress the links between these factors. Therefore, diagnostic-specific content of the HTA core model is relevant for evaluating screening programmes as well.

As with all health technologies intended for population-based screening programmes, the most important determinants of effectiveness are a reduction in disease-specific mortality and morbidity, and a gain in health-related quality of life. However, screening is a complex intervention with several intermediate steps leading to patient-relevant endpoints.

The overall effectiveness of a screening programme is determined by a combination of several factors:

- Prevalence and incidence of a disease
- Natural history of disease and the proportion of subclinical or reversible cases that would not become clinically relevant (potential for overdiagnosis and overtreatment)
- Participation rate as the number of participants divided by the number of eligible individuals in the target screening population
- Screening interval

- Accuracy of the screening test
- Proportion of subjects with positive screening test results which have a diagnostic follow-up
- Test accuracy of the tests used in the diagnostic follow-up
- Impact of the test results on treatment decisions and quality of life
- Effectiveness of the therapies for the cases identified by screening

The evaluation of a screening technology must comprise the whole chain from the screening test: true and false test results, the possibility of adverse effects incurred by the test, the accuracy and potential for adverse effects of the subsequent confirmatory diagnostics, the losses to follow up before providing the therapeutic intervention, and the effectiveness and adverse events of the therapeutic intervention. {3}

There is limited availability of large randomised controlled trials on a representative asymptomatic population, which compare a group invited to screening with a group not invited to screening, and which include a follow-up leading to the analysis of all patient-relevant outcomes. This is especially challenging when the development of the disease takes a long time, e.g., in the case of cancer. Therefore, indirect evidence from different study types often has to be utilised to make links.

Additionally, a fall in effectiveness will probably occur during the early stages of a new screening programme. This is due to a larger number of cases (both early stage and late stage disease) likely being noticed in the first screening round when compared to later rounds. Thus, it is desirable to analyse the results of several screening intervals in order to estimate the effectiveness of a screening programme.

## ***Where to find information?***

The persons performing the analysis should consult many different sources of information, including published and grey literature, journals and trial registries, contacting experts as well as scanning reference lists of relevant papers.

### **Databases and search strategies**

General medical databases such as

- Medline, Medline in Process,
- Embase

Specialised databases for specific questions such as

- CINAHL,
- PSYCINFO,
- ASSIA, (Applied Social Sciences Index and Abstracts)
- SOCIOLOGICAL ABSTRACTS

- Social Services Abstracts,
- Social Care on line/Caredata and SocINDEX,
- ERIC

Administrative studies: General science publishers' databases such as

- Emerald Library,
- Science Direct and Ebsco Academic Search Elite,
- Pub Med Central (PMC),
- Bio Med Central (BMC),
- ProQuest Health Management

Trial registers such as

- Current Controlled Trials (<http://www.controlled-trials.com/>)
- Clinical Trials (<http://www.clinicaltrials.gov/>),
- WHO International Clinical Trials Registries Platform portal

Databases on specific study designs /publication types:

- DARE,
- NHS EED,
- CDSR,
- Cochrane CENTRAL.
- GIN guidelines

### ***Useful other sources***

- Hand searching of journals and abstract books, and the so-called 'grey literature' can be performed if information is scarce (Dissertational Abstracts, Scirus - Reports of hospital studies and doctoral thesis, OAIster).
- Additional information can be collected also by contacting manufacturers and consulting domestic and foreign experts and agencies (Handbooks).
- Performing an additional SCI-search of the included articles is a valuable complementary approach. Add information about other sources and links specific to clinical effectiveness.
- Other sources: Conference proceedings (Web of Science Database), national and regional guidelines, expert opinions, International, national and regional routinely collected statistics (Health Information Database DRG)

## Diagnostics-specific content

### Sources and search strategies for testing accuracy information

Inadequate and inconsistent reporting of diagnostic accuracy studies and their indexing in medical reference databases make their identification particularly challenging. Unpublished and ongoing studies of diagnostic accuracy would be valuable, but are not as easily detected as trials. Reviewers are likely to retrieve thousands of records in order to scan for potentially relevant studies. Routine use of methodological search terms or search filters is not generally recommended because relevant records may be lost, with no significant reduction in the number of records that need to be read {10, 11}. Over 20% of studies included in diagnostic accuracy reviews were not found in MEDLINE and 6 % were not found through electronic searching {12}. The majority of the studies that were not found in databases were identified by scanning reference lists of included articles.

More information on diagnostic search filters and information on their performance can be found at:

- NICE's Information Specialists' Sub-Group's Search Filter Resource <http://www.york.ac.uk/inst/crd/intertasc/diag.htm>
- Scottish Intercollegiate Guideline Network, search filters <http://www.sign.ac.uk/methodology/filters.html>

## Pharmaceutical-specific content

### Source data/database for assessment should normally include all documents:

- Manufacturer's submission file
- Literature references review
- Available EPARs
  - EPARs for main comparators - original studies (if not published)
- Eventually, HT assessments from other HTA agencies

The database for assessment should be complete and comparable from one HTA agency to another (one of EUnetHTA aims).

## *What kind of information is required?*

### Study types, design, outcome measures

It is to be hoped that one is able to identify a systematic review on the topic of interest which is sufficiently comprehensive, satisfies the requirements on methodological quality, and meets the research questions. If the report is deemed to be transferable to one's own healthcare system and local setting, or to the overall goals of a core HTA information collection, then the process may end at this point. Following the hierarchy of study designs {13}, reviews on efficacy/effectiveness are generally limited to randomised designs. To assess their generalisability to routine clinical practice, it might be relevant to distinguish between efficacy (explanatory) and effectiveness (pragmatic)

RCT. A set of criteria has been suggested to differentiate between these two {14}. In addition, registry data which reflects clinical routine care is helpful in judging whether study populations, interventions and outcomes in RCT are comparable to clinical practice. It may be necessary to broaden the inclusion criteria to incorporate other designs, if data from randomised trials are not available or are insufficient (e.g. because they provide only short-term data or surrogate endpoints).

Key elements of a benefit assessed under routine conditions are that (a) effective interventions should be directly compared, and (b) studies should include patients who are typical in day-to-day health care settings {5}. Benefit compared to placebo should have been proven before or parallel to the direct comparison of active treatments. Although data about the relative benefits under routine conditions are preferred for a relative effectiveness assessment, they are rarely available at the usual timing of a rapid assessment (soon after marketing authorisation or start of usage). Where sufficient good quality head-to-head studies are available, direct comparisons are preferred as the level of evidence is high. Should substantial indirect evidence be available, then it can act to validate the direct evidence. When there is limited head-to-head evidence, or more than two treatments are being considered simultaneously, it may be helpful to use indirect methods (See guideline *Comparator and comparisons - Direct and indirect comparisons*).

The assessment of health benefits should primarily consider clinically meaningful endpoints such as mortality, morbidity, and quality of life (See guideline *Endpoints used in REA of pharmaceuticals – clinical endpoints*). Additional intermediate outcomes such as biochemical or physiological markers, or the proportion of early detected cases, may be useful and necessary in order to understand how interventions work or how they can be used as quality assurance benchmarks for health care programmes. Surrogate endpoints act as substitutes for clinically meaningful endpoints and are expected to predict the effect of a technology (benefit and/or harm). Surrogate endpoints should only be used if they are adequately validated. The level of evidence, the associated uncertainties and the limits of using the evidence should be explicitly stated (See guideline *Endpoints used in REA of pharmaceuticals –surrogate endpoints*).

A number of effect measures are in use for describing the treatment's effect. For binary data, it is common to use 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). In order to allow for a comparison across studies these are often converted into 'number needed to treat' (NNT) or 'events per thousand patients'. Since both relative and absolute effect measures carry important complementary information, recent approaches such as the GRADE profiler {[www.gradeworkinggroup.org](http://www.gradeworkinggroup.org)} encourage a presentation of both measures.

Continuous data is often more difficult to summarise. Commonly used effect measures that allow the summary of treatment effects are 'standardised mean difference' or 'weighted mean difference'. Unfortunately, both measures are difficult to interpret in a clinical context. A more recent statistic, the ratio of means, reports the percentage reduction for continuous data such as proteinuria. The ratio of means allows a meaningful interpretation for clinicians {15} For more details about effect measures and their calculations, refer to the comprehensive, user-friendly description of common measures in the Cochrane handbook.

If there are different outcome measures for benefits and harms, it may be difficult to calculate the net benefit quantitatively. For example, in prostate cancer screening, the benefit might be a reduction in disease-specific mortality; on the other hand, both biopsy and surgery may cause sexual dysfunction and incontinence. Therefore, summary measures like the quality-adjusted life year (QALY) or disability-adjusted life years (DALY), or other multi-criteria models where health states are weighted according to their desirability, could be used to create a common measure {16}.

This is a typical example of a situation in which clinical trials should be complemented by decision-analytic modelling to aid decision-making under uncertainty. {17}

## **Extrapolation of efficacy into effectiveness data**

It may be necessary to extrapolate ‘efficacy’ data to information about ‘effectiveness’. This can include (Australian Government Department of Health and Ageing 2008):

- Considering the **applicability** of the trial results to the intended population for treatment (see *Applicability of evidence in the context of a relative effectiveness assessment*);
- **Extrapolation** of the available data to the intended duration of therapy or the time horizon in which expected health and resource impacts will occur (e.g. lifetime for many chronic diseases) in case these data are not present;

## **Transformation of surrogate outcomes into patient-relevant final outcomes of a technology**

This can be done through modelling. The following issues need to be addressed when dealing with models (the list is by no means exhaustive): For further details see also ECO domain’

1. Model should represent appropriate disease processes and should address the decision problem adequately
2. Transparency and clear description of the evidence and the assumptions used in the model
3. Systematic search for evidence to be included in the model
4. Transparent description of the methods used for inferring unobserved model data
5. Transparent description of model calibration and validation
6. Transparent description of methods used to analyse model parameter uncertainty and robustness (i.e. sensitivity analyses should be performed for examining the assumptions used for extrapolation)

For further guidance on modelling studies see ‘ISPOR-SMDM Modeling Good Research Practice’ series {18-24}

## **Diagnostic-specific content**

New diagnostic technologies frequently enter into clinical practice without evidence of improved patient outcomes. Randomised trials of test-and-treatment strategies are not routinely performed, and they are not required for marketing approval. Accuracy studies are far more frequent, but relying only on accuracy information when deciding whether to adopt a new diagnostic test is usually insufficient {25}.

## Study types for the assessment of the effectiveness of diagnostic tests

Randomised controlled trials (RCTs) are the ideal study design for providing **direct evidence** of the effectiveness of a diagnostic technology. However, these studies are rarely available. Furthermore, they are not always feasible or even necessary in determining the effectiveness of the technology. When direct trial evidence is not available, there are other study types relevant to the assessment of effectiveness and that provide evidence about test safety, accuracy, impact on management and the effectiveness of the treatment. Evidence from these studies can be linked so as to yield an estimate of the diagnostic technology's effectiveness (**linked evidence**). When linking evidence across studies, it is essential to assess whether the patient spectrum in the studies is similar (Does the test detect the same disease for which the treatment is effective?).

### Direct trial evidence

The diagnostic RCT is the most reliable study design. The point at which patients in the test-treatment chain are randomised can vary depending on the study question or other constraints. The most simple design randomises subjects who receive either the new test (strategy) or the routine test (strategy) {26}. RCTs measure the difference in health outcomes when patients from the same source population are allocated to different diagnostic pathways. The only difference between groups arises from the selection of the diagnostic pathway and subsequent treatment decisions. Other comparative study designs like cohort and case-control studies have greater potential for bias.

### Linked evidence

When direct trial evidence on test effectiveness is not available, other study types evaluating one or more outcomes in the diagnostic pathway need to be considered.

Study type	Optimal study design
Safety research	All study designs including case series, surveillance registers
Diagnostic accuracy research	Cohort studies of diagnostic accuracy
Change-in-patient-management studies	Diagnostic before-after studies and time series
Treatment effectiveness studies	Treatment RCTs

Evidence of accuracy can be used to infer effectiveness of the technology in cases where the spectrum of patients, disease, technologies and other conditions are similar enough in studies of diagnostic accuracy and treatment effectiveness. The transferability must be reasonably justified. Sometimes evidence from accuracy studies alone is sufficient to infer effectiveness of the technology. This happens when the technology is a cheaper, safer or more accurate replacement for an existing diagnostic strategy.

Change-in-management, therapeutic-impact, or diagnostic before-after-studies measure how often treatment is started, stopped or modified – before and after the incorporation of the new diagnostic technology in the management pathway. This is also compared to the management pathway without the new diagnostic technology {27}. Physicians participating in change-in-management studies are provided with test results from a new diagnostic technology, and the researchers then compare their pre-test management plan to the post-test management plan. The study type is usually applied to add-on type technologies.

In replacement-type new technologies, we usually assume that the behavioural pattern from test result to management decisions remains unchanged. Especially if there is a well-established standard treatment for the condition detected. In other cases, change-in-management studies may be required to demonstrate that the test results are sufficient to alter the clinician's threshold for changing management {28}.

Change-in-management studies are required if there are other factors than the test result influencing the treatment decision, e.g. individual patient characteristics or patient preference. They are also valuable when the impact of test information is uncertain, in such cases, e.g., when the test is used to distinguish between multiple differential diagnoses, or when accuracy studies are conducted on patients with prevalence or severity of disease different than the intended patient population or usual practice.

When there is a trade-off between benefits and harms, e.g., when a new test is safer and less invasive, but also less specific, it needs to be assessed against the possible harms of additional false-positive results. In this case, decision analytic modelling can be used. Decision analysis also allows comparing, on one hand, effectiveness of the test in populations with a different prevalence of the disease and, on the other hand, the effectiveness of multiple test-and-treat strategies, utilising existing tests in clinical practice; in which case it is unfeasible to directly compare all clinical trial strategies. In fast developing fields, completed clinical trials may not be applicable to current practice standards. Modelling can help assess the trade-offs of a newer test and could also consider potential shifts in the disease spectrum. Modelling can explicitly account for uncertainty in key parameters and assumptions {29}. Decision analysis is an appropriate method for linking evidence on test accuracy with the evidence on treatment effect, if patient-relevant long-term outcomes cannot be extracted from trials. The uncertainty of model results due to parameter uncertainty and model assumptions can be transparently evaluated and reported in sensitivity analyses. However, high-quality evidence on patient-relevant long term benefits and harms should be assessed in randomised trials. When trials are conducted, those trials which investigate the effect treatment has on patients who have positive results on the new test, as well as negative results on the old test, may be more efficient and more clinically relevant than trials conducted on all patients who are new-test-positive {30}.

### **Study types for test accuracy studies**

A systematic review and critical appraisal of existing research literature and other data is the basic method of finding answers to research questions on diagnostic accuracy. Regarding some issues, e.g., when asking ‘What are the requirements for accuracy in the specific context?’ or ‘What is the optimal threshold value?’, published research findings may need to be complemented with expert interviews or own reasoning.

The design of a basic diagnostic accuracy study is the following: A group of patients with the suspected target disease undergoes the test (strategy) under consideration (index test), and the best possible test (strategy), to verify the diagnosis (reference standard, gold standard). Positive and

negative results from both tests are shown in a 2x2 table, or in a variation thereof, depending on the number of chosen cut-off points.

If there is no appropriate reference test, it is possible to construct a reference diagnosis by using a predefined rule for a set of other tests, a consensus among experts, or a statistical model based on actual data {31}. Another possibility is to investigate the probability of disease presence with multivariable modelling as a function of all diagnostic variables simultaneously {32}. Problems may arise, for example, from the patient spectrum (patient characteristics, patient selection and setting), the non-optimal reference standard, incorporation bias (the index test is part of the reference standard), partial verification (not all patients receive the reference test) or differential verification (patients receive different reference tests).

If a new technology can **replace** an existing one, the accuracy of the new test (index test) and the routine test (comparator test) has to be compared in comparable groups or preferably among the same patients {33}. This can be done indirectly, by looking at studies where test A has been compared with a reference standard, and then looking at other studies where test B has been compared with the same reference standard. It is preferable to look at studies that do the index test, the comparator test and the reference test on all patients (paired study). If not all patients had verification with the reference standard test, then it is not possible to calculate the sensitivity and specificity of the two technologies. However, relative true and false positive rates can still be estimated, which allows the accuracy of the two tests to be compared against a common reference standard.

Another option is a randomised controlled trial where patients are randomly allocated to receive either the new or the existing test, after which all patients undergo the reference standard testing. Randomised trials are preferred if the new test is too invasive to be done on all patients, or if the tests interfere with each other {34}. For further options see {26}.

In **triage**, the new technology is used before the existing technology, and only the patient with a particular result of the test continues the diagnostic pathway. Triage technologies may be less accurate than existing ones and are therefore not meant as a replacement. Instead, they are simpler or cheaper. If the triage technology can reliably rule out the target condition, it can safely reduce the number of patients who need to be sent further to invasive, cumbersome or expensive testing.

Several designs can be used for comparing the accuracy of the triage pathway to the existing pathway. In a paired study design, all patient undergo the triage technology, the existing technology and the reference standard. Limited verification can be used here as well, but is a source of bias.

An **add-on** technology is positioned after the existing diagnostic technology. This happens when the new technology is more accurate, but too expensive, invasive or poorly available to be used for every patient. The use of the new diagnostic technology may then be reserved only for those patients in whom the existing technologies failed to identify the disease. Add-on technology can increase the sensitivity of the existing diagnostic pathway, usually at the expense of specificity. Conversely, add-on technology may be used to limit the number of false positives (increase specificity) after the existing pathway.

Fully paired or randomised methods are preferred, but not always needed, in researching add-on tests. Rather, limited designs can be more efficient. Namely, limiting the study to patients who test negative after the existing diagnostic pathway, with verification by reference standard only those who test positive on new technology, still allows us to calculate the number of extra true positives and false positives resulting from the new add-on technology {34}.

In screening processes, subjects are typically first tested with a triage technology, then with a more accurate test, and sometimes finally with an add-on technology. The various stages need to be evaluated both separately and as an entity.

### Outcome measures for test accuracy studies

Diagnostic test results are often reported as a numeric quantity on a continuous scale, which is then divided by a threshold value above which the test is positive and below which it is negative. Results may then be summarised in a 2x2 table to reflect the agreement between the ‘true’ disease state and the test result. Sensitivity, specificity and positive and negative predictive values are derived from these 2x2 tables. For further details, see Chapter 2 *Systematic Reviews on Clinical Tests* in {8}.

	Diseased	No disease
Test positive	TP	FP
Test negative	FN	TN

**Figure 1. 2x2 table**

The cells in the table state the number of true-positive, false-positive, true-negative and false-negative results. Changing the threshold in turn changes these figures, and thus the sensitivities and specificities as well as other summary measures calculated from the numbers in the 2x2 table.

### Screening-specific content

The most reliable evidence on whether screening does more good than harm is provided by well-conducted long-term RCTs with a study population representative of those eligible for, and invited to, or informed of, the screening programme. The control group would consist of those who are not informed of the screening programme. Otherwise, the probability of a cross-over of the control group to screening group would increase, and this could result in an underestimation of the screening effect.

Additionally, a fall in effectiveness will probably occur during the early stages of a new screening programme. This is due to a larger number of cases (both early stage and late stage disease) likely being noticed in the first screening round when compared to later rounds. Thus, it is desirable to analyse the results of several screening intervals in order to estimate the effectiveness of a screening programme.

Time trend studies which analyse changes in disease frequency (such as incidence, the distribution of different severity of disease stages and death) can be valuable. However, there are many sources

of bias, such as changes in ascertainment and diagnostic practice, or other influences on outcomes, such as advances in treatment or reduction in co-morbidities.

Case-control studies can be useful for comparing different screening policies, but they cannot give a reliable estimate of the difference between screening and lack of screening because their confounding factors cannot be controlled {35}.

HTA doers often need to evaluate the evidence regarding the test characteristics like diagnostic accuracy – either as additional information, or because better evidence is lacking. Methodological guidance related to diagnostic accuracy studies can be found under diagnostics-specific contents.

Modelling studies are especially useful when comparing many different screening options that vary with regard to test combinations, screening intervals and treatment options which incorporate alternative eligible populations. On the other hand, clinical trials can compare only a limited number of screening options over a short time horizon. When high-quality primary data is available, decision-analytic modelling can synthesise information from a wide range of sources, and can extrapolate from surrogate outcomes of trials (e.g. test sensitivity) to patient-relevant outcomes of the research question (e.g. reduction in cancer incidence). Sensitivity analysis can help to show areas in which further research is likely to be most useful {29, 36}

Beside the benefits of screening, it is also important to consider the harms caused by overdiagnosis and overtreatment stemming from screening programs. ‘Overdiagnosis occurs when people without symptoms are diagnosed with a disease that ultimately will not cause them to experience symptoms or early death.’ {37}

## **Pharmaceutical-specific content**

In the assessment of pharmaceuticals, randomised clinical trials (RCTs) are usually possible and practically feasible. Therefore, as a general rule, undertaking of RCTs should be considered for assessing health benefits of pharmaceuticals. Non-randomised intervention studies or observational studies can be considered in cases where an RCT is not feasible, or where complementary data is presented to RCTs.

If all of the studies concerning a technology have been performed under strict clinical trial conditions, no information on the benefit of the technology under routine conditions will be available –this is often the case just after marketing authorisation. Generally, information on benefits under routine conditions may be collected in trials utilising a pragmatic approach (a trial setting that corresponds to usual circumstances of healthcare instead of a strict protocol-driven setting that is used in trials of an explanatory nature), or in observational studies.

The results of pragmatic trials and country-specific observational studies are usually affected by local clinical practices. Consequently, the transferability and generalisability of the results may suffer and should be considered carefully. For more details see section 2.1 of the WP5 guideline *Applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals*.

For diseases that would be fatal within a short period of time without intervention, for example, several consistent case reports may provide sufficient certainty of results that a particular intervention prevents this otherwise inevitable course (‘dramatic effect’).“Other specific issues are early termination of clinical trials and treatment switching

## Tools for critical appraisals

The effect of a technology in studies on clinical effectiveness should be estimated with little error. Errors are classified traditionally as either systematic or random. Systematic errors or biases describe the opposite of validity, while the opposite of random error is precision. Unbiased estimates are considered valid. The validity of a study is composed by its internal validity (inferences related to the study population) and external validity or generalisability (inferences related to the target population outside the study).{38}

Sources of bias in a systematic review on clinical effectiveness can arise on three different levels:

- The whole base of evidence, through publication and reporting bias (see below: *Analysing and synthesising evidence. Biases, confounding factors, level of evidence.*)
- On individual study level
- For individual endpoints in a study

Sources of bias in studies which were designed to evaluate the effectiveness of a technology can be related to, e.g., differences in patients assigned to intervention and control groups; including differences in the selection process (selection bias); unbalanced provision of care (performance bias); the methods of measuring or interpreting the outcomes (detection bias); or imbalances in patient drop-out (attrition bias {39, 40}). Bias may also result from a manufacturer's involvement in a study. It is important to determine if any trials had been funded through industry sponsorship. It is advisable to compare the results with and without sponsored trials included in the analysis.

A thorough assessment of the methodological quality of the included studies is crucial to any systematic review. Tools for critical appraisal can comprise different quality aspects of studies or publications. The 'risk of bias' tool provided by the Cochrane Collaboration examines internal validity (risk of bias) of studies and endpoints, whereas other checklists combine questions for additionally assessing precision and external validity (see *Cochrane Handbook* Chapter 8 {7}). Good reporting of studies is a prerequisite for the assessment of validity. Therefore, guidelines for reporting have been developed for different study types to improve the reporting quality of studies. They can be found at [www.equator-network.org](http://www.equator-network.org).

It is recommended to have two assessors. The assessors' background should be reported, as should the way in which they resolved disagreements. Results of the quality assessment of the original studies should be presented in a table, or otherwise graphically. Individual quality items should be investigated as a potential source of heterogeneity.

## ***Trials***

The minimum items that need to be looked at when assessing the potential for bias of individual studies in randomised controlled trials are as follows: concealed treatment allocation; blinding of health care provider, patient and outcome assessor to the allocated intervention (experimental or control); a sufficient rate of follow-up and intention-to-treat analysis. Depending on the research question, however, it might be warranted to look at additional features where bias could enter the study design, or where the results might become distorted. The body of checklists for assessing the methodological quality of randomised controlled trials is considerable; most of them (e.g.{41}) are variations of the structure suggested in the *User's Guides to the Medical Literature*{42},

the *CONSORT Statement* {43-46} or the criteria suggested in the *Cochrane Handbook*. See also WP5 guidelines for the Model for Rapid REA on internal validity of randomised controlled trials.

## ***Observational studies***

Agreement on methodological criteria for non-randomised trials and observational studies is considerably less well-developed. However, a methodological HTA report by John Deeks provides a good overview of available instruments for assessing non-randomised intervention studies {47}{48-50} Equator web site). More recently, the Cochrane collaboration developed a risk of bias tool for non-randomised intervention studies ACROBAT-

NRSI (<https://sites.google.com/site/riskofbiastool/>) and ISPOR Task Forces have also been creating checklists on the relevance and credibility of observational studies, which can be found at the ISPOR homepage ([www.ispor.org](http://www.ispor.org)).

## ***Modelling studies***

The validity of modelling studies results are highly dependent on the model structure, the model assumptions, the quality of the data used as model parameter inputs, the model calibration and/or the model validation. There are several publications with recommendations for good modelling and reporting practice available {36, 51-53}. The most recent effort has been done by the ISPOR-SMDM modelling good research practices task force. {18-24}A new checklist for modelling studies is under development and can be found at the ISPOR homepage ([www.ispor.org](http://www.ispor.org)).

## ***Systematic reviews and meta-analyses***

The AMSTAR (“A Measurement Tool to Assess Systematic Reviews”, [http://amstar.ca/About\\_Amstar.php](http://amstar.ca/About_Amstar.php)) is a validated appraisal tool for the evaluation of the methodological quality of systematic reviews. The PRISMA extension for network meta-analyses (<http://annals.org/article.aspx?articleid=2299856>) or the ISPOR taskforce tool (<https://www.ispor.org/indirect-treatment-study-use-guideline.pdf>) can be used to check the quality of network meta-analyses.

## ***Diagnostics-specific content***

### **Quality assessment of the effectiveness of diagnostic tests**

#### **Direct trial evidence**

A diagnostic technology may appear to be effective because of a careless or incomplete pre-test work-up. This occurs when the technology becomes an alternative to careful examination of patient history, physical examination, and a set of less invasive or less expensive procedures. Therefore, it is worthwhile to carefully consider the pre-test examination scheme in the studies.

## Linked evidence

The strengths and limitations of study types other than RCT need to be considered. There are quality checklists available for studies of effectiveness in MSAC{28}.

Change-in-patient-management studies can be appraised using the same criteria as case series (see list of criteria MSAC, page 70){28}. Potential bias is common and it is related to the selection of patients, the objective execution of the diagnostic test, and the measurement of results in all eligible patients. One of the limitations of these studies is that stated plans in the study setting may differ from real life situations where the technology is not available. Physicians' subconscious bias may also occur. Change of management is only relevant when it results in a benefit in patient relevant outcomes. Otherwise, it can be held only as a surrogate endpoint.

## Quality assessment of test accuracy studies

Quality assessment of diagnostic accuracy studies is not as straightforward as assessing interventions. It is hampered by poor quality of reporting and by the fact that, so far, there has been less methodological and empirical evidence on the importance of the different potential sources of bias than for treatment studies. There are many different tools to assess the quality of diagnostic accuracy studies. The *Cochrane Handbook* recommends the QUADAS-2 tool.

## Screening-specific content

There are three main sources of bias which are specific to the evaluation of screening:

- People who take part in screening are usually healthier than those who do not (healthy screener bias.)
- Less aggressive cases of disease have a longer asymptomatic period, and are therefore more likely to be detected by screening. Consequently, patients detected by a screening programme tend to have a better prognosis even without therapy (length-time bias).
- Survival falsely appears to be longer after diagnosis via screening – not because the patients actually live longer, but because the diagnosis had been known earlier, i.e. for a longer period of time (lead-time bias) {35, 54}. The bias occurs, e.g., when two tests are compared, one test diagnoses the disease earlier, but there is no effect on the outcome of the disease. (It may then appear that the test prolonged survival, when in fact it only resulted in earlier diagnosis.)
- If a high proportion of participants in the control group (no screening) cross over to screening, the effects of screening will be underestimated.
- Screening may identify abnormalities that will, in fact, never progress, as causing symptoms or death during a patient's lifetime (e.g. autopsy studies have shown that a high proportion of elderly men who have died of other causes have been found to have had prostate cancer). Apart from causing issues of unnecessary treatment and risk of harms, overdiagnosis also has the effect of inflating survival statistics by contributing disproportionately to early diagnosis of lethal conditions. {55, 56}. Survival rates (e.g. 5-year survival) are calculated as the proportion of patients that are alive after a fixed period (e.g. 5 years) following diagnosis. Overdiagnosis inflates both the numerator and denominator of the survival statistic.

## **Analysing and synthesising evidence**

Ideally, systematic reviews on randomised controlled trials (RCTs) are the basis of knowledge about an intervention's effectiveness. The principles on conducting a systematic review are nowadays widely agreed upon, and most of the methodologies published by different organisations vary only in details.

### ***Biases, confounding factors, level of evidence***

A major problem in assessing health technologies is reporting bias. Effect estimation of the benefit of a technology can be heavily biased by not publishing all studies and by selective outcomes reporting. A systematic review showed reporting bias to be a widespread phenomenon {57} which has to be considered in quantitative (see below *Meta-analysis*) and narrative analysis of the evidence. For detailed literature on reporting bias, see also {58}, {59-76}

Having reviewed the methodological quality of individual studies, researchers attempt to capture the overall quality of the body of evidence. The concept provided by the GRADE Working Group captures the currently most comprehensive approach to this {13, 77}. Besides looking at the quality of individual studies, they also include the consistency or heterogeneity of the results of all included studies, as well as the directness of the comparisons (i.e. how directly does the identified literature address the questions of the HTA-report - regarding the population, the intervention and comparators, and the selected endpoints. Furthermore, they comment on any imprecisions found in the available data (number of total events and width of the confidence interval) and provide an estimate about the likelihood of reporting bias. Deficiencies in any of these considerations can lower the methodological quality of the entire body of evidence. On the other hand, in the presence of strong and plausible associations between intervention and outcome or an obvious dose-response gradient, it is possible to improve the quality of the overall judgment about the methodological quality of the evidence.

### ***Qualitative syntheses and evidence tables***

A meaningful presentation of the study results is essential for an informative and transparent HTA report. Moreover, a high degree of reliability and transparency is required for the transfer of HTA reports from one setting to another. The best guarantee for transparency and reliability are thus comprehensive and informative evidence tables about the methodology and content of individual studies. The tables should support judgments of the included studies' similarities and differences, and should provide the basis for conclusions in the review.

The majority of HTA organisations produce tabulated evidence summaries that follow the PICO structure (ideally, with an additional cell for comments on issues not captured by the PICO cells but which could have an impact on the results). Although the items reported in each cell will always be driven by the review questions, they should follow some core considerations {78}. A description of the data extraction process, including the number of reviewers involved, assures objectivity and reliability of the results.

## ***Meta-analysis***

Studies on the same topic can report their findings in very different ways, which hinders meaningful comparisons across studies and a fair and appropriate interpretation of the body of evidence. Reviewers are encouraged to convert (re-calculate) the results to a joint effect measure and attempt a meta-analysis when the data allows for a summary of the results. However, sufficient clinical homogeneity of the studies is a prerequisite for a meta-analysis.

Although the nature of the data can prevent pooling for a summary estimate, and result in researchers only being able to provide a descriptive summary of the data, it can nevertheless be very helpful to display the results in a forest plot, but omit the summary estimate.

Presenting a measure of precision for the treatment effect estimate (confidence interval) is necessary for the interpretation of data and must not be omitted. Researchers need to report if the primary studies lack this essential information.

When there is limited head-to-head evidence, or when more than two treatments are being considered simultaneously, the use of indirect meta-analytic methods may be helpful. For more information see the WP5 guideline *Comparator and comparisons – Direct and indirect comparisons*. Further exploration of the data: Homogeneity and heterogeneity, sensitivity analysis and publication bias

Reviewers need to provide statements about clinical homogeneity or heterogeneity of the studies and about the studies' results. While homo-/ heterogeneity in clinical data is often a matter of judgment, there are statistical tests available to help assess the presence of statistical heterogeneity {79} which, if found, should then be further explored and considered in the discussion. Pre-specified sensitivity analyses based on clinical or methodological issues allow further exploration of data stability. Researchers should always consider publication and reporting bias, and explore these either graphically, using a funnel plot (provided the number of included studies is large enough), or make a plausible judgment about the likelihood of these biases. If there is information about the existence of unpublished trials, e.g., from clinical trial registries, there is a statistical tool available to perform sensitivity analyses. The statistical programme SAMURAI uses information from trial registries and can help judge whether unpublished studies can heavily bias effect estimation. (SAMURAI version 1.2.1 <http://cran.r-project.org/web/packages/SAMURAI/index.html>)

## ***Diagnostics-specific content***

### **Pooling and meta-analysing test accuracy studies**

#### **A) No heterogeneity present**

A forest plot of sensitivity versus specificity with 95% confidence intervals can be used whenever the results from two or more comparable studies are included in the review. The forest plot illustrates the range of results, enables the reader to assess heterogeneity, possible trade-offs between sensitivity and specificity, and may show a summary estimate where pooling is appropriate.

Another option is to plot pairs of sensitivity and 1-specificity from original studies on a ROC plane. If sensitivity or specificity is constant, or if there is linear relationship between them, it is adequate to use simple summary measures for sensitivity, specificity or likelihood.

When pooling pairs of sensitivity and specificity, the choice of statistical model depends on the selected studies. A fixed effect model, for example, assumes the studies to represent a random sample of one large common study. The differences between study outcomes are considered to be the result of random error. The model weighs individual studies based on the inverse variance of accuracy or number of participants. The random effects model, on the other hand, assumes the differences between studies to be due to real differences between the study populations and procedures. A more complex mathematical model is used to weight studies. Separate estimates of mean sensitivity and specificity underestimate test accuracy.

### **B) Heterogeneity present**

When forest plot or heterogeneity testing shows that there is significant heterogeneity in sensitivities and specificities across studies, it is not appropriate to report pooled values of sensitivity and specificity as a summary estimate. Instead, further analysis of the detected heterogeneity is needed, and it starts with examining of threshold effect. The threshold effect can be seen in a forest plot if there is an inverse relationship between sensitivity and specificity. If this is not apparent, the results should be plotted to a ROC plane in order to examine the data further.

### **C) Threshold effect only**

If there is symmetry in the SROC curve, DOR is constant regardless of the diagnostic threshold, and any variability in the paired sensitivity and specificity between different studies is due to differences in the test threshold. In this case, SROC curve represents the most informative synthesis of evidence about test accuracy and the pooled DOR is a useful single summary measure.

SROC curve does not provide one summary estimate of sensitivity and specificity, but it does allow assessment of their interdependence. Summary of the test's DOR (SDOR) and a comparator test can be presented with 95% CIs in order to compare differences in diagnostic performance. The area under SROC curve and its 95% confidence interval provide a global summary of the test's overall accuracy. The point on the curve where sensitivity equals specificity, the  $Q^*$  statistics, can also be used as a summary measure of the test's accuracy. These summary measures can also be used to compare the accuracy of two test strategies. Possible software which can be used for diagnostic meta-analysis includes Meta-Test, Meta-Disc, Stata and SAS.

### **D) Heterogeneity that is more than just threshold effect**

If the slope  $b$  (the estimated regression coefficient) in the SROC model is statistically significant, the SROC will be asymmetrical and the DOR will change along the threshold. In such cases, advanced methods for fitting the SROC are used. Advanced methods for pooling are indicated when heterogeneity in the results can be attributed to known sources of variation (see chapter above, *Assessing heterogeneity*). Otherwise, the interpretation of the summary estimate is not possible [\[80\]](#).

Advanced models enable incorporation of covariates, e.g. population subgroup, in the meta-regression analysis. However, poor reporting of primary studies may lead to biased estimates. The two main advanced statistical models are hierarchical SROC and bivariate meta-regression, which are mathematically identical (Harbord 2007). Syntax to run these models in SAS, STATA, WINBUGS, S-PLUS and R is or will be available. Hierarchical SROC (HSROC) produces

informative summary measures with confidence ellipses {81}, but this model is infrequently used, probably due to its complex fitting.

## **The problem of imperfect reference standard in test accuracy studies**

If there is an acceptable reference standard test but, for various reasons, not all patients in the study received it, the researchers either impute or adjust for the missing data {31}. The authors of the HTA analysis should, however, be careful with the results in cases where the fraction of patients verified with the reference standard is small, or if the patterns of replacing the missing values are not determined in the study.

The reference standard is sometimes known to be imperfect, i.e., it does not distinguish the diseased from healthy entirely correctly – then it is possible that the researchers have adjusted the estimates of accuracy of the index test. {31} These correction methods can be useful if there is evidence from previous studies about the extent of imperfection in the reference standard, and about the correlation of the errors between the index test and the reference standard. Another way to deal with the problem of an imperfect reference standard is conducting a sensitivity analysis to demonstrate the effect of imperfect reference test to the accuracy of the index test.

## **Assessing heterogeneity across accuracy studies**

Heterogeneity in test accuracy across studies is very common. Any differences found in studies that address the same research question should be clearly identified and interpreted in the diagnostic core HTA. Simple methods of pooling sensitivities and specificities are contraindicated if heterogeneity exists.

Sources of heterogeneity can be:

1. Chance
2. Different test threshold
3. Different study design or method; bias; different reference standard; different versions of the technology
4. Variation by clinical subgroups in terms of age, severity or stage of disease, prevalence of the target condition, differential diagnoses, and setting
5. Unexplained heterogeneity

If differences in the results cannot be attributed to these known sources of heterogeneity, then pooling of results to one summary estimate should not be attempted, because its interpretation will be impossible {80}.

Heterogeneity can be tested using the following methods {28}:

1. Plot the sensitivity and specificity from each study with their 95% confidence interval in a table, and/or forest plot to illustrate the range of estimates and identify outliers.
2. If sufficient data is available, plot the paired sensitivity and 1-specificity results for each study on the ROC plane to detect heterogeneity and to identify outliers. A small number of studies will limit the power of regression in detecting heterogeneity.
3. Use a chi-square test for heterogeneity (Cochran's Q test) or Fischer's exact test for small studies to test the hypothesis that there is no statistically significant difference in the sensitivity and specificity reported.

## Assessing threshold effect in test accuracy studies

Paired estimates of sensitivity and 1-specificity in original studies are plotted in a ROC plane and a regression model is then used to fit the SROC curve {82}. If the SROC curve is symmetrical around the line where sensitivity equals specificity, the studies share one common DOR, and any variability is due to differences in the test threshold. In statistical terms, if the slope  $b$  (estimated regression coefficient) is not statistically significant and approaches zero in the model, The SROC will be symmetrical.

The **accuracy of the screening/ diagnostic test** can be highly dependent on the competence (qualifications, training and experience) of the staff/personnel who are using the device and analysing the test results

## Screening-specific content

For diagnostic and treatment interventions in patients already showing symptoms or already ill, there is a trade-off between benefits and harms of diagnostics and treatment on the individual level. As screening is usually done on asymptomatic people, there is an additional trade-off on the population level between, on one hand, healthy people, who will not benefit from screening but can be harmed by false positive screening results causing a loss in quality of life, or by potential overdiagnosis and over-treatment, and, on the other hand, people who will benefit by an early detection of the disease. Decision-analytical modelling is an explicit and quantitative method which can be used to analyse these trade-offs.

## Reporting and interpreting

Besides the benefits, it is also important to consider the harms of an intervention (e.g. side effects or adverse effects of a treatment, unnecessary treatment due to overdiagnosis, overtreatment caused by screening programs, etc.). Therefore, systematic evidence assessments in the EFF domain should include both (1) evidence assessment of patient-relevant outcomes regarding benefits and harms and (2) a judgment on the benefit-harm balance. Currently, different approaches are used for addressing the benefit-harm balance. The GRADE methodology uses the evidence on benefits and harms of those outcomes identified as critical in order to judge the benefit-harm balance in an expert consensus. {17}

Balancing benefits and harms contains explicit or implicit value judgments. These should be stated transparently.

The following steps are required:

- **Step 1:** Rate the level of the body of evidence as being of high/moderate/low quality (e.g. the GRADE methodology may be used), and clarify the reasons for up-/down-rating (e.g. in footnotes).
  - Another option is a clear distinction between the risk of bias (internal validity) and the aspects of generalisability (i.e. directness, external validity). If all trials concerning a technology have been performed under ideal conditions, the analysis will have to make assumptions about the magnitude of effectiveness based on the available efficacy data. The challenge is then to examine the reasons why the technology works or does not work in specific circumstances.
  - For assessing the risk of bias, 2 categories (low and high) are usually used (according to the Cochrane methodology).
- **Step 2:** Interpreting the clinical relevance of the findings:
  - Statistical significance is an important criterion which quantifies random error—numerically small differences can be statistically significant, but clinically meaningless. One should consider the magnitude (i.e. relevance) of the intervention's effect (independent of its statistical significance) and compare with the minimal clinically important effect size. One approach is to compare the lower 95% confidence interval of an estimated treatment effect with a 'maximal clinically unimportant effect size'. Nevertheless, the limits of hypothesis testing, choosing an arbitrary threshold of 0.05 for decisions should also be kept into mind. Depending on the consequences of the decision threshold values (alpha-levels) other than 0.05 might be chosen.
  - Consider the relevance of outcomes for clinical decision-making (distinguishing between a critical and an important outcome as done when formulating the question)
  - Identify knowledge gaps by comparing the research questions (including the predefined outcome) with the available evidence.

Results of other analyses of the same problem should also be presented and used as a background for discussing the obtained results, addressing possible differences.

### **Insufficient evidence**

If the current body of evidence (a systematic review or a meta-analysis of randomised trials, or a technology assessment report) does not provide sufficiently adequate information on the effectiveness of a technology, new primary research may be warranted in the form of register research, modelling, performing randomised controlled trials or analysing routine data bases. As primary research is often beyond the scope of HTA organisations, the lack of evidence of effectiveness should at least be stated in the discussion.

Issues described in the assessment elements may be answered through primary research if so needed. Detailed descriptions of clinical trials are beyond the scope of this document; whenever possible, however, clinical trials must be randomised, and head-to-head comparisons against the

gold standard therapy should be made. The primary endpoint should be a clinically relevant variable or, if this is not possible, a validated surrogate variable for a clinically relevant variable.

### **Relative effectiveness**

In order to assess relative effectiveness, according to the definition of the Pharmaceutical Forum, a synthesis of both effectiveness and safety data has to be conducted. The adverse effects of the intervention(s) in comparison with the comparator(s) should be presented. These data is presented in the synthesis document.

A further challenge is to define the place the new intervention should have in any existing treatment pathway. Input from clinical experts might be of value here.

It is possible to make only a preliminary interpretation of the results based on effectiveness data only. A global and balanced interpretation of the benefits and harms of a technology also requires the results of other relevant domains. Evidence about benefits and harms can be combined using e.g. decision analytic methods {29}.

## ***Analysing applicability of evidence***

As RCTs are typically conducted in specific optimised settings, it is relevant to consider the applicability of results onto the population intended for treatment (AGDH, 2008). For further details see the guideline *Applicability of evidence in the context of a relative effectiveness assessment*. Moreover, if the studies have used surrogate outcomes, transforming them into patient-relevant final outcomes of treatment could be considered a way of evaluating the applicability of evidence (AGDH, 2008). For details about when and how surrogate endpoints can be used see the WP5 guideline *Endpoints used in REA of pharmaceuticals – surrogate endpoints*.

To allow for transfer of data across countries, HTAs need to be sufficiently transparent and must distinguish between evidence ('facts') and judgments (including values and preferences). Value judgments and preferences (of individuals or of health care systems) have to be labelled as such, as should the anticipated influence of transferring the result from one health care system to another. There will be situations wherein only the body of evidence ['evidence summary'] of an HTA can be used, while the data needs to be interpreted in the context of the health care system and the prevailing values. For this reason, reviewers have flagged context-sensitive outcomes (=issues) when formulating the questions, and have documented the underlying values driving certain decisions.

## **Diagnosics-specific content**

The pair of sensitivity and specificity is a general measure of test performance. The numbers (0.0–1.0) *per se* are not very informative in determining whether the test performs well. Instead, the intended use of the technology determines the requirements for the test accuracy. If sensitivity is sufficiently high, a negative test result rules out the disease. High sensitivity is particularly important if the counter-effect of missing a disease is dangerous. Sufficiently high specificity thus identifies the disease. High specificity is particularly important if a false positive result can harm the patient. Positive and negative predictive values are clinically informative measures of a diagnostic test's accuracy, but they must be considered in relation to the prevalence of the disease.

Estimates of summary likelihood ratios can be drawn from the pooled estimates of sensitivity and specificity. The likelihood ratio is telling of how many times more likely it is for a patient with a certain test result to have a disease, as opposed to the number of patients with the same test results but without the disease. A likelihood ratio 1 indicates that the test does not provide any useful diagnostic information. Positive likelihood ratios of more than 10 and negative likelihood ratios of less than 0.1 can provide convincing diagnostic information. Some guidelines suggest that positive likelihood ratios of more than 5, and negative likelihood ratios of less than 0.2 can provide strong diagnostic evidence. However, the interpretation depends on the context and the prevalence of the condition. Likelihood ratios for a test usually have to be more than 10 in order to be useful {28}, although this is very seldom the case.

The diagnostic odds ratio shows the association between a dichotomous test result and a diagnosis. If the diagnostic odds ratio (DOR) is 1, then the test does not provide any useful information. A DOR size greater than 1 reflects the strength of the test to discriminate between the presence and absence of disease. A DOR of 100 provides convincing evidence of the presence or absence of a disease, and corresponds to a positive likelihood ratio of 10 and a negative LR of 0.1. The DOR is often 50-90, but can be even up to 1000; in a good test, it should be over 80. A DOR of less than 1 indicates that the test identifies more positives among the non-diseased than the diseased. The diagnostic odds ratio is a useful summary measure for meta-analysis, but it does not provide information that can be directly applied onto clinical decisions. {28}

Variation in results by cut-off points, prevalence, or any other covariate and characteristics of the SROC curve, should be explained. The area under SROC curve can be used for comparing the accuracy of two test strategies. The test whose SROC curve encloses the largest area is the most accurate.

It is preferable to use additional methods of expressing test accuracy beyond sensitivity and specificity, e.g., likelihood ratios or diagnostic odds ratios. It may also be illustrative to explain how many patients will be missed (false negative rate) and how many treated unnecessarily (false positive rate) using certain cut-off point in a population with certain disease prevalence.

## Assessment elements

D0001 Assessment element card						
Issue: What is the expected beneficial effect of the technology on mortality?						
Topic: Mortality						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	1
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	1
	Pharmaceuticals (3.0)	Yes	Critical	Complete	Yes	1
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	1
Clarification	<p><b>Common to all used applications</b></p> <p>Mortality is the preferred, objective endpoint for assessments of life-threatening conditions. A distinction is made between overall mortality and disease-specific mortality. Overall mortality refers to all-cause mortality. It is expressed either as mortality rates (incidence in given population, at a 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 the all-cause mortality. Note 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 hazard ratio. It is a frequently used endpoint in screening trials, where it is considered to be subject to bias.</p> <p>Supplement with relevant data if differences can be expected for specific subgroups.</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>In diagnostic and screening technologies, this issue refers to the expected beneficial effect of the test-treatment-chain,</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>See also <a href="http://www.eunetha.eu/eunetha-guidelines">Methodological guideline for REA of pharmaceuticals: Clinical endpoints</a>. Available at <a href="http://www.eunetha.eu/eunetha-guidelines">http://www.eunetha.eu/eunetha-guidelines</a></p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>In diagnostic and screening technologies this issue refers to the expected beneficial effect of the test-treatment-chain,</p> <p>With screening tests, one should consider the effects of lead time bias, length time bias and selection bias to the mortality.</p>					

<p><b>Methodology and sources</b></p>	<p><b>Common to all used applications</b></p> <p>Several methods are used to adjust mortality rates and survival curves - e.g., relative survival (observed versus expected survival), which can be quite misleading; and hazard ratio (derived from a statistical method comparing the median survivals in the two groups). Note that progression-free survival is not a mortality endpoint; it describes the time from the beginning of an intervention until a patient shows signs of disease progression.</p> <p>Absolute mortality (compared to placebo or waiting list) and mortality relative to the comparator should be considered separately. See also <a href="http://www.eunetha.eu/eunetha-guidelines">Methodological guideline for REA of pharmaceuticals: Clinical endpoints</a> available at <a href="http://www.eunetha.eu/eunetha-guidelines">http://www.eunetha.eu/eunetha-guidelines</a>. Systematic reviews of trials, trials, both placebo-controlled and with active control. In the absence of head-to-head trials, studies with indirect comparisons (see <a href="http://www.eunetha.eu/eunetha-guidelines">Methodological guideline for REA of pharmaceuticals: Direct and indirect comparison</a>, available at <a href="http://www.eunetha.eu/eunetha-guidelines">http://www.eunetha.eu/eunetha-guidelines</a>. If these are not available, non-controlled studies and respective systematic reviews. Health care register data. Modelling studies.</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>Submission file, SPC, EPARs</p>
<p><b>References</b></p>	<p><b>Common to all used applications</b></p> <p>Hochman 2011, Black 2002</p>
<p><b>Content relations</b></p>	<p><b>Common to all used applications</b></p> <p>E0005, F0001</p>
<p><b>Sequential relations</b></p>	

D0026 Assessment element card						
Issue: How does the technology modify the effectiveness of subsequent interventions?						
Topic: Morbidity						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	2
	Medical and Surgical Interventions (3.0)	No				
	Pharmaceuticals (3.0)	No				
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	2
Clarification	<p><b>Common to all used applications</b></p> <p>Different tests may detect slightly different subpopulations as test-positive. Results from further diagnostic testing and the effectiveness of subsequent interventions can be different in test A positive compared to test B positive. For example, treatment may work differently in screening-identified cases than in cases that are diagnosed at regular physician's appointment</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Trials, observational studies, accuracy studies</p>					
References						
Content relations						
Sequential relations						

D0005 Assessment element card						
Issue: How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?						
Topic: Morbidity						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	No				
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	2
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	2
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	3
Clarification	<p><b>Common to all used applications</b></p> <p>Describe the efficacy and effectiveness of the technology on relevant disease outcomes and other changes in physical and psychological conditions. Outcomes such as function, quality of life and patient satisfaction are reported in other assessment elements of this domain. Report changes in severity, frequency and recurrence of symptoms and findings, both in absolute terms and relative to the comparator.</p> <p>Supplement with relevant data if differences can be expected for specific subgroups.</p> <p>See also Methodological guideline for REA of pharmaceuticals: <a href="#">Methodological guideline for REA of pharmaceuticals: Clinical endpoints</a> available at <a href="http://www.eunethta.eu/eunethta-guidelines">http://www.eunethta.eu/eunethta-guidelines</a></p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Trials, observational studies</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>SPC and EPAR</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>H0005, E0005</p>					
Sequential relations						

D0032 Assessment element card						
Issue: How does the test-treatment intervention modify the magnitude and frequency of morbidity?						
Topic: Morbidity						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	3
	Medical and Surgical Interventions (3.0)	No				
	Pharmaceuticals (3.0)	No				
	Screening Technologies (3.0)	No				
Clarification	<p><b>Common to all used applications</b></p> <p>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, with it, improved outcomes.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Accuracy and other observational studies, trials, qualitative research</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>H0005</p>					
Sequential relations						

D0006 Assessment element card						
Issue: How does the technology affect progression (or recurrence) of the disease or health condition?						
Topic: Morbidity						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	No				
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	3
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	3
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	4
Clarification	<p><b>Common to all used applications</b></p> <p>Report outcomes such as complete cure, progression-free survival, time-to-event (next stage of disease, relapse). Furthermore, describe the effect that duration of treatment has on symptoms, as well as on findings – whether the effects are permanent, short term, long term, intermittent, undulating. Report the results both in absolute terms and relative to the comparator. Methodological guideline for REA of pharmaceuticals: <a href="#">Methodological guideline for REA of pharmaceuticals: Clinical endpoints</a> available at <a href="http://www.eunetha.eu/eunetha-guidelines">http://www.eunetha.eu/eunetha-guidelines</a></p> <p>Supplement with relevant data if differences can be expected for specific subgroups.</p> <p>For technologies used for infectious diseases, such as drugs or vaccines consider acquisition of resistance or external effects, which can influence the spread of the disease such as herd immunity.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Trials, prognostic studies</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>SPC and EPAR</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>E0005</p>					
Sequential relations						

D0011 Assessment element card						
Issue: What is the effect of the technology on patients' body functions?						
Topic: Function						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	4
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	4
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	4
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	5
Clarification	<p><b>Common to all used applications</b></p> <p>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 functions; and skin functions. Report the results both in absolute terms and relative to the comparator.</p> <p>Supplement with relevant data if differences can be expected for specific subgroups.</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>See also <a href="#">Methodological guideline for REA of pharmaceuticals: Clinical endpoints</a>. Available at <a href="http://www.eunethta.eu/eunethta-guidelines">http://www.eunethta.eu/eunethta-guidelines</a></p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Trials and observational studies with functioning as an outcome. The instruments for outcome reporting should be validated</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>SPC and EPAR</p>					
References	<p><b>Common to all used applications</b></p> <p><a href="http://apps.who.int/classifications/icfbrowser">ICF</a>, available at <a href="http://apps.who.int/classifications/icfbrowser">http://apps.who.int/classifications/icfbrowser</a></p>					
Content relations	<p><b>Common to all used applications</b></p> <p>H0005; E0005; F0101</p>					
Sequential relations						

D0014 Assessment element card						
Issue: What is the effect of the technology on work ability?						
Topic: Function						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	5
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	5
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	5
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	6
Clarification	<p><b>Common to all used applications</b></p> <p>Describe the intervention's effects on sick leave, absenteeism, presenteeism, return-to-work, retirement and other relevant outcomes describing working ability</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Trials and other studies with return-to-work or work ability outcomes reported.</p>					
References	<p><b>Common to all used applications</b></p> <p><a href="http://www.fitforworkeurope.eu">Fit for Work Europe</a> website. Available at: <a href="http://www.fitforworkeurope.eu">www.fitforworkeurope.eu</a> European Commission (2007). <a href="http://ec.europa.eu/health-eu/doc/whitepaper_en.pdf">Together for Health: A Strategic Approach for the EU 2008-2013</a>. Available at <a href="http://ec.europa.eu/health-eu/doc/whitepaper_en.pdf">http://ec.europa.eu/health-eu/doc/whitepaper_en.pdf</a></p>					
Content relations	<p><b>Common to all used applications</b></p> <p>H0005; E0001</p>					
Sequential relations						

D0015 Assessment element card						
Issue: What is the effect of the technology on return to previous living conditions?						
Topic: Function						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	6
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	6
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	6
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	7
Clarification	<p><b>Common to all used applications</b></p> <p>Discharge of the patient to the living conditions in which they lived before admission is one of the most important treatment goals, particularly for elderly patients. Implications for family members and caregivers should be considered too.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Trials and observational studies using one of the several evaluation tools, such as the Katz ADL scale, the Lawton IADL scale or the Bristol Activities of Daily Living Scale.</p> <p>Health care service providers may use ADL evaluations in their practice, using models such as the Roper-Logan-Tierney model of nursing, and the resident-centred models, such as the Programme of All-Inclusive Care for the Elderly (PACE).</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>H0005</p>					
Sequential relations						

D0016 Assessment element card						
Issue: How does the use of the technology affect activities of daily living?						
Topic: Function						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	7
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	7
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	7
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	8
Clarification	<p><b>Common to all used applications</b></p> <p>Activities of Daily Living (ADL) is used in rehabilitation as an umbrella term relating to self-care, and comprising those activities or tasks that people undertake routinely in their everyday lives. The activities can be subdivided into personal care, and domestic and community activities.</p> <p>Report the results both in absolute terms and relative to the comparator. For further information see Methodological guideline for REA of pharmaceuticals: 1) Health-related quality of life and 2) Clinical endpoints, both available at <a href="http://www.eunetha.eu/eunetha-guidelines">http://www.eunetha.eu/eunetha-guidelines</a></p> <p>Supplement with relevant data if differences can be expected for specific subgroups.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Trials and observational studies reporting ADL outcomes</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>SPC and EPAR</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>H0005</p>					
Sequential relations						

D0012 Assessment element card						
Issue: What is the effect of the technology on generic health-related quality of life?						
Topic: Health-related Quality of life						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	8
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	8
	Pharmaceuticals (3.0)	Yes	Critical	Complete	Yes	8
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	9
Clarification	<p><b>Common to all used applications</b></p> <p>Health-related quality of life (HRQL) is typically measured with self- or interviewer-administered questionnaires which measure either cross-sectional differences in quality of life between patients at a point in time (discriminative instruments) or longitudinal changes in HRQL within patients during a period of time (evaluative instruments). There are two available basic approaches to quality-of-life measurement: (1) generic instruments that provide a summary of HRQL, and (2) 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. See also <a href="http://www.eunetha.eu/eunetha-guidelines">Methodological guideline for REA of pharmaceuticals: Health-related quality of life</a> available at <a href="http://www.eunetha.eu/eunetha-guidelines">http://www.eunetha.eu/eunetha-guidelines</a></p> <p>Supplement with relevant data if differences can be expected for specific subgroups.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Trials, observational and qualitative studies</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>SPC and EPAR</p>					
References	<p><b>Common to all used applications</b></p> <p>EMA 2005, FDA 2009, Chassany 2002, Terwee 2007, Revicki 2008, Puhan 2006</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>H0005; E0005</p>					
Sequential relations						

D0013 Assessment element card						
Issue: What is the effect of the technology on disease-specific quality of life?						
Topic: Health-related Quality of life						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	9
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	9
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	9
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	10
Clarification	<p><b>Common to all used applications</b></p> <p>Health-related quality of life (HRQL) is typically measured with self- or interviewer-administered questionnaires which measure either cross-sectional differences in quality of life between patients at a point in time (discriminative instruments) or longitudinal changes in HRQL within patients during a period of time (evaluative instruments). There are two available basic approaches to quality-of-life measurement: (1) generic instruments that provide a summary of HRQL, and (2) specific instruments that focus on problems associated with single disease states, patient groups, or areas of function. Each approach has its strengths and weaknesses and may be suitable for different circumstances. See also <a href="http://www.eunetha.eu/eunetha-guidelines">Methodological guideline for REA of pharmaceuticals: Health-related quality of life</a> available at <a href="http://www.eunetha.eu/eunetha-guidelines">http://www.eunetha.eu/eunetha-guidelines</a></p> <p>Supplement with relevant data if differences can be expected for specific subgroups.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Trials, observational and qualitative studies</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>SPC and EPAR</p>					
References	<p><b>Common to all used applications</b></p> <p>EMA 2005, FDA 2009, Chassany 2002, Terwee 2007, Revicki 2008, Puhan 2006</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>H0005; E0005</p>					
Sequential relations						

D0030 Assessment element card						
Issue: Does the knowledge of the test result affect the patient's non-health-related quality of life?						
Topic: Quality of life						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	10
	Medical and Surgical Interventions (3.0)	No				
	Pharmaceuticals (3.0)	No				
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	11
Clarification	<p><b>Common to all used applications</b></p> <p>The test result may alleviate, trigger, or worsen symptoms, as well as improve or worsen the quality of life, although there is no effectiveness on the primary outcome.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Qualitative research, observational studies, trials</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>H0005, H0006, F0001, F0003</p>					
Sequential relations	<p><b>Common to all used applications</b></p> <p>H0006</p>					

D0017 Assessment element card						
Issue: Were patients satisfied with the technology?						
Topic: Patient satisfaction						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	11
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	10
	Pharmaceuticals (3.0)	Yes	Optional	None	No	10
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	12
Clarification	<p><b>Common to all used applications</b></p> <p>Describe patients' overall perception of the value of the intervention and their satisfaction with the treatment. ('Was the use of the technology worthwhile?')</p> <p>Differences in acceptability may predict the overall uptake of the technology and would impact on the overall effectiveness. If a technology can be used repeatedly it can also be asked whether the patient would be willing to use this technology again. See also <a href="#">Methodological guideline for REA of pharmaceuticals: Clinical endpoints</a> available at <a href="http://www.eunetha.eu/eunetha-guidelines">http://www.eunetha.eu/eunetha-guidelines</a></p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Surveys, qualitative research, observational studies, trials</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>H0006; F0001, F0011</p>					
Sequential relations	<p><b>Common to all used applications</b></p> <p>H0006</p>					

D0024 Assessment element card						
Issue: Is there an effective treatment for the condition the test is detecting?						
Topic: Test-treatment chain						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	12
	Medical and Surgical Interventions (3.0)	No				
	Pharmaceuticals (3.0)	No				
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	13
Clarification	<p><b>Common to all used applications</b></p> <p>The effectiveness or clinical utility of a test usually requires the existence of an effective treatment for the target condition, and its availability to the patients.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Trials, observational studies</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>F0001</p>					
Sequential relations						

D1001 Assessment element card						
Issue: What is the accuracy of the test against reference standard?						
Topic: Test accuracy						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Complete	Yes	13
	Medical and Surgical Interventions (3.0)	No				
	Pharmaceuticals (3.0)	No				
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	14
Clarification	<p><b>Common to all used applications</b></p> <p>Accuracy in terms of sensitivity and specificity, and other measures such as likelihood ratios, pre-test probabilities, SDORs, AUC or Q*.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>In screening programmes one should separately consider the accuracy of the screening test and the accuracy of subsequent diagnostic tests.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Accuracy studies</p>					
References						
Content relations						
Sequential relations						

D1002 Assessment element card						
Issue: How does the test compare to other optional tests in terms of accuracy measures?						
Topic: Test accuracy						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Complete	Yes	14
	Medical and Surgical Interventions (3.0)	No				
	Pharmaceuticals (3.0)	No				
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	15
Clarification	<p><b>Common to all used applications</b></p> <p>Consider also how the technology compares to other development stages of the same technology.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Accuracy studies</p>					
References						
Content relations						
Sequential relations						

D1003 Assessment element card						
Issue: What is the reference standard and how likely does it classify the target condition correctly?						
Topic: Test accuracy						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	15
	Medical and Surgical Interventions (3.0)	No				
	Pharmaceuticals (3.0)	No				
Screening Technologies (3.0)	Yes	Important	Partial	Yes	16	
Clarification	<p><b>Common to all used applications</b></p> <p>In addition, consider the situations where there is no proper reference standard.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Accuracy studies</p>					
References	<p><b>Common to all used applications</b></p> <p>Rutjes AWS, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt PMM. Evaluation of diagnostic tests when there is no gold standard. A review of methods. Health Technol Assess 2007;11(50).</p>					
Content relations						
Sequential relations						

D1004 Assessment element card						
Issue: What are the requirements for accuracy in the context the technology will be used?						
Topic: Test accuracy						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	16
	Medical and Surgical Interventions (3.0)	No				
	Pharmaceuticals (3.0)	No				
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	17
Clarification	<p><b>Common to all used applications</b></p> <p>Discussion of what could be an estimate for an acceptable number of false negative and false positive test results in different situations, e.g., in replacement/triage/add-on situations, and in life-threatening/harmless conditions.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>With regard to screening programs, one should separately consider the screening test and the subsequent diagnostic tests.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Descriptive ethical literature, expert advice, prevalence data, modelling studies, calculations</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>F0017</p>					
Sequential relations						

D1005 Assessment element card						
Issue: What is the optimal threshold value in this context?						
Topic: Test accuracy						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	17
	Medical and Surgical Interventions (3.0)	No				
	Pharmaceuticals (3.0)	No				
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	18
Clarification	<p><b>Common to all used applications</b></p> <p>Sensitivity and specificity vary according to the threshold value. An optimal combination of sensitivity 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.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>With regard to screening programs, one should separately consider the screening test and the subsequent diagnostic tests.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Screening studies with varying thresholds, accuracy studies with varying thresholds, modelling studies</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>F0017</p>					
Sequential relations						

D1006 Assessment element card						
Issue: Does the test reliably rule in or rule out the target condition?						
Topic: Test accuracy						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	18
	Medical and Surgical Interventions (3.0)	No				
	Pharmaceuticals (3.0)	No				
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	19
Clarification	<p><b>Common to all used applications</b></p> <p>This question is relevant in, e.g., triage situation where the aim of the test is to rule out a severe condition in order to avoid further testing which may be more harmful to the patient, and more expensive.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>When assessing screening programs, one should consider the combination of the screening test and the subsequent diagnostic tests.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Accuracy studies, modelling studies</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>C0008, F0017</p>					
Sequential relations						

C0006 Assessment element card

Issue: What are the consequences of false positive, false negative and incidental findings generated by using the technology from the viewpoint of patient safety?

**Topic: Patient safety**

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	22
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	11
	Pharmaceuticals (3.0)	No				
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	23
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Describe the consequences of false positive, false negative and incidental findings generated by using the technology.</p> <p>False negative test results (Type II error) incorrectly identify sick people 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.</p> <p>False positive test results (Type I error) incorrectly identify healthy people as sick with the possible consequence of overtreatment. 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 overdiagnosis and overtreatment.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>In screening programmes, one should separately consider the false negative screening test results and the subsequent false negative diagnostic test results</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Research articles, manufacturers' product data sheets, safety monitoring databases</p>					
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Welch G et al 2011 {34} from the SAF domain.</p>					
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>D0028, D0027, D0009; B0001; E0001; F0001; G0001, G0100</p>					

<b>Sequential relations</b>	<b>Common to all used applications</b> B0001
<b>Other domains</b>	Also in: Safety

<p>D0010 Assessment element card</p> <p>Issue: How does the technology modify the need for hospitalisation?</p> <p>Topic: Change-in management</p>						
<b>Application-specific properties</b>	<b>Application</b>	<b>Used</b>	<b>Importance</b>	<b>Transferability</b>	<b>Core</b>	<b>Order</b>
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	26
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	12
	Pharmaceuticals (3.0)	Yes	Important	Partial	Yes	11
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	27
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>In addition, consider changes at different levels of care e.g. ward instead of intensive care.</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Trials, observational studies</p>					
<b>References</b>						
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>E0001; G0001</p>					
<b>Sequential relations</b>						

D1007 Assessment element card						
Issue: How does test accuracy vary in different settings?						
Topic: Test accuracy						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	19
	Medical and Surgical Interventions (3.0)	No				
	Pharmaceuticals (3.0)	No				
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	20
Clarification	<p><b>Common to all used applications</b></p> <p>Describe how patient spectrum, disease prevalence, disease severity, and properties of the technology itself, affect the accuracy of the test. This may have implications on how frequently a test needs to be repeated, on optimal age range for a screening programme and on adjustments in different populations.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Accuracy studies in different settings, descriptive literature, expert advice</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>B0004</p>					
Sequential relations	<p><b>Common to all used applications</b></p> <p>B0004</p>					

D0029 Assessment element card						
Issue: What are the overall benefits and harms of the technology in health outcomes?						
Topic: Benefit-harm balance						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	27
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	13
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	12
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	28
Clarification	<p><b>Common to all used applications</b></p> <p>This question integrates all benefits and harms concerning mortality, morbidity, QoL and further patient-relevant outcomes, also considering the amount of false positive and false negative test results. There is no common quantitative summary measure, and a balanced and meaningful presentation is difficult to reach even qualitatively.</p> <p>The integration of information across domains into the benefit-harm-balance is essential. This issue provides input for ETH (F0010) and ECO (E0005) in order to calculate the incremental effectiveness of the new technology. Information from SAF is needed for this issue: all harms to the patient are listed in outcomes and units which are comparable to the outcomes in EFF domain representing benefits.</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>In diagnostic and screening technologies, the problem of overdiagnosis and overtreatment should be covered, as should the benefits and harms of subsequent diagnostic testing and treatments in patients with a true positive test result in a prior diagnostic or screening test.</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>See Template 7 in the HTA Core Model for Rapid Relative Effectiveness Assessment of pharmaceuticals at <a href="http://mekat.thl.fi/htacore/BrowseModel.aspx">http://mekat.thl.fi/htacore/BrowseModel.aspx</a></p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>In diagnostic and screening technologies, the problem of overdiagnosis and overtreatment should be covered, as well as the benefits and harms of subsequent diagnostic testing and treatments in patients with a true positive test result in a prior diagnostic or screening test.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Trials, observational studies, modelling studies</p>					
References						

<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>A0007, A0011; C0008, C0003, C0004, C0005, C0006, C0007, C0061; E0005; F0001, F0011</p>
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>A0007, A0011, C0008, C0003, C0004, C0005, C0006, C0007, C0061</p>

<p>D1008 Assessment element card</p> <p>Issue: What is known about the intra- and inter-observer variation in test interpretation?</p> <p><b>Topic: Test accuracy</b></p>						
<b>Application-specific properties</b>	<b>Application</b>	<b>Used</b>	<b>Importance</b>	<b>Transferability</b>	<b>Core</b>	<b>Order</b>
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	20
	Medical and Surgical Interventions (3.0)	No				
	Pharmaceuticals (3.0)	No				
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	21
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>This is especially relevant in tests with subjective assessments, such as most imaging tests.</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Accuracy studies, trials, observational studies</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>Accuracy studies, trials, observational studies</p>					
<b>References</b>						
<b>Content relations</b>						
<b>Sequential relations</b>						

D1019 Assessment element card						
Issue: Is there evidence that the replacing test is more specific or safer than the old one?						
Topic: Test accuracy						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	21
	Medical and Surgical Interventions (3.0)	No				
	Pharmaceuticals (3.0)	No				
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	22
Clarification	<p><b>Common to all used applications</b></p> <p>If there is effective treatment for a condition, then a new diagnostic technology with similar sensitivity, but greater safety or specificity, may be seen as improved effectiveness.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>With regard to screening programmes, one should separately consider the screening test and the subsequent diagnostic test.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Accuracy studies, trials, observational studies</p>					
References	<p><b>Common to all used applications</b></p> <p>Lord SJ et al., 2006 {83}</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>C0008, F0001</p>					
Sequential relations	<p><b>Common to all used applications</b></p> <p>C0008</p>					

D0020 Assessment element card						
Issue: Does use of the test lead to improved detection of the condition?						
Topic: Change-in management						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	23
	Medical and Surgical Interventions (3.0)	No				
	Pharmaceuticals (3.0)	No				
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	24
Clarification	<p><b>Common to all used applications</b></p> <p>Although the test is reliable, the information it provides does not necessarily affect clinical decision-making. If it does not sufficiently change the pre-test probability that the added value of the information may be low; e.g., there may be routine preoperative lab tests that nobody uses in decision-making. Moreover, the ability of users to make a correct diagnosis may depend on their knowledge and their ability to interpret the results.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Trials, accuracy studies, before-after studies, interrupted time series, change-in-management studies</p>					
References	<p><b>Common to all used applications</b></p> <p>Guyatt GH et. al, 1986 {84}</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>G0001</p>					
Sequential relations						

D0021 Assessment element card						
Issue: How does use of the test change physicians' management decisions?						
Topic: Change-in management						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	24
	Medical and Surgical Interventions (3.0)	No				
	Pharmaceuticals (3.0)	No				
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	25
Clarification	<p><b>Common to all used applications</b></p> <p>There may be technology-related or non-related factors that might influence the physicians' perceptions of, ability for, and attitude toward decision-making. Management decisions subsume both testing and treatment decisions.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Change-in-management studies, qualitative research</p>					
References	<p><b>Common to all used applications</b></p> <p>Guyatt GH et. al, 1986 {84}</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>G0001, G0008, G0009</p>					
Sequential relations						

D0022 Assessment element card						
Issue: Does the test detect other potential health conditions that can impact the subsequent management decisions?						
Topic: Change-in management						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	25
	Medical and Surgical Interventions (3.0)	No				
	Pharmaceuticals (3.0)	No				
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	26
Clarification	<p><b>Common to all used applications</b></p> <p>Management decisions subsume both testing and treatment decisions. Notice issue C0006 which deals also with incidental findings.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Trials, accuracy studies</p>					
References	<p><b>Common to all used applications</b></p> <p>Guyatt GH et. al, 1986 {84}</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>F0003</p>					
Sequential relations						

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# Costs and economic evaluation (ECO)

## *Description*

### What is this domain about?

Economic evaluation has been defined as a comparative analysis of alternative courses of action in terms of both their costs and consequences {1}. The aim of the Costs and Economic Evaluation domain (abbreviated as ECO) within HTA is to inform value-for-money judgements about health technologies with information about costs, health-related outcomes and economic efficiency {2} In this way, it often utilises evidence from the SAF domain and the EFF domain to make economic evidence available when allocating resources to emerging, new and existing health technologies {3}.

In publicly funded healthcare systems, finite resources mean that not all technologies can be provided in every situation for all who may need or want them. The concept of opportunity cost is central to this area of health economics: choices have to be made between alternative, effective health technologies; a decision to fund one technology may mean that others cannot be funded, or that their use must be restricted {2}. Economic evaluations of health technologies often focus on efficiency considerations in the production of health, with economic efficiency providing an indication of how resources should be allocated or utilised for maximizing health-related outcomes in an economic manner {4}. Although societal objectives other than economic efficiency, such as equity of access, reduction of inequalities, and deontological considerations can typically be part of a full HTA report, they are usually not incorporated in economic evaluations and need to be considered separately by decision-makers (see, e.g., {5}, {6}).

The primary aim of this chapter is to encourage a more transparent and structured way of reporting evidence related to the costs and economic evaluation of healthcare technologies both in national (regional) HTA production and in collaborative projects aiming to produce core HTA information. The chapter identifies good research practices for dealing with aspects of validity and transferability, including analytic strategies and guidance for considering the appropriateness of transferring evidence to other settings. This domain does not aim at a global harmonisation of requirements or methods for economic evaluation. Instead, it highlights the importance of transparent and structured *reporting* (both in methods and results) so that the study users can assess the relevance of the information in their own setting or adapt the information to their own setting when needed.

Methodological guidelines on the methods for economic evaluation have been developed {92}. The EUnetHTA guideline “Methods for health economic evaluations - A guideline based on current practices in Europe” acknowledges the possibility of variations in requirements for economic evaluations across countries or jurisdictions. This guideline aims to improve the usefulness of economic evaluations performed within EUnetHTA and move ECO closer towards the possibility of a common European framework for conducting health economic evaluations. One important, related objective of the HTA Core Model itself is to encourage the sharing of information between

the SAF and EFF domains and ECO domain (See section **Relations to other domains** for more details).

Table 1 lists the topics and issues included in the ECO domain. The topics and issues are limited to items that are important for all healthcare settings and are required for other jurisdictions in assessing the transferability of ECO information into their own setting. This is in line with one of the main objectives of the HTA Core Model, which is to allow agencies to use core HTA information produced by other agencies.

**Table 1: Topics and issues in this domain**

Topic	Issue	Assessment element ID
Resource utilisation	What types of resources are used when delivering the assessed technology and its comparators (resource-use identification)?	E0001
Resource utilisation	What amounts of resources are used when delivering the assessed technology and its comparators (resource-use measurement)?	E0002
Resource utilisation	What were the measured and/or estimated costs of the assessed technology and its comparator(s) (resource-use valuation)?	E0009
Resource utilisation	How does the technology modify the need for other technologies and use of resources?	D0023
Resource utilisation	What are the likely budget impacts of implementing the technologies being compared?	G0007
Measurement and estimation of outcomes	What is(are) the measured and/or estimated health-related outcome(s) of the assessed technology and its comparator(s) (outcome identification, measurement and valuation)?	E0005
Examination of costs and outcomes	What are the estimated differences in costs and outcomes between the technology and its comparator(s)?	E0006
Characterising uncertainty	What are the uncertainties surrounding the costs and economic evaluation(s) of the technology and its comparator(s)?	E0010
Characterising heterogeneity	To what extent can differences in costs, outcomes, or 'cost-effectiveness' be explained by variations between any subgroups using the technology and its comparator(s)?	E0011
Validity of the model(s)	What methodological assumptions were made in relation to the technology and its comparator(s)?	E0013
Validity of the model(s)	To what extent can the estimates of costs, outcomes, or economic evaluation(s) be considered as providing valid descriptions of the technology and its comparator(s)?	E0012

## Why is this domain important?

In recent decades, the share of healthcare costs as a proportion of GDP has risen in many countries, placing increasing pressure on the finite resources available to fund this expenditure. This growth in costs has been fuelled in part by the rate of technological development. Increasingly, there is a conflict between what is technologically possible and what is economically feasible. In a HTA evaluating a technology, it is often not sufficient to systematically consider only aspects of safety, efficacy, clinical effectiveness or ethics; information on costs, cost-effectiveness, or opportunity costs from economic evaluations, is also needed.

Increasingly health-economic information is requested in more jurisdictions, increasing the burden on HTA-agencies, study sponsors and researchers. Conducting economic evaluations can be both time-consuming and demanding, for instance, in terms of the need for multidisciplinary input in the form of statistical, modelling and clinical expertise. For this reason, it would be advantageous to spread the workload between organisations and jurisdictions. On the other hand, the recommendations, methods and data requirements for estimating, for example: baseline risk; treatment effect; resource utilisation; health-state measures; and costs differ across populations or healthcare systems (see, e.g., {7} and {8}). Such differences lead to different evidence being used as inputs in decisions about reimbursement and access for new health technologies. Indeed, having the same clinical and economic evidence will not necessarily result in the same decision across, e.g., jurisdictions, because of national and regional differences in decision-making processes and because of value judgements (see, e.g., {9}).

Information concerning costs and economic evaluation, although important, forms only two of the many considerations which may be taken into account when allocating resources {6}. The importance of this domain depends, in large part, on the transparency and validity of both the information presented and the analysis which produced that information. In particular, the nature of the evidence used by this domain is of paramount importance when assessing the applicability of costs and economic evaluation results *for* potential use in the decision-making process. Ideally, this domain would therefore also aim to provide information on the credibility of the reported cost and cost-effectiveness estimates. However, there will remain a more general need to investigate all potential threats to the applicability of information produced in the ECO domain both within the ECO domain itself and through the ECO domain's relations to other domains (see, e.g., {10} and {11}).

## Relations to other domains

The Costs and Economic Evaluation domain should collaborate with the Clinical Effectiveness (EFF) and Safety (SAF) domains in order to receive timely and appropriate information on efficacy or effectiveness, and to ensure that the outcome measures considered appropriate for the economic evaluation are also included in these domains. However, ECO may also benefit from information gathered by the Health Problem and Current Use of the Technology (CUR), and Patients and Social Aspects (SOC) domains in order to specify appropriate populations, interventions, comparisons and outcomes for the “Costs and economic evaluation” -research questions. In addition, the work undertaken in the ECO domain is likely to be of importance for organisational considerations, too. The production of information about the impact of health technologies on the budgets of different stakeholders should be shared with the Organisational Aspects (ORG) domain in Assessment Element G0007. A dialogue between research in the ECO and ORG domains should be initiated at

an early stage, so that ECO-researchers understand the organisational context and can work together with the ORG researchers to provide relevant information. There is also a possibility of overlapping work, especially with the CUR and SAF domains, and co-operation is likely necessary even when drawing up the domain-specific protocol.

Depending on the technology, the Ethical Analysis (ETH) and Patients and Social Aspects (SOC) domains may provide important information in helping to decide the appropriateness of the type or perspective of study undertaken within the ECO domain. For instance, the research in ETH, regarding the benefits and harms of the technology for patients or any other stakeholders (relatives, other patients, organisations, commercial entities, society, etc.), should be reflected upon, including any other hidden or unintended consequences of the technology and its applications for the whole range of stakeholders. In a similar manner, the SOC domain may investigate the value of the technology in terms of return to employment, e.g., from the viewpoint of the patient; a wage rather than pension, for instance, may have a substantial impact on an individual or family. SOC considerations increasingly fall within the scope of some cost estimates and economic evaluations, if they attempt to encompass wider outcomes.

ECO may also be related to the Legal Aspects (LEG) domain, e.g., when there is a need for legal provision for a public health programme (such as mandatory vaccination or mass screening).

## ***Methodology***

There are three approaches that are typically used in answering the research questions in this domain. These are (1) review of published economic evidence; (2) critical review of an existing economic evaluation submitted by, e.g., a market authorisation holder; or (3) *de novo* economic evaluation. In this section we briefly describe the process for answering research questions, including the main processes through which existing information can be utilised by conducting literature reviews. This is followed by a description of the kind of information that is usually required, including a description of the study types, study designs, outcome measures, and a brief overview of some of the tools available when undertaking critical appraisals. It should be noted that the chapter makes very few recommendations as to the types of approach(es) investigators should take, as this may often be dictated by national guidance or procedures. As an alternative to recommending any particular approach, the reader is presented with some commonly-used approaches when conducting research on costs and economic evaluation.

## **Process for answering research questions**

An analysis of costs and economic evaluation normally starts by initially scoping and structuring a decision problem with accompanying identification of evidence needs. It then proceeds by searching for existing evidence, as described in the section *Gathering information*. This can be followed by qualitative and/or quantitative synthesis of existing evidence. The commonly used approaches in *de novo* economic evaluation, i.e. economic evaluation which is tailored towards a specific decision problem from the beginning of the process, are described in the section *Analysing and synthesizing evidence*.

## Gathering information

### *Where to find information?*

The relevant places to find information depend on the type of information being sought. There are two main purposes for information searching in economic evaluation: review of existing economic evidence, and review of evidence to populate an economic model.

### **Review of existing economic evidence**

The results of economic evaluations are usually not generalizable, e.g., between different jurisdictions or time periods. Not only do the methods used in economic evaluations vary across studies, but also more profound elements of the research questions, comparators, perspectives, healthcare systems, clinical guidelines, resource use, and time horizon, differ significantly { 12 } (See section *Transferability of evidence concerning costs and economic evaluation* for more details).

However, even if the generalisability of results of economic evaluation is limited, a systematic review can, for example, be used to inform the development of a new decision-analytic model or reveal the most important drivers of previous economic models { 13 }. Literature reviews may also yield information, for example, on developing model structures, on potentially useful methodological choices, and on the reasons for using certain simplifying assumptions.

In cases where *de novo* analysis will not be conducted, reviews can be used to, e.g. help identify the most relevant studies in informing a particular decision in a jurisdiction, or to identify a potential absence of such information { 14 }. When assessing relevance, the identified studies should be critically appraised (see section *Tools for critical appraisals*) and their transferability assessed (see *Transferability of evidence concerning costs and economic evaluation*).

When undertaking reviews of existing economic evidence, their overall purpose should be made explicit (e.g., whether the purpose is to inform the development of a new model or to inform a particular decision) { 14 }.

### **Meta-analysis of economic evidence**

It is theoretically and practically possible to conduct meta-analyses of economic evaluations. However, their use is not widespread, as the heterogeneity which exists between studies would often demand major adjustments. Indeed, such adjustments are often not either possible or practical { 14 }.

## **Review of evidence to populate or develop an economic model**

Various data sources are usually used in order to populate an economic model with appropriate structures and parameters. These include, for example, RCTs, observational studies, administrative-record databases, disease registers, and expert opinion. Typically, systematic literature review can identify at least the evidence concerning the health effects and transition probabilities of the technologies under assessment. The methods used in systematic reviews of health effects have been described in the SAF and EFF domains.

### **Databases and search strategies**

The [Sure Info](#) (Summarized Research in Information Retrieval for HTA) resource, from the HTAi Vortal, summarises the databases and search strategies used when searching for specific aspects of HTA (in this case ‘[costs and economic evaluation](#)’). In addition, the Centre for Reviews and Dissemination (CRD) has published [guidance for undertaking systematic reviews](#) of economic evaluations.

## ***What kind of information is required?***

### **Study types, design, outcome measures**

#### **Types of economic evaluation**

Five main types of economic evaluation can contribute to HTA: cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-consequences analysis (CCA), cost-benefit analysis (CBA), and cost-minimisation analysis (CMA). However, it is known that these terms are used in various ways by different authors and do not always accurately describe the nature of published studies {90}.

Choosing between the different types of economic evaluations for answering a specific question depends on a combination of at least three considerations: (1) the purpose of the economic evaluation; (2) the availability of suitable data and (3) any guidelines for economic evaluations that should be followed in any specific context. The difference between them is based on how health outcomes are measured and valued and whether they are commensurable or not, it should also be noted that a combination of more than one type of analysis can be useful {1}.

**Cost-effectiveness analysis (CEA)** is traditionally associated with the economic concept of technical efficiency, CEA compares the costs and effects of at least two alternative technologies. The effects of the different technologies are usually measured using unidimensional final (e.g., life-years gained) or surrogate outcomes (e.g., progression-free survival), providing information on the ‘greatest effect for a given cost’, or alternatively, one that achieves a ‘given effect at minimum cost’ {15}. One potential disadvantage of CEA is that, because the different disease areas use different natural units (or metrics) to measure outcomes, the results are not comparable between disease areas in the same way as they are in cost-utility analysis (CUA). The results of such analysis are generally expressed in the form of an incremental cost-effectiveness ratio (ICER). An ICER represents the estimated difference in costs between the comparators divided by the estimated difference in effect between the comparators. In an example where the effects of the comparators are measured in life years, the estimated ICER could be reported as the cost per life-year gained. One difficulty is that

the measure of effectiveness used must be appropriate and common to the treatments being compared {1}. In addition, CEA, in the form of CUA, is also widely associated with the economic concept of allocative efficiency, through the production of information which directly relates to the economic opportunity costs of technologies.

**Cost-utility analysis (CUA)** is a form of CEA which uses health-related outcomes that share many of the characteristics of ‘utility’, such as QALYs (Quality-Adjusted Life Year) {15}. The most common form of CUA can also be referred to as cost-per-QALY analysis. CUA uses health-state-value scores as a measure of outcome which, conceptually, allows the measurement and comparison different outcomes with the same metric (e.g., QALY or DALY (Disability-Adjusted Life Year)). The term ‘cost-utility analysis’ is widely used, but should be used in the knowledge that, here, ‘utility’ refers to a constrained valuation of health-related outcome. The QALY approach is one of the most used approaches in CEA, involving the incorporation of both health-related quality of life (HRQoL) and survival information, i.e., CEA with QALYs as the measure of effectiveness. See the section *Health-related outcomes* for further details.

**Cost-consequences analysis (CCA)** examines costs and consequences, without the necessity of focussing on a single consequence, and without combining disparate consequences into a single, commensurable measure (see, e.g., {15}, {16} and {17}). It has been classified both as a variant of CEA {90} and as a balance sheet approach to CBA {4}. It can be useful in enhancing transparency of reports {18} and, despite its known limitations {20}, it can be especially useful when the outcomes are not adequately measured with e.g. generic HRQoL measures {19}. This approach may be preferred to CEA or CUA by policy makers when multiple consequences are to be weighed together simultaneously. In this situation, CUA and CEA can be considered to be inappropriate, as they may conceal important information through the calculation of a single ratio and, therefore, may not allow decisions to be made which are in wholly in line with societal values (see, e.g., {21} or {6}).

**Cost-benefit analysis (CBA)**, in the form of comparative analysis of costs and money-valued benefits, is currently not very widely used as a type of health-economic evaluation {15}. One main reason for its limited use are the problems associated with the production of the unbiased and precise estimates of costs and benefits required for its successful application. The methodology of economic valuation of such benefits is advancing, but numerous methodological uncertainties and problems still remain {22}.

**Cost-minimisation analysis (CMA)** can be performed if the technologies under comparison can be assumed to have, e.g., the same desired effects (benefits) and undesired effects (risks/harms) {15}. The appropriateness of conducting CMA has been questioned, mainly due to its assumption(s) concerning the equivalence of the effects of the technologies being compared {23}. If measured or hypothesised differences between the technologies in outcomes cannot be adequately distinguished, then CCA, CEA or CUA with sensitivity analysis could be more useful {24}.

The purpose of economic evaluation is different from the objective of a budget impact analysis (BIA). Economic evaluations attempt to provide information about the most economically efficient ways to utilise or allocate available healthcare resources. BIA, on the other hand, estimates the financial and organisational consequences of adopting a new technology in healthcare without directly taking health consequences into account. In the HTA Core Model, BIA is to be shared between the ORG domain and the ECO domain (see the section *Relations to other domains* for further details). ISPOR, for instance, has defined good practices for BIA {25}. However, national differences in the structure and funding of healthcare systems, resource utilisation and costs will generally limit the transferability of BIA.

## Model-based economic evaluation

Considering that all relevant evidence needed in economic evaluation is rarely available from a single source, decision-analytic modelling provides a framework for synthesising data from various sources, taking into account all relevant comparators, adopting sufficiently long time horizons, and taking uncertainty into account {26}. In the context of economic evaluation, a decision-analytical model has been defined as a model that “uses mathematical relationships to define a series of possible consequences that would flow from a set of alternative options being evaluated” {26}.

The use of modelling should be justified, e.g., by the available data being insufficient, and the limitations of the modelling undertaken should always be made as clear as possible {57}.

Decision-analytic modelling can be conducted using, e.g., decision trees, Markov models (cohort state-transition models), microsimulation or first-order Monte Carlo -models (individual-based state-transition models), discrete-event simulations, dynamic transmission models, or combinations of these (see, e.g., {27} or {28}). For technical details on the use of models for economic evaluation, a number of general textbooks have been published (for example, {29}, {30} and {31}, {32}). In addition, ISPOR has published a series of articles that relate to the application of modelling techniques to the healthcare decision-making area. These articles cover the following topics: conceptualising a model {33}, state-transition models {34}, discrete event simulations {35}, dynamic transmission models {36}, parameter estimation and uncertainty {37}, transparency and validation {38}.

There are different requirements for modelling in different jurisdictions or healthcare systems. To be able to evaluate validity and applicability of modelling results to a particular setting, both non-technical and technical documentation are usually needed. Non-technical documentation provides an overview of the model and what it does. Full technical documentation, on the other hand, is a more detailed description of the model, including its structure, components, equations, and possibly even programming code or modelling files, enabling those with expertise to reproduce the model {38}.

Models are often used when localising international economic evaluations to a national or jurisdictional setting. Model parameters would often need to be changed in order to better represent the population, jurisdiction, or healthcare system. The values of some parameters, e.g., those relating to prices and baseline risk, typically need to be specific to the decision-making setting. On the other hand, treatment effect as estimated by the relative risk reduction may be more transferable. There might also be a need to change the structure of the model, if, e.g., the clinical pathway or course of the disease differs between jurisdictions {39}. ISPOR has also identified good research practices for addressing transferability issues in models {39}.

## Single-study-based economic evaluation

Health-economic data can be collected alongside a randomised clinical trial, sometimes referred to as ‘piggyback evaluation’. The advantages of this are the internal validity of trial design and the collection of data on both resource use and effectiveness. The aims of the underlying trials and the economic evaluations, however, may differ in significant respects, which can lead to disagreements concerning the suitability of trial-based economic analyses (time horizon, sample size, etc.) {1}. Despite its aims generally being somewhat different than model-based economic evaluation, trial-based economic analyses may provide individual-level analysis of the impact of the technology and its comparator(s) {29}. This can facilitate useful subgroup analyses as well as potentially provide a

detailed description of costs and outcomes related to the technology and its comparator(s) (see, e.g., {40-42}). It should be kept in mind that modelling may generally still be useful even when information is available from a trial-based economic evaluation, e.g., in order to estimate final outcomes from the intermediate outcomes measured in the trial, or to make extrapolations beyond the trial population or duration. However, the suitability of, e.g., subgroup analyses or modelling will also depend on the availability of appropriate data or evidence, as well as on the availability of appropriate statistical or mathematical models in order to estimate differences in costs or outcomes.

## Outcomes of economic evaluation

The choice of economic evaluation outcome(s) is associated with the type of economic evaluation used, i.e., CCA, CEA, CUA, CMA, CBA or a combination of these. Typically, one or more of the following outcomes or approaches are used when reporting the results of health-economic evaluations:

- Listing the cost and outcomes of each technology in tabular form ({43}, {44}, {16}) (typically used in CCA)
- An incremental cost-effectiveness ratio (ICER) {45} (CEA and CUA)
- An incremental cost-effectiveness plane {45} or efficiency frontier {46} (CEA and CUA)
- The net monetary benefit (NMB) and/or net health benefit (NHB) {47}(CEA and CUA)

The ICER approach is currently the most widely used outcome of economic evaluations. However, the ICER reduces a large amount of information to a single ratio. Therefore, it is recommended that not only any ICER estimates are presented, but also the separate components of any ICER estimates, i.e. the costs, number of life years, HRQoL outcomes, or QALYs associated with each technology, as well as the incremental costs and outcomes with their confidence intervals or credibility intervals {21, 48}. A credibility interval is a form of 'confidence interval' around a cost-effectiveness ratio resulting from an economic model. In contrast to statistical confidence intervals, credibility intervals are generally the result of a mathematical model, which includes assumptions about the relationships between, and distributions of, input variables {48}.

Whether a technology can be referred to as 'cost-effective' depends on its relation to any extant "decision-makers' willingness-to-pay" or "societal willingness-to-pay" for an additional unit of health outcome (so-called 'ICER threshold'). If one main aim of a health system is to maximise health-related outcomes given the resources available, a technology can be considered as being 'cost-effective', i.e. improving economic efficiency in health care, if its ICER estimate is lower than a threshold value (or threshold range). If the estimated ICER is higher than the threshold, the technology is not considered to be cost-effective and hence allocation of resources to this technology would be unlikely to increase economic efficiency in health care {49}. It is recognised that a single ICER threshold value that fits all decisions for all decision-makers does not exist. For some decision-making authorities, the ICER threshold may vary between technologies or diseases, depending on the characteristics of the technology or disease that are not necessarily directly reflected in ICER estimates {6}.

It should also be noted that, if economic efficiency is not a primary concern for the decision-maker, an ICER threshold value approach may not offer much relevant information. Even if this is the case, the impact of a technology on the separate ICER components, such as life expectancy, health-related quality of life and healthcare expenditures (e.g., through Budget Impact Analysis), may be

of prime importance. Indeed, the relevance of a threshold value approach is usually specific to particular jurisdictions and may change over time. In addition, there are wide variations in the extent to which decision processes utilise or implement thresholds, even within jurisdictions and how other factors are taken into account in these processes alongside cost-effectiveness evidence. The relevant outcomes from the ECO domain should therefore generally reflect the context in which the evaluation is likely to be used, as well as the research question(s) posed.

## Tools for critical appraisals

Several published guidelines and checklists for critical appraisal of economic evaluations are available {50}. These guidelines and checklists can be used when reviewing published economic evidence or economic evaluation submitted by, e.g., a market authorisation holder. They also help in conducting and reporting *de novo* economic evaluations. However, it should be kept in mind that these guidelines and checklists usually cannot separate the quality of reporting from the validity of the design and conduct of analyses.

Currently, the most contemporary reporting guidance is the CHEERS statement {51}, which attempts to consolidate and update previously published guidelines (e.g., {52}). In addition, a checklist developed to assess the quality of decision-analytic models used in economic evaluation is available {53}.

These guidelines and checklists are typically used for obtaining an overview of the completeness of reporting and the quality of methodology. However, when undertaking a critical appraisal of economic evaluations, a more detailed descriptive assessment is often required. Compared to the use of checklists, a more detailed descriptive approach enables one to assess the implications that the analyses' strengths and weaknesses have on the credibility and quality of the results. It should also be noted that a thorough critical appraisal is not possible without full technical documentation.

## Analysing and synthesizing evidence

This section contains a description of commonly-used approaches in *de novo* economic evaluation, i.e. economic evaluation which is tailored to informing a specific decision-making problem from the beginning of the process. Each subsection describing *de novo* economic evaluation will start with a *General description* of the topic and will be followed by *Transferability considerations*. When appropriate, links to (indicate) other useful material will be provided under the subheading *Tools*. In the section following this one, *Reporting and interpreting*, a common reporting structure for analyses of costs and economic evaluation will be provided.

## *Study frame for de novo economic evaluation*

**General:** The study frame defines the elements of an economic evaluation which would normally be included in a 'base case' or 'reference case', and the recommended methodology associated with the case. Using a 'reference case' for each economic evaluation is a way to attempt to move towards methodological consistency in undertaking economic evaluations.

**Transferability considerations:** As reference cases are often defined in local guidelines, their content may vary substantially between settings, jurisdictions or healthcare systems. Therefore, in the study frame presented below, the elements usually included in a reference case are listed. For any particular economic evaluation, a 'base case' would entail the assumptions and methodological choices, as set out in a jurisdiction-specific 'reference case' or using the study frame below. A base case would form a starting point for any subsequent sensitivity analysis.

**Tools:** National guidelines. Typical aspects defined in a reference case are listed in the table below.

**Table 3. Elements of economic evaluation usually included in a 'reference case' or 'base case'.**

Elements in an economic evaluation	Clarification
Type of economic evaluation	The chosen type(s) of economic evaluation (e.g., cost-effectiveness, cost-utility, cost-benefit, cost-minimisation or cost-consequence -analysis)
Target population and subgroups	Criteria for defining the patient population and subgroups to which the HTA or economic evaluation applies.
Technologies under assessment	Criteria for defining the technologies under assessment.
Comparators	Criteria for defining the comparators that are included in the HTA or, more specifically, in the Costs and economic evaluation domain.
Resource use and costs	Criteria for identification, measurement and valuation of resource use and costs.
Health-related outcomes	<p>Preferred measure(s) of health effects that are to be used in the analysis or analyses (e.g., QALY, LYG).</p> <p>Preferred source of data for measurement of health-related quality of life, if applicable.</p> <p>Source of preference data for valuation of health-related quality of life, if applicable.</p>
Perspective	The perspective from which costs and health outcomes are to be assessed.
Time horizon	The time frame during which cost and health outcomes are to be assessed.
Discount rate	The rate(s) at which future costs or health outcomes are to be discounted.
Characterising uncertainty	The preferred types of sensitivity analyses (e.g., one-way sensitivity analyses and probabilistic sensitivity analyses (PSA)). Adherence to relevant recommendations for presenting the results of the sensitivity analyses may be applicable.

## Target population

**General:** The target population can be defined in terms of patient characteristics (e.g. demographics, risk factors, life-expectancy and compliance), disease characteristics (e.g. epidemiology, disease severity and case mix) and setting (e.g. community or hospital). The characteristics of the target population may affect both the baseline risk of disease and the capacity to benefit from treatment. Ultimately this can impact both on the estimated treatment effects and also on the estimated costs of care.

The target population should be chosen so as to represent the characteristics of the patient population(s) in the jurisdiction(s) or the healthcare setting for which the economic evaluation is intended. For that reason, the target population in the economic evaluation can be more restrictive than that described in the scope of the rest of the Core HTA. In addition, there is often a need to specify the target population in greater detail in this domain. If a more restricted target population or subgroup is to be used in this domain, it should also be included in the scope of the other domains in order to avoid it being isolated from the rest of the domains, especially the CUR domain.

**Transferability considerations:** Because the characteristics of target populations can vary both across jurisdictions and within national borders, the characteristics of target populations are one of the key features that can limit the transferability of economic evaluation. For example, parameters related to baseline risk typically need to be specific to a population, jurisdiction or healthcare setting.

**Tools:** National guidelines.

### ***Pharmaceutical-specific content***

Typically, the approved indication of the technology under assessment serves as the basis for defining the target population for the economic evaluation.

## Subgroup

**General:** The capacity to benefit from treatment or costs of care can differ in subgroups of patients. The differences in treatment effects are typically caused by differences in their baseline risk of the condition or event under assessment and/or differences in relative treatment effects (e.g. hazard ratio or odds ratio of an event).

In general, any subgroup analyses should be pre-specified in order to avoid unwarranted post-hoc-analysis-driven conclusions (see, e.g., {54}, {55} and the (EFF domain). However, it might not always be possible to identify all important subgroups in the scoping stage of an HTA {56}. It should also be noted that it is possible to specify more subgroups for ECO than for EFF and SAF.

**Transferability considerations:** There might be differences between jurisdictions or healthcare systems in how subgroups are operationalised in routine clinical practice and in informed decision-making.

**Tools:** All the subgroup analyses should be clearly defined and clinically justified. In addition, the methods for conducting subgroup analyses should be described {56}.

There is currently a lack of literature concerning the conduction of subgroup analyses in economic evaluation. However, Sculpher (2008) {56} and Cleemput et al. (2012) {57} provide guidance on the various forms of subgroups and heterogeneity in cost-effectiveness analyses, and how they should be identified.

## Technology under assessment and its comparators

**General:** The comparators in economic evaluation can be chosen from a range of alternatives, e.g., the alternative(s) most likely to be replaced in clinical practice if the technology under assessment is adopted or the next best alternative on the efficiency frontier. When defining the technology under assessment and its comparators, it is also important to state the assumptions being made about practice patterns. For example, does a model assume perfect compliance with medical guidelines, or is the model based on observed treatment mixes which might differ quite markedly between countries.

**Transferability considerations:** Treatment practices and requirements for selecting comparators for economic evaluation vary across jurisdictions or healthcare systems. In any application of economic evaluation it is important to provide a detailed description of the alternatives and justify their choice, so that study users can assess their transferability to their own setting. What represents ‘current practice’ is likely to vary over time and between countries.

**Tools:** REA guideline [for criteria for the choice of the most appropriate comparator\(s\)](#), national guidelines.

### **Screening-specific content**

With regards to screening, it is critical to define the entire screening-programme pathway, i.e., screening intervention and diagnosis, surveillance and treatment, following the screening test or its comparator.

## Resource use and costs

**General:** Costing processes can be usefully divided into three phases: First, the relevant resources used have to be identified, then the volume or number of units of the resource used has to be measured and, finally, these volumes need to be valued. Cost items may be classified in numerous ways, such as the costs of healthcare technologies that are borne by the healthcare sector, other sectors, and patients and families. Time, productivity or wider-economic costs can also be classified separately. The inclusion or exclusion of cost items may depend upon the chosen perspective or analytical approach. An important parallel consideration is, therefore, the choice of the time period for estimating costs, which may also depend on the ability to robustly estimate future resource use (see *Time horizon* for further details).

Costs can be defined to include some or all costs ‘directly’ related to a disease or the use of a technology. They may include costs borne inside the healthcare sector (e.g., materials, equipment, personnel and tests – often referred to as direct healthcare costs), as well as outside the healthcare sector (e.g., patients’ travel time – often referred to as direct non-healthcare costs). A broad agreement exists, on a theoretical level, that all costs related to the disease or technology in question should be included in the analysis. However, the way in which this is applied may vary between jurisdictions or healthcare systems. A particularly debated issue is whether to include the unrelated future healthcare costs or not, such as healthcare costs of other diseases which people experience

when they live longer due to treatment. The answer to the question of whether any such related, or unrelated, future costs should be discounted is associated with the chosen perspective of the analysis and may depend on national guidelines, if such guidelines exist and are considered to be applicable to the Core HTA in question.

An example of one class of costs which may or may not be deemed appropriate in economic evaluations, is what are often referred to as indirect costs. Indirect costs can be defined to include any costs resulting from patient's temporary absence from work due to illness, reduced working capacity due to illness and disability, including reduced productivity while being at work, or lost productivity due to early death. Lost production can be estimated either by means of, e.g., the human capital method or the friction cost method. Lost production is often reported separately and not integrated in the cost estimate used for the calculation of the incremental cost-effectiveness ratio or 'cost-utility ratio'. Valuation and inclusion of such 'indirect costs' should be made in situations where it is judged to be relevant. The concept of lost production should not be confused with a 'transfer payment'-like sickness benefit. Inclusion of transfer payments depends on the perspective of the analysis; they are a cost to the paying organisation (e.g., government), a gain to the recipient, but from a societal point of view, not either a cost or a gain, in static economic evaluation.

Physical units or volumes of resources used should be reported separately from the unit costs of resources to allow other researchers, or decision-makers, to assess how applicable the resource use estimates are to their own setting. In addition, it may be useful to report direct costs separately from indirect costs. It is also useful to adjust all costs to a common price level, e.g., to the year of analysis, using appropriate price inflators or deflators.

**Transferability considerations:** Costs of technologies are generally not transferable from one country to another. However, transferability of individual elements of data differs. Table 4 contains an assessment of transferability for each element. Although the resource utilisation and unit cost elements are only partially transferable or not transferable at all, they are all essential parts of an economic assessment. The relevance of economic evaluations cannot be easily judged without information on these elements. Moreover, data on types and amounts of resources used in one country are often valuable information for researchers performing an HTA in another country. Indeed, information on cost-related consequences of treatment from other settings can therefore often be usefully replaced by, or supplemented with, national data in order to adapt an analysis to a national context.

**Table 4. Transferability of estimated resources and costs**

Data Element	Transferability
What types of resources are used when delivering the assessed technology and its comparators (resource-use <b>identification</b> )?	Partially transferable. In many cases the types of resources will be completely transferable, but this should be tested, if appropriate.
What amounts of resources are used when delivering the assessed technology and its comparators (resource-use <b>measurement</b> )?	Partially transferable. It is well-known that resource utilisation can differ between countries when delivering a specific technology, e.g., the average number of hospital days for a specific procedure may vary considerably. Other types of resource utilisation may vary little between countries. Transferability for this issue is an empirical question that needs to be addressed carefully.
What were the measured and/or estimated costs of the assessed technology and its comparator(s) (resource-use <b>valuation</b> )?	Not transferable. Although some types, amounts or unit-cost prices are comparable between countries, it cannot generally be assumed that the measured and/or estimated costs will be transferable.

**Tools:** For more details on how to handle currency, price date, and conversion see national guidelines and, e.g., {58} as well as {29}, {19}, {59} and {1}.

### **Screening-specific content**

The economic evaluation of a screening programme differs in a number of respects from that of other health technologies. In general, the resources ‘committed’ when introducing screening programmes are substantial, with follow-up and treatment potentially imposing major long-term burdens on healthcare. This encompasses the costs of the screening procedure itself, in a usually large number of people, the costs of follow-up procedures in people with a positive screening result, as well as the costs of organising the programme. Screening is rarely limited to a single screening test, but may include confirmatory tests and subsequent interventions for those with a positive result; the evaluation of a screening programme may need to incorporate other health technologies in the analysis.

When identifying the costs of screening, all the costs associated to the screening programme should be included. This means, that in addition to the costs of screening test itself, the analysis must also include costs of the screening organisation, invitations to screening, further examinations as well as possible treatment costs. In the HTA Core Model, BIA is to be shared between the –ORG domain and the ECO domain. In addition, travel costs to and from the screening location, depending on the chosen perspective, may also be taken into account.

In many cases, the screened populations will be otherwise healthy, working-age people. In that case, the lost time as a consequence of undergoing the screening programme can be considered as lost productivity and be included as a cost in the economic evaluation, depending on the chosen perspective.

## Health-related outcomes

**General:** There are a wide range of health-related outcomes which can usefully be incorporated into an economic evaluation. The choice of health-related outcomes in an economic evaluation depends, to a large extent, on the purpose(s) of the information being produced, with different recommendations existing in different jurisdictions or healthcare systems. For instance, the use of disease-specific measures is often recommended for comparing technologies which address similar health problems. In addition, the use of generic health-state-value or composite measures is also often recommended for comparisons of technologies addressing diverse health problems, as these measures form a more comparable core set of health indicators. The use of a combination of both these types of measures and other measures of health outcome has been widely advocated (see, e.g., {18}, {60} and {61}). The suitability of using one (or more) health-outcome measure(s) depends on the type of technology that is being analysed, as well as on the plausibility of it appropriately describing relevant aspects of health relevant to the study question or decision problem (see, e.g., {61} and {60}).

Although many health-related outcomes are dealt with in the EFF domain, there are health outcomes which are more specific to the ECO domain. Within ECO, some of the terminology used for health outcomes frequently somewhat differs from that used in the EFF and SAF domains. In the health-outcomes literature, the terms 'endpoint' and 'outcome' are often used interchangeably. However, in this domain the term 'outcome' will be used as it is more frequently used and encountered in the health-economic evaluation literature. Further, we will use the term "**surrogate outcome**" instead of the closely-related term, "intermediate endpoint" and the term "**final outcome**" instead of terms such as "true health outcome" or "actual endpoint". The term "**wider outcome**" will also be used to express the renewed interest in considering some of broader effects of technologies, such as the impact of technologies on individual wellbeing and social functioning, innovation, and the impact on other stakeholders, such as family, informal carers, and pharmaceutical industry (see, e.g., {62}, {63} and {64}). Health outcomes may be measured, estimated or valued as changes in clinical indicators, number of health-related events (e.g., cases of diseases or deaths), QALYs or any other effects which could be deemed important to, or by, decision-makers, such as:

- Surrogate outcomes (e.g., mmHg or maximal isometric handgrip strength)
- Final outcomes (e.g., deaths prevented or QALYs 'gained')
- Wider outcomes (e.g., broader effects on other stakeholders or effects on communities at large)

There are also a wide range of ways to estimate or value, for example, health outcomes:

- Measures related to mortality (e.g., 'life-years gained' (LYG))
- Measures of self-rated health (e.g., individuals evaluate their own health status)
- Generic health-status measures (e.g., RAND-36)
- Disease-specific measures (e.g., EORTC QLQ C-30 and UCLA Prostate Cancer Index)
- Health-state-value measures (e.g., EQ-5D, SF-6D, 15D)
- Direct 'utility' measures (e.g., Standard Gamble or Time Trade-Off -approaches)

- Composite measures (e.g., using QALY, DALY, or HYE -approaches)

When conducting economic evaluations, **Direct ‘utility’ measures**, **Health-state-value measures** and **Composite measures** are often used as estimates of the value of health-related outcomes. Hence, the focus of this section will be on these measures. However, this should not be taken as indicating that measures of self-rated health, generic health-status measures or disease-specific measures are of little importance to economic evaluation. On the contrary, it is widely recognised that multiple health outcomes are useful and necessary complements to the composite measures often used in economic evaluations (see, e.g., {65} and {61}).

### Composite measures

One of the most widely-used forms of health outcomes are the composite measures referred to as QALYs. QALYs refer to a type of outcome measure that takes into account both aspects of quantity (longevity/mortality) and aspects of quality of life (morbidity, psychological, functional, social, and other factors) {69}. QALY approaches can be considered as an important set of health outcomes when technologies affecting a wide range of medical conditions are being compared. Rather than being just one approach, QALYs can be both ‘preference’ based and, e.g., ‘social-value-of-health’ based {15}. The valuation of health states is generally dependent on the method or methods used to obtain such ‘utility’ estimates. The valuations for use in QALY approaches can be both through HRQoL measures and/or through direct elicitation using approaches such as the Standard Gamble (see *Health-state-value measures* and *Direct ‘utility’ measures* for further details).

**Transferability considerations:** The QALY-approach and similar approaches can be seen as useful in policy analysis and decision-making processes because they are generic and can consequently facilitate broad comparisons between technologies and across diseases. In order to usefully facilitate comparisons across diverse technologies, care should be taken that the same methodology is being used and applied consistently. It is also important to note that using QALYs as an outcome measure in economic evaluations has both methodological and practical weaknesses. Despite QALYs currently being the most widely-used health-related outcome in health economic evaluation it may not always be considered to be the most useful or appropriate measure of effectiveness (see, e.g., {91} and {92}).

**Tools:** Further details related to health outcomes can be found from the **Clinical effectiveness** domain. Many relevant issues related to HRQoL have also been dealt with in the guideline which gives general recommendations related to HRQoL that are applicable to Relative Effectiveness Assessment (REA) of pharmaceuticals (Endpoints used for relative effectiveness assessment of pharmaceuticals: [Health-related quality of life and utility measures](#))

### Health-state-value measures

Health-related quality of life (HRQoL) refers to aspects of quality of life that are related to health. Different health-state-value measures can be used to estimate HRQoL and there is no single measure which has been accepted as a gold standard. Health-state-value measures, also referred to as indirect ‘utility’ measures, are generic instruments capable of providing single-index scores suitable for the calculation of QALYs. These generic instruments include the AQoL (Assessment of Quality of Life), EQ-5D (EuroQol), 15D, HUI (Health Utilities Index Mark II/Mark III), QWB (Quality-of-Well Being Scale), and SF-6D (based on a selection of questions from the RAND-36 or SF-36 survey instruments). Single-index HRQoL scoring systems combine the answers from individual questions into a single index number (usually ranging between 0 and 1, although negative scores for states do occur, e.g., when using the UK-TTO scoring system of the EQ-5D-3L) {66}.

## **Direct 'utility' measures**

A direct 'utility' measure, or direct preference elicitation technique, is one which values health states without using the intermediary of a descriptive system. The main methods include standard gamble (SG), time trade-off (TTO) and visual analogue scale (VAS), but related methods include, e.g., person trade-off (PTO) and discrete choice experiments (DCE). These techniques generally ask respondents to make choices between two hypothetical situations, or indicate relative value, and then derive 'utility' values for health states based on the responses. The choice between these preference elicitation techniques, the way they are administered, and the context in which they are used, all have important implications for the validity and reliability of the estimates of 'preference' or 'utility' elicited {66}.

### ***Screening-specific content***

An economic evaluation of a screening programme may be able to take the following into account in a useful way: the sensitivity and specificity of the screening technology; the number of positive and negative results (true and false, i.e. positive predictive value PPV and negative predictive value NPV); and the implications of false-positive and false-negative results. The potential benefits of screening include a more timely diagnosis, thus allowing more timely treatment with associated reductions in morbidity or mortality. Some of the potential harms of screening include the false-positive results which are commonly associated with screening modalities; anxiety associated with the screening process; the possibility of overdiagnosis (detection of cases that would not have caused a problem during the remaining lifetime of a person screened) and the associated possibility of overtreatment. In addition to the above considerations, taking into account both the direct cost of the screening modality, as well as any potential reductions in costs associated with changes in morbidity or mortality due to screening, should be considered.

Screening programmes differ fundamentally from the situation where a patient seeks care due to symptoms, as screening is usually targeted to populations who are mostly healthy. This implies that these ostensibly 'healthy' people may become patients due to the screening results and thus the effect of screening on their utility may be significant, although data on such effects is fairly limited {67}. Screening may cause anxiety and concern, especially in the case of false-positive test results. Hence, another issue to be considered is the incorporation of 'utilities' in the analyses. Since screening targets populations which are asymptomatic with respect to the target condition, screening programmes profoundly differ from a situation where a patient seeks care due to symptoms. Otherwise healthy people may receive a feared or stigmatising diagnosis due to their screening result and thus the effect of screening on their utility may be significant. Economic evaluations of screening programmes should consider incorporating any potential reduction in utility associated with a positive screening result as well as the change in utility associated with a negative result, e.g., increase in utility due to justified relief (or decrease in utility due to unjustified relief in case of a false-negative screening result). The effects on patients' utility or HRQoL of screening results are still not well known, yet some qualitative evidence exists, from cancer screening studies, that false-positive screening results, including abnormal findings, have a negative impact on certain psychosocial domains (see, e.g., {67} and {68}).

Furthermore, false-positive and false-negative test results may have impact on peoples' behaviour, and this in turn, may change, e.g., the resulting effectiveness of the technology. The investigation of such issues has been fairly limited thus far, although some implications may exist that false-negative test results might lead to more risk-taking behaviour (e.g., a person who gets a low cholesterol reading may choose a less healthy diet). Researchers should consider such possible effects and try to assess their impact (e.g., how any ICER might change if false negative screens changes people's behaviour in a specific direction).

Screening models are often more complex than models dealing with only diagnostic or curative technologies, because screening targets the early stages of a disease. This often leads to the need to model the natural history or pathogenesis of the whole disease, often with very limited empirical data. Evidence is rarely available directly from RCTs of screening programmes but rather has to be evaluated from ‘linked’ or ‘chained’ evidence. The generalisability of clinical trial data may be limited due to the range of choices concerning the preferred screening test, screening interval, the eligible population and the organisation of the screening programme. There may also be difficulties in extrapolating benefits from clinical trial data due to the extended time interval between screening and the development or progression of the condition of interest {67}.

## Study perspective

**General:** The chosen perspective of an economic evaluation is a key element in defining which costs and consequences are included in the analysis; a second key element is the analytical perspective used by researchers or analysts {1}. For instance, the choice of perspective affects the way of handling direct and indirect costs (including, e.g., productivity losses).

The chosen type of perspective often depends on the purpose of the information being produced, regarding costs and economic evaluation. Welfare-economic theory suggests that economic evaluation should be conducted from the most comprehensive perspective possible, where all relevant costs and outcomes of the technologies have to be identified, measured and valued, no matter onto whom these costs and consequences fall. However, the way in which ‘the societal perspective’ is defined varies, e.g., between healthcare systems and between pragmatic applications (see, e.g., {44} and {1}).

Other possible perspectives include those of a specific institution, individual patients, or the target group for a specific technology. If the purpose is to inform societal resource allocation, it may be most appropriate to take a societal perspective. For hospital HTA, the perspective of a particular hospital organisation may be more appropriate. If information from the ECO domain is intended to improve decision-making within the healthcare sector, an appropriate viewpoint may be, e.g., a ‘healthcare payer’ (either public, private, or both), or a ‘healthcare sector’ perspective (see, e.g., {1} and {69}), or even a ‘societal perspective’.

**Transferability considerations:** The perspective of the study is of fundamental importance for its transferability. Care should be taken that the perspective is appropriate with respect to the purpose for which the information is produced.

**Tools:** National guidelines, sensitivity analysis and reasoning concerning the appropriateness for the decision problem.

## Time horizon

**General:** An important consideration is the choice of the time period, i.e., the choice regarding for how long costs and effects should be measured or estimated. The length of the time horizon may depend on the perspective of the economic evaluation, which in some cases may extend to the expected remaining lifetime of the patients or population under investigation. The modelling of longer-term costs and effects should take into account their potential importance for the analysis, the burden of undertaking such analyses, as well as relevant guidelines for economic evaluation. For certain technologies, such as the use of DDT for the prevention of malaria, the effects of a program may even require a time horizon that extends beyond the current generation. Although it should be

noted that the time horizon of a study may be effectively limited by the use of discounting, as future costs and effects of the technology (see *Discount rate* for further details) {44}.

**Transferability considerations:** In order to promote comparability between analyses, the time horizon of the economic evaluations should extend far enough into the future to capture the main costs and effects, both intended and unintended, of the assessed technology and its comparators. However, as the appropriate time horizon often extends beyond the availability of primary or secondary data, modelling may be the only way to obtain estimates of longer-term costs and effects. Justification should always be provided for the modelling undertaken, and for the choice of time horizon. It is usually informative to analyse the data using different time horizons, e.g., a shorter-term horizon that includes only primary data and a longer-term horizon that also incorporates modelled data ({51} and {44}).

**Tools:** National guidelines, sensitivity analysis and reasoning concerning the appropriateness for the decision problem.

## Discount rate

**General:** Economic theory suggests that costs and outcomes that occur in the future should be discounted (see, e.g., {1}, {70}, {71} and {72}). Discounting, i.e. calculating the present values of future costs and consequences, may help in the comparison of health technologies whose costs and outcomes do not occur at the same time. The decisions to be made are; whether to discount both costs and effect or not; which discount rate to use; and should both costs and effects be discounted using the same discount rate?

In the use of many technologies the costs are incurred within a relatively short time period, whereas the benefits (e.g., life-years gained) may not be accrued for many years. This is in contrast to many curative technologies, where both the costs and the effects occur within a relatively short time period. The impact of discounting in economic evaluation is often substantial and this means that the questions related to discounting need to be carefully examined. By attaching a lower weight to future health outcomes, preventive health care is likely to appear to be less cost-effective because such technologies typically involve current costs and future effects.

**Transferability considerations:** Different perspectives, e.g., healthcare sector, or a more general, public-sector perspective, may differ in terms of the application of discount rate(s) (see, e.g., {73}). In addition, there may also be differences in the applicable discount rate(s) between different forms of economic evaluation, e.g., CBA and CUA {71}, as well as the differences in the recommended discount rate(s) which exist between country-specific guidelines.

**Tools:** Decisions regarding discounting should be reported with clear reasoning or justification and, where relevant, according to available, e.g., country-specific guidelines. The use of thorough sensitivity analyses concerning variations in discount rates is particularly advisable when a time horizon of extended duration is used.

## Characterizing uncertainty

**General:** In economic evaluation, there are numerous sources of uncertainty and these can be characterised in different ways. In decision-analytic models, uncertainty is commonly classified into stochastic uncertainty, parameter uncertainty, heterogeneity and structural uncertainty {37}. However, these terms are used in a variety of ways by different authors. In an attempt to avoid such confusion, it has been recommended that authors carefully define the terminology that they use when reporting their results {37}.

**Stochastic uncertainty** refers to random variability in outcomes between identical patients {37}. It has also been called first-order uncertainty.

**Parameter uncertainty** usually refers to uncertainty in the estimation of the parameter(s) of interest {37}. Parameter uncertainty has also been called second-order uncertainty. Parameter uncertainty can be usefully investigated via both probabilistic (PSA) and deterministic sensitivity analyses (DSA).

**Heterogeneity** relates to variability between patients that can be attributed to characteristics of those patients {37}. Heterogeneity has also been called variability. Heterogeneity is described using subgroup analyses (see section **Subgroup** for more details).

**Structural uncertainty** refers to uncertainty about the extent to which a model adequately captures the relevant characteristics of the health condition and technology under evaluation {74}. Structural uncertainty has also been called model uncertainty. Since models are always simplifications of a complex reality, testing structural uncertainties is likely to be difficult in some cases. However, it may be possible to parameterise some of the structural uncertainties into the model, conduct scenario analysis, or utilise alternative model structures.

In addition, **methodological uncertainty** is a specific type of uncertainty that relates to methodological choices that are part of economic evaluation {75}. These include the study perspective, discount rate(s), time horizon, the way health effects are valued, and so on. Methodological choices often relate to both the disease and to the research question, but are often based on local guidelines, and many aspects of methodological uncertainty can be resolved by making use of a 'reference case'.

**Transferability considerations:** In terms of transferability, sensitivity analyses are likely to be more informative than the base-case analyses *per se*. It might be particularly informative to conduct univariate sensitivity analyses to identify parameters which may have substantial impact on the results of economic evaluations.

The extent to which uncertainty analyses are included in prior economic evaluations is likely to depend, e.g., on the type of decision that the economic evaluation seeks to support, or on the requirements defined in national guidelines. From the transferability point of view, it is useful to undertake a full set of sensitivity analyses so that different researchers or decision-makers are more easily able to choose the information they require for their work. Since the requirements and methods of economic evaluation differ across jurisdictions or healthcare systems, it is also useful to address methodological uncertainties via sensitivity analyses when reporting.

**Tools:** Deterministic and/or probabilistic sensitivity analyses should be an integral part of an economic evaluation (see, e.g., {18}, {48}). General guidance on uncertainty estimation has been published in a number of sources (see, e.g., {74}, {75}, {76} and {77}).

## *Other considerations*

### **Transferability of evidence concerning costs and economic evaluation**

Many terms have been used to describe the extent to which the results of existing studies are likely to reflect the results expected in the population of interest in different jurisdictions or healthcare systems {78}. These terms include generalisability, applicability, relevance and external validity. However, in the field of economic evaluation, transferability appears to be the most commonly used term to describe this issue (see, e.g., {39}, {7} and {79}). Also the term generalisability is used {80}.

According to Barbieri {7} economic evaluations can be considered generalizable, transferable or non-transferable. Studies are considered generalizable if their results and conclusions can be applied to a range of jurisdictions or healthcare systems without any adjustments. Studies are transferable if they can be adapted in order to be applicable in other settings. Finally, some economic evaluations are so specific to, e.g., a given jurisdiction, that they simply are not able to be transferred to any other jurisdiction.

There are many potential causes of variation in the results of economic evaluation between locations. Factors potentially affecting transferability of economic data include {81}:

- Patient characteristics (e.g., demographics, risk factors, life expectancy or ‘utilities’)
- Disease characteristics (e.g., incidence, severity or case-mix)
- Population characteristics (e.g., variations in the health-state values used to form quality weights for the calculation of QALYs)
- Provider characteristics (e.g., clinical practice or quality of care)
- Healthcare system characteristics (e.g. available treatment options or unit prices)
- Methodological characteristics (e.g., study perspective or discount rate).

These factors are discussed in more detail, for example, in the papers by O’Brien {82}, Sculpher et al. {80} and Goeree et al. ({81} or {79}), and in the *Analysing and synthesizing evidence* section of this domain text.

Even though some aspects of economic evaluation can be highly context-specific, there is, for example, scope for transferring the following elements of information concerning costs and economic evaluation to other settings:

- The types of resource consequences considered
- Structure of the decision-analytic or other models
- Relative effect measures (e.g., hazard ratio [HR], risk ratio [RR])
- Available work related to model validation
- Results of literature reviews (i.e., reviews of existing economic evidence and reviews of other pertinent evidence to populate an economic model)

Transparency in reporting costs and economic evaluation is critical in allowing the transferability of economic evaluations performed as part of an HTA which is going to be assessed for different settings. There are many approaches and applications for assessing the transferability potential of economic evaluations. These include EUnetHTA's [HTA adaptation toolkit](#) and other approaches that have been identified and described in the review by Goeree et al. {79}.

Analytic strategies for dealing with aspects of transferability are different for model-based and single-study-based economic evaluation. These methods have been described in a number of articles (see, e.g., {83}), and are covered in more detail in *Model-based economic evaluation* and *Single-study-based economic evaluation* sections of this work.

## Assumptions

There are many types of assumptions and simplifications that have to be made in the course of economic evaluation, especially when it is model-based. These include, for example, assumptions related to the extrapolation of treatment effects, model structure, definition of treatment and disease processes, and the extent of correlation between individual parameters in the model. In general, the assumptions made affect the results of economic evaluations and should always be reported in a transparent way, and clearly justified. It is also important to investigate, e.g., using sensitivity analysis, the ways in which assumptions affect the results of economic evaluations and how assumptions may affect the interpretation of results.

In order to increase transferability, all assumptions can be systematically presented, e.g., in a tabular form, and can include appropriate reasoning and all references to support the assumptions made. If statements are made concerning the 'conservative' nature of assumptions, these statements too should include appropriate reasoning and all references to support such claims. For example, an important assumption concerns the modelling of current practice: Does the model under consideration adhere perfectly to existing medical guidelines, or is the potential impact of non-adherence to such guidelines also taken into account? Appropriate assumptions may vary greatly between settings or depend on the research question.

When there are alternative plausible assumptions, sensitivity analyses or scenario analyses should be undertaken to assess their effects on the results of economic evaluation. See section *Characterising uncertainty* for more details.

## Model validity

To fully evaluate how the results of a model should be used, model users would need to be able to know how well the model predicts the outcome(s) of interest. To be able to do this, the model needs to be reported in a transparent way and validated.

In this context, transparency means that model users can see how the model was built and, here, validation relates to the methods of evaluating how accurate a model is in making relevant predictions or abstracting from a complex reality. Five main types of validation have recently been described: face validity, verification (or internal validity), cross validity, external validity and predictive validity {38}. In comparative analysis of alternative technologies, one of the key questions is how well the model predicts health outcomes (external and predictive validity). Therefore, validation is recommended in cases where it is possible, e.g., using a relevant data set.

It should be noted that sensitivity analyses can be used to explore how input variation changes the results of the model. However, sensitivity analyses alone do not evaluate how accurately any modelling processes used within the economic evaluation model predicts the outcomes of interest.

Often the same model structure is used for different jurisdictions or healthcare settings and the economic evaluation model is merely localised (e.g., by the substitution of parameter values). If the validity of the model has been investigated, and the results of validation have been transparently reported, this is often useful to others using or assessing the same model, even when the requirements for model validation may vary between jurisdictions.

The health effects predicted by the model are often at least partly transferable between populations, in many instances due to the same underlying biological processes. For that reason, the results of external and predictive validation (of health effects) may apply from one population to another. In contrast, practice patterns (which may not always impact greatly on health effects) and unit costs can vary widely across settings. For that reason, predictive and external validation of model components related to resource use and costs is problematic. From the point of view of transferability, issues such as the face validity of the technology and its chosen comparator(s); the estimated costs and consequences, could be usefully checked with clinical or organisational experts, e.g., that the model includes all aspects of resource use and costs considered important.

A task force appointed by the ISPOR and SMDM has recommended the best practices for making models transparent and for validating them {38}.

## **Biases, confounding factors, level of evidence**

The parameters related to EFF and SAF are key inputs used in economic evaluation. For that reason, the quality of evidence and the validity (or risk of bias) of these estimates should be explicitly stated. Validity describes the extent to which a result is likely to be ‘true’ and free of bias. ‘Quality of evidence’ is a wider concept that reflects the extent of our confidence that the estimates of the effect are ‘correct’ {84}. Further details on the assessment of internal validity (or risk of bias) and rating the quality of the body of evidence are available from the EFF and SAF domains and from the [REA-guideline of internal validity of randomised controlled trials](#). On the other hand, the extent to which model parameters need to be appraised is difficult to define *a priori*, since different organisations, authorities or jurisdictions may consider the importance of parameters differently.

## **Identifying future research needs from the evidence**

While conducting literature reviews and economic evaluations, evidence gaps are likely to be identified. To inform policy decisions about future research priorities, formal value-of-information (VOI) methods can be used when answering questions such as {85}:

- What parameters appear to have the biggest impact on the decision problem?
- Is further research required to support the use of a technology?
- What type of research would be most valuable?
- Which patient subgroups should be included in subsequent research?
- Which comparators and endpoints should be included, and what length of follow up would be most valuable?

VOI-analyses use probabilistic sensitivity analyses, and they can be conducted as a part of cost-effectiveness analyses. The methods have been described in detail elsewhere (see, e.g., {86}, {87} and {77}). Although the results of VOI analysis are potentially important in decision-making, their suitability depends on a number of strong assumptions and on the availability of skilled analysts to undertake the analysis. In addition, institutions that produce HTA-reports are not usually the same institutions which commission future research. For these reasons, VOI approach may not always be appropriate.

It should also be kept in mind, that because VOI analyses are based on probabilistic cost-effectiveness analyses, the same transferability considerations also apply (see *Transferability of evidence concerning costs and economic evaluation* for more details).

## Reporting and interpreting

This section aims to facilitate transparent and structured reporting of *both* the methods used to derive the results *and* the results themselves. The methods used in literature reviews of economic evaluations, *de novo* analysis or critical review of *de novo* analysis should be reported in the domain's *Methodology* section. Similarly, the result cards for each of the assessment elements can be used when reporting results of literature reviews, *de novo* analysis or critical review of *de novo* analysis.

When economic evaluation is part of a project aiming to produce Core HTA information, it is practical to conduct and report the evaluation so that it reflects the characteristics of a specific jurisdiction(s) or healthcare system(s) (see the section *Transferability of evidence concerning costs and economic evaluation* for more details). However, full technical documentation of the model, including its structure, components, equations, and possibly even programming code or modelling files, should be made available in the core HTA database. This would facilitate the use of core HTA information in national analyses and may enable reproduction of the model so that it can be applied in other settings.

Transparency and structure in reporting ensures that economic evaluations are organised consistently and presented thoroughly in order to facilitate assessment of both validity and transferability. Work Package 7 of the EUnetHTA Joint Action 2 will develop guidelines as to how economic evaluations can be undertaken and presented in a way that makes them useful for as many European countries as possible. We intend to subsequently update the text here to correspond to these guidelines.

## ***Literature review***

If a literature review has been undertaken to identify existing economic studies, the methods of the review should be reported in sufficient detail to enable the review to be reproduced. The methods of the literature review should be reported in the domain's *Methodology* section, e.g., under the heading 'Review of existing economic studies'. It is suggested that when reporting methods of a literature review, the following subheadings should be followed as closely as possible:

- Eligibility criteria
- Literature search
  - Including the search strategies for individual databases
- Study selection and data collection
  - A copy of the data extraction can be included
- Additional analyses

There is no separate results card within the ECO domain for literature reviews. Instead, the results related to study selection, and characteristics of included studies should be reported in the domain's appendices under the heading 'Results of review of existing economic studies'. It is suggested that the following subheadings are used:

- Study selection
  - Including a flow chart of included and excluded studies
- Summary of existing economic studies
  - It is suggested that characteristics (e.g., authors, country, type of economic evaluation, target population, technology, comparators, perspective, time horizon and discount rate) of the included studies are presented in tabular format, whenever practical

In addition, the detailed results of literature review that relate to identification, measurement and valuation of resource utilisation (E0001, E0002, E0009), measurement and estimation of outcomes (E0005), examination of costs and outcomes (E0006), uncertainty (E0010), heterogeneity (E0011) and validity of models (E0012) should be reported in the associated result cards under the heading 'Results of review of existing economic studies'.

## *De novo analysis and critical review of de novo analysis*

When reporting the methods and results of *de novo* economic evaluation, the recommendations of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement could be followed {51}; the associated checklist is also recommended {88}. In the domain's *Methodology* section, the methods used in the base-case analyses should be described under the heading 'De novo analysis' or 'Critical review of *de novo* -analysis'. It is suggested that following subheadings are used, when applicable:

- Target population(s)
- Subgroup(s)
- Setting and location
- Study perspective(s)
- Comparator(s)
- Time horizon(s)
- Discount rate(s)
- Choice of health outcome(s)
- Measurement of effectiveness
- Measurement and valuation of preference based outcomes
- Estimating resources and costs
- Currency, price date, and conversion rate
- Choice of model
- Assumptions
- Analytic methods
- Summary of all study parameters

The details of **methods** that relate to sensitivity analysis (and VOI, if applicable), subgroup analysis and validation should be reported in the methods section of the relevant results cards (based on assessment elements E0010, E0011 or E0012, respectively).

The **results** of any 'base case' analysis, sensitivity analysis (and VOI, if applicable), subgroup analysis and validation are reported in the results cards of this domain.

If economic evaluation submitted by, e.g., a market authorisation holder is critically appraised, each of the above mentioned sections can be further divided into 'submitted evidence' and 'critique of the submitted evidence'. In the result cards, 'critique of the submitted evidence' can be placed in the discussion section of the card. If any checklists for critical appraisal of economic evaluations were used, these can be included in the appendices.

## Comparison of costs and outcomes

Different jurisdictions or healthcare systems have different approaches for conducting and reporting the results of economic evaluations, e.g., decision-makers might put different weights on gains in life expectancy or other health-related outcomes. For that reason, it is recommended that the results should first be presented in as disaggregated a format as possible.

- For costs, it is suggested that the results are presented in a disaggregated format that allows different viewpoints (e.g., patient, third-party payer, hospital, societal) to be separated.
- For health outcomes, it is suggested that the estimates are expressed in natural units first, wherever possible, before translating them to alternative units such as QALYs.
- Consideration should also be given to separately presenting costs and outcomes associated with different stages of the disease.
- Both the discounted results and results without the application of discounting should be shown.
- For ICER, the alternative-specific-components of numerator (cost of each alternative) and denominator (outcomes of each alternative) should be shown.

## Characterising uncertainty

The reporting of uncertainty analyses should be tailored to inform the decision-making situation the economic evaluation seeks to support {37}. On the other hand, especially when using the HTA Core Model, reporting a full set of sensitivity analyses may help in assessing the transferability of economic evaluations to other settings.

The results of deterministic sensitivity analyses (DSA) can be shown, for example, in tabular form or using Tornado diagrams. The results of probabilistic sensitivity analyses (PSA) can be presented using either confidence ellipses and/or scatter plots on cost-effectiveness planes, cost-effectiveness acceptability curves (CEAC) or using cost-effectiveness acceptability frontiers (CEAF) {29, 89}.

When reporting the results of uncertainty analyses it may be useful to follow the recommendations of the ISPOR-SMDM Modelling Good Research Practice Task Force {37}. This document also includes more about the ability for the different approaches to gauge aspects of the uncertainty surrounding economic evaluation.

## Characterising heterogeneity

The results should be given for all subgroups analysed. For ICER estimates, the components of numerator (cost of each alternative) and denominator (outcomes of each alternative) should be shown.

## **Model validation**

The report should describe the process of validation and the types of validation addressed in the model, in order to help assessment of validity.

It would be valuable if the results of validation included at least the following:

- How well the model predicts health effects
- Whether the model includes all important aspects of resource use and costs considered important (by, e.g., clinical or organisational experts )
- Estimates of the potential direction or potential magnitude of bias induced (e.g., has sensitivity analysis been conducted concerning validity-related assumptions)
- An attempt to identify key factors that could compromise the validity of the model (e.g., the extrapolation technique used, structural assumptions in the model, base-case parameters)

## Assessment elements

E0001 Assessment element card						
Issue: What types of resources are used when delivering the assessed technology and its comparators (resource-use identification)?						
Topic: Resource utilisation						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	1
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	1
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	1
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	1
Clarification	<p><b>Common to all used applications</b></p> <p>Report the resource items taken into account for each technology, as well as the sources of information used when identifying these and the reasons for their inclusion. Providing the results in tabular form is recommended.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Healthcare registers and databases, RCTs with resource utilisation data, reimbursement databases, micro-level costing studies/ABC-costing studies. Data may be available from different registers, and sources e.g., on sick leave, sickness allowance, patient administration systems/ clinical databases, earlier studies, cost diaries.</p>					
References	<p><b>Common to all used applications</b></p> <p>Gold et al. {59}; Drummond et al. {1}; CADTH {18}; Kristensen and Sigmund {3}; Cleemput et al. {57}; Husereau et al. {51}.</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>A0011, A0024, A0025; B0007, B0008, B0009; D0010, D0014, D0023;                      F0012; G0001, G0003, G0004, G0005, G0006, G0007; H0003, H0010</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>G0010</p>					

<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>A0024, A0025; B0007, B0008, B0009; D0010, D0023; G0001</p>
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<p>E0002 Assessment element card</p> <p>Issue: What amounts of resources are used when delivering the assessed technology and its comparators (resource-use measurement)?</p> <p><b>Topic: Resource utilisation</b></p>						
<b>Application-specific properties</b>	<b>Application</b>	<b>Used</b>	<b>Importance</b>	<b>Transferability</b>	<b>Core</b>	<b>Order</b>
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	2
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	2
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	2
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	2
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Report the parameters required to estimate overall costs (E0009). Include the appropriate values, ranges, probability distributions, as well as all references used. Providing the results in tabular form is recommended.</p> <p>Report the approach(es) and data source(s) used to measure resource use associated with the technologies.</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Healthcare registers and databases, RCTs with resource utilisation data, reimbursement databases, micro-level costing studies/ABC-costing studies</p>					
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Gold et al. {59}; Drummond et al. {1}; CADTH {18}; Kristensen and Sigmund {3}; Cleemput et al. {57}; Husereau et al. {51}.</p>					
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>E0001</p>					
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>E0001</p>					

E0009 Assessment element card

Issue: What were the measured and/or estimated costs of the assessed technology and its comparator(s) (resource-use valuation)?

Topic: Resource utilisation

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	3
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	3
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	3
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	3
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>For each technology report, provide mean values of estimated costs and, where possible, information concerning distributions surrounding these estimates. Cost estimates from different viewpoints can be reported here (e.g., patient, hospital, societal). In addition, reporting disease-stage-specific cost estimates and costs estimated using varied discount rates. It is recommended to provide the results in tabular form.</p> <p>Report the approach(es) and data source(s) used to estimate the costs associated with the technologies.</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Market prices, companies, hospital accounting or reimbursement systems, as well as micro level costing studies/ABC-costing studies, or other information on unit costs.</p>					
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Gold et al. {59}; Drummond et al. {1}; CADTH {18}; Kristensen and Sigmund {3}; Cleemput et al. {57}; Husereau et al. {51}.</p>					
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>E0001, E0002</p>					
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>E0001, E0002</p>					

D0023 Assessment element card						
Issue: How does the technology modify the need for other technologies and use of resources?						
Topic: Resource utilisation						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	4
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	4
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	4
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	4
Clarification	<p><b>Common to all used applications</b></p> <p>New (less invasive) interventions may reduce the need for surgical interventions. Some treatments require ongoing monitoring and healthcare visits, including hospitalisation.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>Screening tests may cause further diagnostic testing and different treatment due to having detected the disease at an earlier stage.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Trials and pharmaco-economic studies, guidelines on utilisation of resources. Observational studies, statistics</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>B0013, E0001, E0002, E0009, F0003, G0001, G0003, G0004, G0007</p>					
Sequential relations	<p><b>Common to all used applications</b></p> <p>G0001, G0003, G0007</p>					
Other domains	Also in: Organisational aspects					

G0007 Assessment element card

Issue: What are the likely budget impacts of implementing the technologies being compared?

Topic: Resource utilisation

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	None	Yes	5
	Medical and Surgical Interventions (3.0)	Yes	Critical	None	Yes	5
	Pharmaceuticals (3.0)	Yes	Critical	None	Yes	5
	Screening Technologies (3.0)	Yes	Critical	None	Yes	5
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Whenever a technology is introduced, there will be an impact on health care budgets. It is possible to undertake a budget impact analysis which attempts to examine the likely impact of introducing a technology on finances or budgets from e.g. the perspective of different payers. Different payers include: government-level institutions; regions; municipalities; employers; insurance companies and patients/participants. The relevant perspective from which to estimate budget impact may change during different phases of the management process, and incentives are connected to this issue.</p> <p>For example: What kind of incentives does the budget impact impose on different actors? How might this potentially impact on each organisation? What is the estimated net financial (e.g. annual) cost of introducing the technology? Budget impact analysis provides data to inform an assessment of the affordability of a technology. It also provides a service planning tool to inform decisions about taking the technology into use.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>The relevant 'payer' can change during the screening process (e.g. a municipality pays for the screening test but then a hospital district pays for further investigations). Screening is usually free of charge for people, but sometimes participants have to pay e.g. a hospital fee for further investigations. Note that when initiating a new screening programme, initial cost outlays may be necessary.</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Literature searches, reports questionnaires and interviews of different actors of the screening process (monitoring authorities, hospitals, hospital districts, laboratories), as well as information from manufacturers.</p>					
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Kristensen and Sigmund, 2007 {14}; Sullivan et al., 2014 {28}, both from the ORG domain</p>					

<b>Content relations</b>	<b>Common to all used applications</b> A0011; B0007, B0009, B0012; D0023; F0012
<b>Sequential relations</b>	
<b>Other domains</b>	Also in: Organisational aspects

E0005 Assessment element card

Issue: What is (are) the measured and/or estimated health-related outcome(s) of the assessed technology and its comparator(s) (outcome identification, measurement and valuation)?

**Topic: Measurement and estimation of outcomes**

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	6
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	6
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	6
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	6
Clarification	<p><b>Common to all used applications</b></p> <p>For each technology, report mean values of estimated effects and, where possible, information concerning distributions surrounding these estimates. It is suggested that estimates are expressed in natural units first, whenever possible, before expressing outcomes in alternative forms such as QALYs.</p> <p>Report the approach(es) and data source(s) used to estimate the health-related outcomes associated with the technologies, in a way which makes the identification of relevant health-related outcomes transparent. The measurement or estimation of health-related outcomes should reflect the information available from the SAF domain and the EFF domain, or should be otherwise justified. The valuation of health-related outcomes should also be reported in a transparent manner.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>An estimation of the incremental or other effects can be based on information provided in the EFF domain (e.g., mortality data) or on information from the SAF domain (e.g., morbidity data related to adverse events). Additional information collection may be needed (e.g. on health-related quality of life indices). The incremental effectiveness may result from an economic model, where inputs from the EFF domain are used.</p>					
References	<p><b>Common to all used applications</b></p> <p>Gold et al. {59}; Drummond et al. {1}; CADTH {18}; Kristensen and Sigmund {3}; Cleemput et al. {57}; Husereau et al. {51}; Williams {60}; Johannesson et al. {61}.</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>A0004, A0005, A0006, A0009; C0008, C0002, C0004, C0006; D0001, D0003, D0005, D0006, D0007, D0011, D0012, D0013, D0029; F0003, F0010, F0011; H0100</p>					
Sequential relations						

E0006 Assessment element card						
Issue: What are the estimated differences in costs and outcomes between the technology and its comparator(s)?						
Topic: Examination of costs and outcomes						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	None	Yes	7
	Medical and Surgical Interventions (3.0)	Yes	Critical	None	Yes	7
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	7
	Screening Technologies (3.0)	Yes	Critical	None	Yes	7
Clarification	<p><b>Common to all used applications</b></p> <p>For each technology, report mean values of estimated costs and effects together. There are numerous ways of highlighting or comparing the differences in the costs and effects of the technologies under assessment.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Typically, one or more of the following outcomes or approaches are used when reporting the results of health-economic evaluations:</p> <ul style="list-style-type: none"> <li>• Listing the cost and outcomes of each technology in tabular form</li> <li>• An incremental cost-effectiveness ratio (ICER)</li> <li>• An incremental cost-effectiveness plane or efficiency frontier</li> <li>• The net monetary benefit (NMB) and/or net health benefit (NHB)</li> </ul> <p>Report the approach(es) and data source(s) used to estimate the of costs, outcomes, or economic evaluation(s) associated with the technologies.</p> <p>Relevant sources of data and evidence are specified in the relevant issues under the SAF, EFF and ECO domains (bringing together the information collected in assessment elements E0009 and E0005). For example, ICER estimates from a de novo economic model could be reported, synthesising inputs from SAF, EFF and ECO.</p>					
References	<p><b>Common to all used applications</b></p> <p>Gold et al. {59}; Drummond et al. {1}; CADTH {18}; Kristensen and Sigmund {3}; Cleemput et al. {57}; Husereau et al. {51}; Briggs et al. {26}; Glick et al. {29}; Johannesson et al. {61}.</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>E0001, E0002, E0005, E0009</p>					

<b>Sequential relations</b>	<b>Common to all used applications</b> E0001, E0002, E0005, E0009
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E0010 Assessment element card						
Issue: What are the uncertainties surrounding the costs and economic evaluation(s) of the technology and its comparator(s)?						
Topic: Characterising uncertainty						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	8
	Medical and Surgical Interventions (3.0)	Yes	Important	Partial	Yes	8
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	8
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	8
Clarification	<p><b>Common to all used applications</b></p> <p>Report the effects of uncertainty should be separately for structural, methodological and parameter uncertainty, whenever possible. The methods used in the sensitivity analysis should be reported in detail here.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>For example:</p> <ul style="list-style-type: none"> <li>• Deterministic sensitivity analysis in tabular form or using a Tornado diagram</li> <li>• Probabilistic sensitivity analysis, e.g., in the form of a CEAC</li> <li>• Value-of-information analysis</li> </ul> <p>Relevant sources of evidence are specified under relevant issues under SAF and EFF domains, as well as from within the ECO domain.</p>					
References	<p><b>Common to all used applications</b></p> <p>Gold et al. {59}; Drummond et al. {1}; CADTH {18}; Kristensen and Sigmund {3}; Cleemput et al. {57}; Husereau et al. {51}; Bojke et al. {74}; NICE {69}; Briggs et al. {26}.</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>E0006</p>					
Sequential relations	<p><b>Common to all used applications</b></p> <p>E0006</p>					

E0011 Assessment element card

Issue: To what extent can differences in costs, outcomes, or 'cost-effectiveness' be explained by variations between any subgroups using the technology and its comparator(s)?

Topic: Characterising heterogeneity

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	9
	Medical and Surgical Interventions (3.0)	Yes	Important	Partial	Yes	9
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	9
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	9
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>If applicable, describe differences in costs, outcomes, or cost-effectiveness that can be explained, e.g., by variations between (pre-defined) subgroups of patients with different baseline characteristics or other observed variability in effects. Providing the results in tabular form is recommended, but graphical representation using, e.g., 'Forest' plots may also be useful.</p> <p>The methods used in any sub-group analysis should be reported in detail here.</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Relevant sources of evidence are specified under relevant issues in SAF and EFF domains, as well as from within the ECO domain.</p>					
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Gold et al. {59}; Drummond et al. {1}; CADTH {18}; Kristensen and Sigmund {3}; Cleemput et al. {57}; Husereau et al. {51}; Sculpher et al. {56}; Cleemput et al. {57}</p>					
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>C0005, E0006, H0012</p>					
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>E0006</p>					

E0013 Assessment element card						
Issue: What methodological assumptions were made in relation to the technology and its comparator(s)?						
Topic: Validity of the model(s)						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	10
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	10
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	10
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	10
Clarification	<p><b>Common to all used applications</b></p> <p>Report the following aspects of the research, with appropriate justification:</p> <ul style="list-style-type: none"> <li>• Perspective(s) of the analysis or analyses</li> <li>• Time horizon(s)</li> <li>• Discount rate(s) used</li> <li>• To what extent the model includes all aspects of resource use and costs which could be considered important</li> <li>• To what extent the model includes all aspects of effectiveness which could be considered important</li> </ul>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Relevant sources of evidence are specified under relevant issues in SAF and EFF domains, as well as from within the ECO domain</p>					
References	<p><b>Common to all used applications</b></p> <p>Gold et al. {59}; Drummond et al. {1}; CADTH {18}; Kristensen and Sigmund {3}; Cleemput et al. {57}; Husereau et al. {51}; Eddy {38}</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>E0001, E0002, E0005, E0009, E0010, E0011</p>					
Sequential relations	<p><b>Common to all used applications</b></p> <p>E0001, E0002, E0005, E0009, E0010, E0011</p>					

E0012 Assessment element card

Issue: To what extent can the estimates of costs, outcomes or economic evaluation(s) be considered as providing valid descriptions of the technology and its comparator(s)?

Topic: Validity of the model(s)

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	11
	Medical and Surgical Interventions (3.0)	Yes	Important	Partial	Yes	11
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	11
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	11
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>It would be valuable to report any of the numerous ways of assessing to what extent the estimates for the technologies can be considered valid, For example:</p> <ul style="list-style-type: none"> <li>• How well the model can be expected to predict health effects</li> <li>• How well the model can be expected to predict resource use and costs</li> <li>• Estimates of the potential direction and/or potential magnitude of bias induced</li> <li>• An attempt to identify key factors that could compromise the validity of the model</li> </ul> <p>Here, report the process of validation and the types of validation addressed in the model.</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Relevant sources of evidence are specified under relevant issues in SAF and EFF domains, as well as from within the ECO domain</p>					
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Gold et al. {59}; Drummond et al. {1}; CADTH {18}; Kristensen and Sigmund {3}; Cleemput et al. {57}; Husereau et al. {51}; Eddy {38}</p>					
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>E0001, E0002, E0005, E0009, E0010, E0011, E0013</p>					
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>E0001, E0002, E0005, E0009, E0010, E0011, E0013</p>					

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# Ethical analysis (ETH)

## *Description*

The term ‘ethics’ is broadly used to describe activities relating to the understanding and study of ‘the moral life’. The term ‘morality’ encompasses beliefs, standards of conduct, principles and rules which may guide personal and professional behaviour and the behaviour of institutions. Morals are standards that are widely shared, and that form some degree of social consensus {1}.

The Ethical Analysis (ETH) domain considers prevalent social and moral norms and values relevant to the technology in question. It involves an understanding of the consequences of implementing or not implementing a healthcare technology in two respects: with regard to the prevailing societal values and with regard to the norms and values that the technology itself constructs when it is put into use. The moral value that societies attribute to the consequences of implementing a technology is affected by socio-political, cultural, legal, religious and economic differences. However, many ethical considerations are common to all countries and societies.

In addition to the ethical aspects of using technology, the domain also covers moral and ethical issues related to the consequences of performing the health technology assessment (HTA). These are, for example, questions about the ethical consequences of choosing specific endpoints and about whether there are any ethical problems related to the economic evaluation. There are, however, also various ethical considerations that should be taken into account when choosing what technologies to assess and when planning to conduct the assessment. This is to ensure that the assessments themselves are designed and conducted in such a way that key ethical principles are considered and respected. These types of consideration are not part of this domain but presented in the introduction to the Core Model.

The ETH domain includes six different topics, which together cover nineteen issues. These are presented in Table 1. The issues stem from the general values of the population, aims of the healthcare system and values arising from the use of a technology.

**Table 1: Topics and issues in this domain**

Topic	Issue	Assessment element ID
Benefit-harm balance	What are the symptoms and the burden of disease or health condition for the patient?	A0005
Benefit-harm balance	What are the known and estimated benefits and harms for patients when implementing or not implementing the technology?	F0010
Benefit-harm balance	What are the benefits and harms of the technology for relatives, other patients, organisations, commercial entities, society, etc.?	F0011
Benefit-harm balance	Are there any other hidden or unintended consequences of the technology and its applications for patients/users, relatives, other patients, organisations, commercial entities, society etc.?	F0003
Benefit-harm balance	Are there any ethical obstacles for evidence generation regarding the benefits and harms of the intervention?	F0104
Autonomy	Is the technology used for individuals that are especially vulnerable?	F0005
Autonomy	Does the implementation or use of the technology affect the patient's capability and possibility to exercise autonomy?	F0004
Autonomy	Is there a need for any specific interventions or supportive actions concerning information in order to respect patient autonomy when the technology is used?	F0006
Autonomy	Does the implementation or withdrawal of the technology challenge or change professional values, ethics or traditional roles?	F0007
Respect for persons	Does the implementation or use of the technology affect human dignity?	F0008
Respect for persons	Does the implementation or use of the technology affect the patient's moral, religious or cultural integrity?	F0009
Respect for persons	Does the technology invade the sphere of privacy of the patient/user?	F0101

Justice and Equity	How does implementation or withdrawal of the technology affect the distribution of health care resources?	F0012
Justice and Equity	How are technologies with similar ethical issues treated in the health care system?	F0013
Justice and Equity	Are there factors that could prevent a group or person from gaining access to the technology?	H0012
Legislation	Does the implementation or use of the technology affect the realisation of basic human rights?	F0014
Legislation	Can the use of the technology pose ethical challenges that have not been considered in the existing legislations and regulations?	F0016
Ethical consequences of the HTA	What are the ethical consequences of the choice of endpoints, cut-off values and comparators/controls in the assessment?	F0017
Ethical consequences of the HTA	Are there any ethical problems related to the data or the assumptions in the economic evaluation?	F0102
Ethical consequences of the HTA	What are the ethical consequences of conducting the technology assessment at this point of time?	F0103

## Why is this domain important?

Technologies can influence norms and values. Ethical analysis aims to provide a thorough understanding of norms and values that need to be taken into account during the HTA and in the decision making process. Moral values and norms form the basis of social life and they play a key role in shaping the context in which health technologies are used. Ethical analysis also reflects the fact that HTA is a value-laden process. Performing an HTA should not be considered as a purely technical tool for maximising the health benefits of technology, since benefit maximising is of itself a normative aim that carries *a priori* assumptions about the goals of healthcare and healthcare expenditure.

Although addressing ethical issues is generally accepted as an important component of the HTA process, their integration has to date often been limited. It can be argued that ‘integration’ is not the right word since ethics is already a part of HTA {2}. The challenge is to make it more explicit and visible. The need for, and weight placed on, ethical analysis can differ greatly between technologies depending on the purpose and context of their use {3}. For example, a new test that targets the same

biomarker, but does so with better specificity, sensitivity, safety and at lower cost than the test it is intended to replace, is likely to be less problematic than a new, risky technology for a previously undiagnosable disorder. The need, weight and complexity placed on the ethical analysis can hence differ between technologies.

It should be noted that when taking ethical considerations into account in HTA, two separate but interconnected steps must be taken. One is to identify moral issues relevant to drawing conclusions, and in some settings to make decisions, about use of the technology, and the other is to perform an ethical analysis relevant to the HTA. The analysis will generally consist of using structured methods to expose the relevant, often competing, moral values in the HTA, and to weigh their relative merits. Those drawing conclusions about the use of the technology will need to apply this framework(s) during the course of the HTA so as to decide which of these possibly competing values should be most dominant.

## ***Screening-specific content***

Ethical considerations are especially relevant to screening, because:

- It targets healthy or asymptomatic persons, or those in whom disease is unsuspected
- The risk/benefit balance is different from targeted diagnostics
- Test efficacy is reduced in low prevalence populations
- The balance of risks and benefits of interventions may be different for screened early detected cases than for later diagnosed cases
- Screening raises moral questions of overdiagnosis and overtreatment.

## **Relations to other domains**

Although Ethical Analysis is a separate domain in the HTA Core Model, moral issues are relevant to several HTA domains and the methods of ethical analysis should take this into account. Rather than being a 'one session' task or an add-on, the various ethical topics and issues described in the assessment elements need to be identified and addressed at different phases of the assessment process {4}. This is important in order to ensure that decision-makers are presented with a complete picture, but also because not all ethical considerations are apparent early in the HTA: sometimes they emerge alongside clinical or cost-effectiveness evidence. In this way, the results and insights gained from the other domains guide the ethical analysis. However, the ethical analysis phase should add to the process in a way that the other domains cannot.

The results of the ethical analysis closely relate to the evaluation of legal, patients and social aspects (LEG and SOC domains). These domains may overlap with the ethical analysis, though the angle of evaluation may differ. The legal framework forms a basis for professional ethical codes for instance, with regard to abortion, prenatal screening, and euthanasia. The social consequences of implementing a technology may differ largely from consequences of patient-level primary outcomes (e.g. avoidance of death at patient level, avoidance of impaired working ability at societal level). The implementation of a new technology will not only have an effect on health, functional abilities and psychosocial well-being but also on social networks and need of support.

## Diagnostics-specific content

In addition to the issues that are common for all technologies, there are specific questions for ethical consideration when analysing diagnostics. These are presented here

### 1) What is the aim of the diagnostic test?

Different aims can be, e.g.:

- Guiding further (invasive) diagnostic strategies
- Guiding treatment by confirming or excluding disease
- Grading severity in order to adjust or time intervention
- Patient (or relative) or physician reassurance by knowing the probability of or excluding a disease
- Predicting risk, susceptibility for some disease or condition (in patients or in relatives, or in occupational medicine setting)
- Legal purposes (for instance for malpractice suits, disability benefits, life insurance, etc.)
- Public health protection (e.g. case finding of highly contagious disease carriers with the aim of interrupting the transmission chain)
- Social, economic or research purposes

Different aims can be of different value. For example, are physician or patient reassurance legitimate aims and, if they are, at what costs? The aim is also relevant for the trade-offs between a test's safety and benefit. For example, the willingness to undergo risky tests is probably lower among healthy people offered a screening, than among severely ill persons who expect a better management of their condition as a consequence of the test.

### 2) What kind of roles will the diagnostic technology have with respect to other diagnostic tests?

Within established diagnostic pathways, a new diagnostic test can theoretically have three different roles: replacement, triage or add-on (see the description of accuracy in the Clinical Effectiveness (EFF) domain for definitions). The intended and actual roles of technologies may however differ. Thus, it is essential to try to predict how the test is going to influence the whole clinical pathway of disease, and whether the new test will contribute in a relevant way to the clinical outcome in practical implementation. For example: Will tests intended as replacement actually become replacements, or are they more likely to be used as triage or add-on? Will tests intended as triage introduce new risks and new kinds of consequences for false results, and will these have an impact on new populations? How likely is it, that the test will be used outside diagnostic pathways for other purposes, such as predicting risk or screening?

### **3) What are the unintended implications of the diagnostic technology?**

First, diagnostic tests may directly harm even healthy people (see Safety (SAF) domain). The direct harms of the test (mostly physical e.g. infection, injury, radiation) are easily grasped as risks, although for many diagnostic procedures, direct risk is considered almost negligible (e.g. tests performed on fluid samples, echography, etc.). Apart from direct risks, diagnostic tests are often perceived as harmless, and ‘information only’. This perception ignores the potential consequences of specific test results, especially the consequences of false results. Positive test results may initiate a chain of further diagnostic measures and/or treatments which usually have higher direct risks than the initial test, exposing the healthy individual (e.g. the false positive) to additional unnecessary risks. On the other side, false negative results may cause delays or even withholding of an appropriate treatment, this unnecessarily prolonging suffering or reducing example survival chances. More diagnostic tests may consequently produce more risks, and it is therefore important that the benefits are proven. In order to balance harms and benefits, not only the direct risks but also the consequences of all four possible tests results (false positive (FP), false negative (FN), true positive (TP), true negative (TN)) should be known and understood.

Second, diagnostic tests may change care in ways which are difficult to foresee. Diagnostic tests are a crucial part of care pathways and treatment processes. A diagnosis, or a positive triage test, often has ethical and practical consequences insofar that they require further tests, treatments or other modes of care. However, patients and their families may value information about their condition even if the condition is untreatable, e.g. for reproductive decisions and time allocation. Thus increasing diagnostic tests alone may lead to far-reaching changes in the requirements placed on health care systems, and also on individual patients and professionals.

Third, diagnostic tests may change the way we see diseases and illnesses. A diagnostic technology may not become a pure replacement of an existing test, especially if the new test is substantially different from the old one (e.g. different biomarkers for the same disease, genetic test instead of biochemical markers, imaging instead of laboratory tests). This may lead to a shift towards being able to diagnose milder cases, thus leading to increasing prevalence in the diagnosed population. A change in the diagnosed population may, in turn, require different therapeutic approaches – and, with them, also new effectiveness studies.

Fourth, diagnostic technologies tend to obtain substantial symbolic value, e.g., genetic tests and advanced imaging technologies like PET, MRI and ultrasound for prenatal screening. These tests may have profound consequences on an individual’s self-image and behaviour.

Fifth, diagnostic test information may be of different value to different stakeholders. Information on contagious diseases and other health conditions, as well as the results of predictive (genetic) tests are not only of interest and importance for the patient and the treating physician. Considering to whom diagnostic test information may and must be communicated is also an ethical issue, and along with it comes the danger of ‘labelling’ a healthy person as unhealthy by communicating predictive test results.

#### 4) Normative issues in assessing effectiveness and accuracy

First, the proper endpoints for assessment must be determined. Endpoints can be determined based on:

- Technical or diagnostic accuracy
- Reduced risk / increased safety
- Diagnostic or therapeutic impact (health improvement)
- Other patient outcome (knowledge, increased autonomy, lifestyle modification, worry)

More than one endpoint may be legitimate and expected. For example, a new test may increase test safety but reduce patient outcome, influence costs and social justice. The decision of using a technology with several endpoints requires making judgments at the planning, analysing and reporting stages of an HTA. It is necessary to be transparent on how, on what grounds and by whom these value-decisions are done.

For pragmatic reasons, it is often necessary to focus the technical assessment on some of the endpoints where there is sufficient direct data (e.g. accuracy) and then use linked evidence (e.g. treatment trials) and expert opinions (e.g. whether the patient populations and care pathways used in treatment trials and accuracy studies match) to assess the likelihood of an effect on final patient-related outcomes from implementing the new diagnostic technology.

Deciding cut off values and balancing accuracy measures (e.g. sensitivity versus specificity) requires value decisions with regards to the moral value of different results (goodness of true positive and true negative and badness of false negative and false positive). Proper cut-offs will depend on the population on which the test will be used, and on the consequences of different diagnostic alternatives. Even if a ROC curve is interpreted so that the point closest to the upper left corner equals 'best accuracy' (see EFF domain), this may not be the most ethically acceptable cut-off to use (see *Context-related requirements for accuracy* under EFF). The patient population determines the rates of different outcomes, so the balancing of harms and benefits will depend on the population to which the test will be administered.

## Screening-specific content

As stated in the criteria for a screening programme {5, 6}, screening technologies present participants, their relatives, the health care system and the society with many ethical questions. The screening technology should target a health problem sufficiently important to both the individual and the society, in order to justify allocating resources to that screening programme. Nevertheless, the decision to define a disease as an important health problem is, in itself, a normative decision {7}.

Ethical considerations will vary depending on whether the subject of the HTA is a diagnostic test used in primary or secondary screening. Primary screening deals with asymptomatic populations in which a disease is possible, even if actually not yet suspected. For primary screening, the test is given to an asymptomatic individual and this raises significant ethical issues. In secondary screening, on the other hand, the population has already come into contact with the healthcare system as the symptoms have already arisen. In secondary screening for conditions with known

adverse effects there may therefore be a greater imperative to identify and treat the condition, as the natural history of the disease – once it has been found – might dictate early treatment.

There are a number of considerations that govern the introduction of organised screening programmes. Some national agencies have criteria for determining the appropriateness of programmes being considered for introduction across the population (e.g. UK National Screening Programme criteria, criteria for screening programmes in Finland). Such criteria can form a useful basis for the classification of issues to consider when initiating an HTA on screening technologies. Some of these considerations are now discussed in more detail.

Organised screening programmes are usually targeted at healthy individuals, and involve the health care system contacting an individual and proposing an intervention to prevent disease and promote health. This implies a special responsibility for the health care system - the effectiveness and the safety of screening must be guaranteed, as must the treatment that follows should the patient be found to have the disease. Ethical analysis needs to be applied to the consequences of ‘false positive’ and ‘false negative’ test results; the consequences of possible over-diagnosis and over-treatment also have to be carefully evaluated and weighed against the expected benefits. There should be a suitable test or examination for screening, where the following characteristics are known (e.g. UK national screening programme criteria):

- Validity of the testing system
- Sensitivity and specificity
- Predictive value of the test(s)
- Any concerns about safety or adverse events

The screening test should be acceptable for the target population. Equity of access is a further consideration, as is investigating whether participation in the screening programme might stigmatise the participants, or the individuals that test positive (e.g. in the case of HIV testing).

Ethical evaluation of a screening programme has multiple perspectives, as it may encompass the healthcare system from primary to tertiary level. General and technology-specific ethical issues and consequences for various stakeholders (e.g. participants, their relatives in case of hereditary disorders, various levels of the health care organisation, screening test providers, and screening health care professionals) need to be identified both before and during the HTA process. For each stakeholder, possible consequences of both proceeding with and refraining from the screening technology’s implementation have to be identified.

## **Pharmaceutical-specific content**

Issues on possible medicalisation and unintended harms have to be identified and analysed when novel pharmaceuticals are marketed for health conditions without a universal and individually applicable definition. In cases where pharmaceuticals are used for secondary prevention, it is also important to discuss the ethical consequences of the criteria for starting preventive medication.

When pharmaceuticals replace an existing invasive treatment option (e.g. continuous medication vs. surgery), the decision on a treatment option can have a large impact on the patient's quality of life and also interfere with their social and family life.

# Methodology

## Process for answering research questions

Even though there is a wide consensus that ethical analysis should be an element of HTA, there has been no generally accepted, structured method for performing ethical analysis. The INAHTA Working Group on Ethical Issues has identified and defined various methodological approaches that are used by HTA agencies {8}. These are presented in the section *Methods for ethical analysis – different approaches*. The INAHTA working group concluded that no single ethical method is likely to be sufficient {9}; however, the ‘axiological’ approach, which aims to elicit ethical reflection by highlighting value issues through a set of questions, was mentioned as the most promising. The questions in the assessment element table of this domain are intended especially for identifying ethically relevant issues and conflicts. These relevant issues can then be answered by performing a more detailed ethical analysis. Standard HTA practices such as evidence grading are redundant in this context and should preferably not be done, as they infringe upon the discretionary room for appraising the technology by (national or regional) decision-makers.

For each core HTA project, it is recommended that there be a person, preferably an ethics expert, responsible for facilitating and reporting the ethical analysis. However, the ethical analysis of the HTA process should also be done together with scientific and clinical experts.

The choice of approaches and processes for conducting a formal analysis of ethical aspects depends on a number of interacting factors:

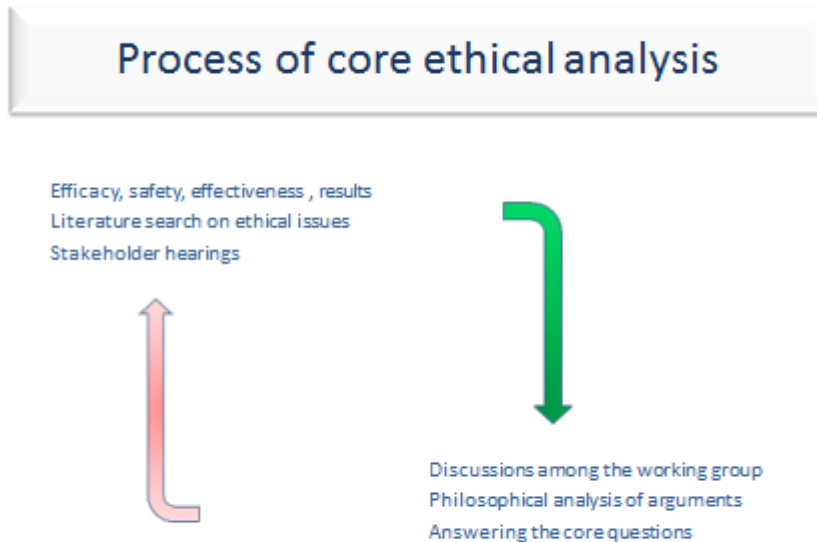
1. The type of technology being assessed
2. The role and authority of the HTA organisation in the national decision-making procedure
3. The time and resources available for the assessment
4. The methodological expertise and experience with ethical analysis that are available within the organisation

The relative weight placed on the ethical analysis and the selection of methods depends heavily upon the technology being evaluated {2, 10}. The more the technology presents new, severe or fundamental value conflicts, or challenges to everyday norms or beliefs, the more emphasis should be placed on the ethical analysis. For example, technologies with strong *prima facie* moral implications (like genetic testing or aggressive cancer treatments in children), technologies concerning diseases involving strong interest groups (e.g., cochlear implants) or other ‘extraordinary’ new technologies that appear to challenge commonly held values or everyday beliefs (like home-care nurse robots) require a more elaborative ethical analysis.

Technologies used for vulnerable patient groups (critically ill, children, individuals with impaired cognitive capacity, etc.) also require special ethical analysis with regard to the patients’ diminished autonomy. The same consideration goes for technologies for which there is a specific religious or philosophical belief.

HTA organisations differ in their resources and decision-making mandate. While some only provide synthesis of evidence, others conduct appraisal of evidence and formulate recommendations, or produce clinical practice guidelines. Decision-making bodies and guidance-providing agencies may

have more explicit transparency requirements for their stakeholders than do academic or other bodies carrying out HTA. They may also have legal duties requiring them to avoid discrimination and promote equality. This may, in turn, affect their approach to ethical analysis. If the HTA organisation is clearly separated from decision-makers, it may be enough to describe the different norms, values, attitudes and arguments that should be considered by the decision-makers.



**Figure 1. The iterative process of ethical analysis**

## Gathering information

### *What kind of information is required?*

The entire working group defines the focus of the assessment, the specific questions to be answered, the study inclusion criteria, and the primary outcome points for analysing the consequences of implementing a technology. These choices may be incorporated into a formal scope or decision problem document.; The choices are also value-laden and can have a major impact on the content and conclusions of the HTA report – this is why they need to be carefully scrutinised before proceeding.

It is important to consider whether there are issues of potential ethical significance related to the disease or health problem, even before any factual considerations about consequences of implementing/not implementing the related technology. For example, some types of technologies may introduce gender bias or be used in conditions that are considered by some to be ‘self-inflicted’, which could lead to debates about access to treatment. Furthermore, some technologies involve complex relationships, interests and outcomes. For example, prenatal screening tests may raise fundamental questions about the value of life and autonomy, and may highlight competing interests of the embryo, mother, father, siblings or future possible siblings.

Some issues in the assessment elements table deal with the direct consequences of implementing a technology (e.g. can the technology harm the patient?). Other issues relate to questions of value that need to be addressed when deciding on implementation, such as the impact of the technology on the availability of healthcare resources for different patient groups, or the balance of benefit and harm for the population as a whole. Competing ethical considerations generally do not lead to clear conclusions and therefore judgment must be made by assessors as well as decision-makers. Philosophical techniques such as deductive reasoning may be helpful in testing the logic and coherence of the arguments from different viewpoints of the stakeholders (see *Methods for ethical analysis – different approaches*).

The perspectives of all relevant stakeholders should be reflected in the process. It is usually fairly easy to identify the primary stakeholders for each technology - patients, family members or informal caregivers, patient organisations, health care providers, health insurers, industry, etc. (see Table 1). Making HTA project plans public as early as possible and allowing for public consultation may help identify relevant stakeholders and their fears early on in the process. It is equally important to identify those stakeholders who will be indirectly affected if the technology is implemented, such as patient groups with competing interests in accessing healthcare resources. The views of stakeholders are best acknowledged early on in the process rather than during the external peer review process.

## Where to find information?

Issues requiring ethical analysis should be identified systematically at the start of the HTA but assessors and decision-makers should be prepared to consider relevant issues that arise at any point during the HTA process. Information and evidence required to carry out ethical analysis in HTAs may need to be gathered from a number of sources, using various procedures. These may include:

- Systematic literature searching covering a broader range of sources than for standard HTA
- Professional guidelines
- Expert opinion
- Patient/service user opinion
- Views of organisational stakeholders, e.g., the health system within which the technology is to be used.

The information gathering phase may require several iterations, where previous phases identify new needs and questions that might then be answered from other sources (Figure 1). Thus, it may be useful to repeat some phases following new insights.

### Databases and search strategies

Evaluation of the principal questions about the technology, and the consequences of its implementation/non-implementation are based on the information received from ongoing research on efficacy, safety, effectiveness and cost-implications of the technology.

Organisations carrying out ethical analysis in HTA will need to consult a wider range of literature sources than would normally be considered for scientific evidence on clinical effectiveness. Academic sources encompassing philosophy, particularly ethics, law and social sciences should be searched. Examples of related fields are applied ethics, innovation studies, science and technology

studies, technology forecast studies, etc. Grey literature, including legal case law, books and other monographs may also be informative. Information retrieval for ethical assessment is likely to require more hand-searching than information retrieval for the assessment of effectiveness. If these sources do not contain suitable literature in relation to the technology under consideration, searching should be extended to include other related technologies with similar ethical challenges (see *Casuistry* below). Droste et al {11} have identified databases and MeSH terms that can be useful for the ethical analysis and propose a methodological approach to literature searching {12}.

#### Expert and stakeholder opinion

Discussions among the working group and with experts are effective in identifying important ethical issues related to the technology. The questions in the assessment elements table of this domain are a good starting point for discussions with experts and other stakeholders, but additional content-specific ethical issues or challenges may also be identified during the discussions. Qualitative analysis of the expectations and fears of various stakeholders may reveal questions that cannot be identified by the content or methodological expert group or from the literature review. This information can be derived from stakeholder meetings or by conducting primary studies.

## ***Methods for ethical analysis - different approaches***

This section presents the various methodological approaches used by HTA agencies that were identified by INAHTA ethics working group. The approaches have also been supplemented by the EUnetHTA ethics working group. However, it must be noted that it is beyond the limits of this document to present concrete examples of how to apply these methods.

### **Casuistry**

Casuistry entails solving morally challenging situations ('cases') by referring to relevantly similar 'paradigmatic' cases for which an undisputed solution has been found {13-16}.

The methodology of casuistry comprises of three steps. First, the case at hand is sorted into one of the broad categories of problems, 'topics' (e.g. medical indications, patient preferences, quality of life, contextual features). Details should be described in a standardised way (who, what, where, when, why, how, by what means). Second, common sense moral rules, 'maxims', related to the case are explored (e.g. 'the wish of the patient has to be respected'). If the maxims are contentious, the underlying moral principles of the case at hand are explored. Third, the case at hand is compared with a set of paradigmatic cases on the same topic that have been solved in agreement previously. Comparing the details of the case at hand, including the underlying maxims and principles, with the details of the paradigmatic case may then suggest a solution for the current problem {17}.

In HTA, especially for coverage decisions, a casuistic approach (precedence method) is suggested as at least a part of the ethical analysis. It means first establishing an inventory of past coverage decisions. The aim is to generate a typology of paradigmatic, covered technologies, which would represent the basic moral principles that underlie decision-making in the respective health care systems. Next, the relevant qualitative and quantitative characteristics of the new technology are identified, and the technology is compared to similar, preceding paradigmatic cases. Ideally the solution may, following this, be applied to the new technology. However, in addition to applying the solutions of past precedents to current cases, it is also necessary to reflect on the possibility that

the value base has changed since the paradigmatic decisions were made. It may be that this reflection leads to a need to reconsider previous decisions.

In pure casuistry, cases are approached without referring to ethical principles, norms or theories. The process might resemble coherence analysis insofar that it explores solutions to similar cases, or interactive approaches that aim for a consensus of relevant stakeholders. A pragmatic, 'moderate' form of casuistry as described above can include an element of principlism, as referring to ethical maxims and principles is done if a clear enough solution is not provided by comparison to previous cases. It also includes an element of wide reflective equilibrium, in that applying past precedents to new cases might reveal a need of reconsidering previous decisions.

## Coherence analysis (CA)

The main idea of CA is to reflect upon the consistency of ethical argumentations or broader theories on different levels, without prescribing which facts, arguments or principles are relevant *prima facie*. It is a procedural, pragmatic approach, i.e. it describes a procedure of approaching moral issues without claims of providing direct answers on 'right or wrong'. CA can be compared to test-reliability and internal consistency of tests in empirical research. It cannot, however, ensure validity – an immoral system can be as coherent as a morally justified one {3, 18}.

CA considers the logical (possibly also emotional or intuitive) consistency of facts, norms and arguments relevant for the HTA. Thus CA is critically dependent on the material input, i.e. the comprehensive identification of facts, values and principles, the coherence of which is to be considered.

Some kind of consideration of logical coherence is necessary for any ethical analysis of HTA. The more 'extraordinary' the technology under evaluation is, the more useful a formal CA can be.

For CA the evidence can be summarised with regards to:

1. Society's normative framework relevant to the technology (legislation, practice norms and guidelines, decision making procedures)
2. Society's, patients' and scientists' expectations regarding the impact of the technology (fears, expectations)
3. Society's general objectives and visions (concepts of justice, autonomy, reasonable development and other ideals)
4. Interpretation of the past and present 'biography' of the society, or parts of it (deeply held, fundamental values and views central to individuals' and society's self-image)

CA is a reflective procedure (internal monologue/group discussion) which tries to help in achieving a logically consistent HTA. The identification of inconsistencies should lead to attempts to solve them (using, for example, discussions, wide reflective equilibrium, interactive technology assessment, normative approaches based on common principles etc.). The norm on which conflicting ideas are evaluated, edited and possibly abandoned is high observable consistency. In contrast to interactive approaches (see below), opinions of important stakeholders can, but need not be, taken into account.

However, reaching consistency might not succeed, and in that case the analysis should aim to identify incommensurable beliefs or values, or contradictions between empirical claims, normative frameworks, or scientific and societal understandings and needs.

In conclusion, CA does not provide an unequivocal normative ‘ethical recommendation’, but it still is an essential part of all ethics analysis. It may be especially useful early on in the HTA process, in order to help identify central issues in need of further scrutiny.

## **Interactive, participatory HTA approach (iHTA)**

iHTA aims for an intersubjective consensus on ethically problematic issues, reached through real discourse. It integrates patients’, professionals’ and other stakeholders’ perspectives into HTA. It is a procedural approach (like coherence analysis), meaning that it describes a procedure one should have in approaching ethical problems rather than providing an ideal solution. In contrast to coherence analysis, however, iHTA also aims to improve the validity of the whole HTA process through empowering and involving the stakeholders. Although iHTA aims for a consensus, one may not always be reached together with the stakeholders. It may also be decided that the conclusions should be drawn from a stakeholder hearing by the method experts {19-23}.

The iHTA process begins by asking what kinds of values are at stake, whose values these are, and who the important stakeholders are. Second, an interactive procedure to clarify these values is chosen, depending on the presumed severity of value conflicts and on the resources available. For example, the Delphi procedure, citizen juries, focus groups or deliberative polls could be used. The results of the interactive process inform the HTA process, i.e. help to identify relevant questions and relevant parameters for assessing the (health) effects of the technology.

iHTA informs, but does not dictate, the normative ethical conclusions necessary in reporting the results of the HTA. It can inform the expert group of important opinions and values that may otherwise have been ignored. Ethical conclusions cannot, however, be directly derived from any naturalistic population consultation: it is not possible to deduce how things ought to be from how things are. The description of possibly differing valuations of different stakeholders discovered with the iHTA process can, however, be important for the application of the results.

## **Principlism**

Principlism is based on the idea that there are principles, rooted in society, that are based on a common morality. These principles form a core dimension of all morals occurring in the world, and are presumed to be shared by every serious moral person. Principlism does not imply a specific method of reasoning, but describes a specific content of ethics: the principles form the essence of considered judgments. Principlism considers the validity of ethical analysis {1, 24}.

Principlism recognises that there are several ethical principles, in contrast to foundational theories like utilitarianism or Kantian deontology that recognise only one supreme principle. The most influential principlist approach to bioethics {1} comprises of four principles, representing several clusters of practice norms:

- Respect for autonomy: a norm of respecting the decision-making capacities of autonomous persons
- Non-maleficence: a norm of avoiding the causation of harm
- Beneficence: a group of norms for providing benefits and balancing benefits against risks and costs - also referred to as the 'proportionality principle', highly relevant for HTA and research ethics
- Justice: a group of norms for a fair distribution of benefits, risks and costs

These norms are assumed to form a comprehensive analytical framework for bioethics. The principles are *prima facie* binding, meaning that they are always important in every situation, but are not absolute because they can come into conflict. Highly relevant for HTA is, for example, the conflict between autonomy and beneficence for single persons on the one hand, and the just distribution of resources and beneficence for society on the other.

In practice, considering that the principles are abstract, they must always first be specified according to the current context. Following this, if all principles cannot be realised fully (as is most often the case), the specified principles must be balanced against each other. A principle should only be overridden if:

- Better reasons have been given to act according to the principle that overrode the other one
- The moral objective which justifies the infringement must have a realistic chance of being achieved
- The infringement must be the only way to realise one principle at the cost of the other
- The form of the infringement must be fitting to the achievement of the primary goal
- Any negative effects of the infringement must be minimised
- The decision must be impartial with regards to all affected parties.

The major advantage of principlism is that it delivers a comprehensive, normative framework for ethical analysis, in contrast to procedural, non-normative approaches like CA, iHTA, wide reflexive equilibrium (WRE) (see below) and casuistry. Conversely, normativity is also the main problem of principlism, as not all ethicists agree in that these and only these principles are universal. If so, the normative framework of four principles might not be valid for every technology and every population.

Explicit principlistic considerations are useful for increasing the transparency and transferability of the ethical analysis. To balance the principles in a context-sensitive manner in practice, WRE or participatory methods can be useful.

## Social shaping of technology

The social shaping of technology (SST) approach {20, 25, 26} views technology as the product of societal processes (within industry, research institutes, governmental bodies, and society at large) rather than an independent artefact that has a certain, measurable impact on its target. The aim is to understand what technology is and how its development is interwoven with its social context (e.g. the engagement and strategies of various actors, and the way various problems are defined and resolved). In this context, assessing the role, merit, and value of technology becomes important. The social shaping perspective also implies an opportunity to manage technology through its social context. If technology is, in fact, technology-in-context, then both technology and its context can be influenced or adjusted so as to improve the outcomes of using technology. The societal processes underlying technology development can be explained, to some extent, through the values relevant in different contexts.

From the ethics point of view, the SST approach emphasises

1. Reflexive focus on the range and values of relevant actors and their conditions of involvement
2. Considerations of how technology can influence society and how technology can be best managed by society
3. The inadequacy of evaluating a technology without considering the local social environment

Within this framework, many of the other methodological approaches to ethical questions in HTA can also be applied (e. g. participatory approaches such as iHTA).

## Wide reflective equilibrium (WRE)

The WRE {27-30} is an ideal, perpetual goal of justification in modern philosophical inquiry. It is based on pragmatism and social constructivism, which claim that ethical truths cannot be revealed or directly experienced, and that there are no static, fundamental *a priori* valid universal principles. On one hand, the normative framework of society may change over time. On the other hand, humans need stability, cognitive coherence and some degree of reconciliation between individual and social norms and values. WRE is a central methodological part of the ‘four principles’ approach, discussed above {1}.

When using WRE, the reflection starts from the most frequently considered judgments and moral feelings that have a *prima facie* credibility. This has to be done behind a ‘veil of ignorance’ (i.e. imagining we do not know which position we would have in the society our decisions concern) to try to be as impartial as possible. To approximate WRE, all possible situations, arguments, and judgments need to be taken into account and brought into a coherent whole through rational reflection (see coherence analysis above). This might entail that some of our primary considered judgments have to be adjusted.

WRE is an important political and philosophical goal of coherence analysis and discourse ethics with regards to decision making. However, it represents an ideal goal of a theoretical procedure, and may as such be difficult to apply in real-world HTA processes. As a goal-emphasizing, individual and inter-subjective consensus, WRE may also neglect true conflicts between arguments that cannot be judged by the same standards. Essentially, WRE emphasises open, honest and impartial

discourse, conducted by rational, sensible actors in democratic, pluralistic societies who want to reach a consensus through finding the most valid claims.

## **The 'triangular model' based on the human person-centred approach**

The triangular model is based on a substantial conception of human person. It considers the man as reference-value in the reality, around which all the ethical judgments are coordinated. Based on a cognitivist approach to the ethics, this model considers it possible to get some truths, concerning man and his/her praxis, recognizable by everyone through a rational activity {31}.

The methodology of the triangular model comprises of three steps of analysis: 1. Data collection; 2. Anthropological aspects, 3. Ethical-normative evaluation. The first step, 'scientific moment' consists of an in-depth study of all facts/data, including qualitative and relational ones. The second step, 'anthropological moment', consists of the anthropological understanding of facts; in other words, the analysis of eventual values at stake, related to human life, integrity and dignity. According to this analysis, it is possible to find values which should be promoted and defended, and norms which should guide human action on individual and societal levels. The third, 'ethical-normative' step consists of evaluation of practical choices that should be made.

This model highlights a triangular connection between biomedicine, anthropology and ethics, set on two levels – the explanation of a certain topic (descriptive step), followed by a normative phase, from which we can draw conclusions within a debate of meta-empirical perspectives (relating to the steps 2 and 3 described above). It is evident that such a comprehensive process needs all three theoretical steps.

The normative framework within this model {32, 33} consists of four principles of reference: (1) the defence of human physical life as a whole and its integrity; (2) the principles of freedom (capability of the human will) and responsibility (an intra- and inter-subjective evaluation of subject's own acts and will); (3) the therapeutic principle, according to which the human person has to be treated as a whole of body-mind reality; (4) the principles of sociality and subsidiarity, according to which public or private authority is called to intervene and to help the person only if he is not able to manage, promote or safeguard him/herself {31}.

## **Axiological (Socratic) approach**

The axiological approach is based on the idea that science and technology is a social activity governed by a wide variety of norms and values. Health technology is thus applied in a social setting where there is interplay of different kinds of norms and values. HTA should therefore highlight and address the norms and values involved in the implementation and use of a health technology. The reason why the axiological approach is also called a Socratic method is because it is based on a set of questions which are aimed at highlighting normative issues in the HTA as well as in the decision making process.

The (32) questions relate to:

- General moral issues, such as integrity, human rights, patient autonomy, benefit, harm, respecting social and religious convictions
- Moral issues related to stakeholders (patients, relatives and important others, health care providers, health insurers, industry, policy makers)
- Moral issues due to methodological challenges (end-point selection, evidence generation, quality assessment of study design)
- Issues typical to the technology (function, purpose, intention, consequences of use, potential misuse)
- Moral issues related to the process of HTA and decision making.

The axiological/Socratic approach consists of six steps {2}.

1. Identify and analyse the moral challenges that are typical for the health technology
2. Identify stakeholders
3. Select a set of morally relevant issues from a list of questions {2, 34} which highlight value issues with regards to the implementation of health technology; justify the selection
4. Perform literature search on the basis of the steps 1-3
5. Analyse the selected questions (in step 3) on the basis of the literature search (step 4), hearings with stakeholders, and results from qualitative research
6. Summarise the analysis and highlight the most important value issues

The aim in addressing norms and values through the set of morally relevant questions is to provide an open, transparent and informed decision-making framework.

The axiological/Socratic approach has been applied to bariatric surgery {35}, screening of newborns {36-38}, HPV-vaccine {39, 40}, welfare technology {40, 41}, palliative surgery {10}, obstipation treatment in cancer care {42}, ICSI {43}, amalgam replacement {44}, autologous stem cell transplantation in advanced breast cancer {45}, and other technologies. Moreover several HTAs include subsets of the questions in the axiological approach {46}.

Examples of local application of these and other methods can be found in appendix ETH1.

## *Analysing and synthesizing evidence*

### **Qualitative synthesis**

Once the ethically relevant issues have been identified and analysed, the results have to be synthesised and reported transparently, so they can be subject to consideration when deciding whether to implement a technology. No single solution to every ethical problem exists, nor is it possible to list ethical issues according to a commonly agreed-upon weighted value. Answers to the core set of issues may also reflect the variation in norms and values found within most societies. The synthesis of ethical analysis has to be performed in an open way. Either the interests of various stakeholders are kept as ‘unweighted’ as possible, or the weighing is done transparently, i.e. by describing the procedure and participants of the analysis. Ideally, the decision on ‘whose values are to be weighted’ need to be in the hands of the decision-makers. There can be different decision-makers for different types of technologies within the same country and between countries. The ideal way to present the synthesis of the analysis may vary accordingly.

Ethical analysis of the consequences of implementing or not implementing a technology may be conducted by using an open framework {47}. The possible consequences of proceeding with or refraining from the implementation of the technology can be listed separately for each stakeholder in an open table, as the answers for various parties may differ significantly (Table 1). The identified issues are not prescriptively value-weighted against each other. In fact, the table offers a transferable list of aspects that need to be considered in the final decision making process.

**Table 1. A framework for ethical analysis**

<b>Stakeholder</b>	<b>Benefits when proceeding with implementation</b>	<b>Adverse consequences when proceeding</b>	<b>Benefits when refraining from implementation</b>	<b>Adverse consequences when refraining</b>
Patient				
Family and important others				
Health care providers				
Society				
Others				

In addition, it is important to identify those areas where values may differ significantly between the various stakeholders (e.g. attitude towards the care of patients with non-treatable diseases, extremely costly interventions or conditions perceived as ‘self-inflicted’). The main areas of ethical controversy should be clearly stated in the final document.

## ***Reporting and interpreting***

The results of the ethical analysis will usually be reported as a separate chapter, in order to assure transparent reporting of value issues. The ethical implications of implementing or refraining from the implementation of the technology, however, need to be discussed in a balanced way so that the health policy makers have a wider view on all possible consequences of their decision. The open framework presented in Table 2 can be a helpful tool in this process. The decision to implement a new technology requires careful deliberation of the balance between benefit and harm, cost-effectiveness, impact on (re)allocation of resources, etc. Discussing the context-specific ethical issues within the respective domain (e.g. EFF, SAF and ECO) may thus also help the decision-makers to identify various scenarios.

## **Transferability of ethical analysis**

The ethical analysis and its outcome have to be described in an open way, so as to enable judgments of their transferability across different national or local settings. Many of the ethical implications are common to various nations but some value-laden issues are likely to be country- or community-specific, and will crucially relate to factors such as the ‘social contract’, the country’s healthcare financing system and the country’s GDP growth prospects. Analyses related to ethical principlism, coherence or paradigmatic approaches are likely to be more easily transferable than argumentation based on interactive approaches, relying on local values, stakeholder attitudes and available health care resources.

## Assessment elements

A0005 Assessment element card						
Issue: What are the symptoms and the burden of disease or health condition for the patient?						
Topic: Benefit-harm balance						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Complete	Yes	1
	Medical and Surgical Interventions (3.0)	Yes	Critical	Complete	Yes	1
	Pharmaceuticals (3.0)	Yes	Critical	Complete	Yes	1
	Screening Technologies (3.0)	Yes	Critical	Complete	Yes	1
Clarification	<p><b>Common to all used applications</b></p> <p>Describe the patient's relevant symptoms before intervention with the technology, their severity, their urgency 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. For example, back pain is rarely caused by a life-threatening disease, but it can still very negatively affect patients' quality of life and ability to work.</p> <p>This issue is especially relevant when the patient or individual is expected to undergo a substantial change in pain, disability, psychosocial issues, or other determinants of quality of life.</p> <p>Knowing the severity and/or urgency level of the condition the technology is directed to is relevant in the ethical analysis of the technology. Information about the severity level is also important to decision-makers when making decisions about whether or not to implement a technology.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Sources: text books, HTAs, quality of life studies, qualitative patient perception studies. Method: A descriptive summary.</p>					
References	<p><b>Common to all used applications</b></p> <p>Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24} from the CUR domain</p>					
Content relations						
Sequential relations						
Other domains	Also in: Health Problem and Current Use of the Technology					

F0010 Assessment element card						
Issue: What are the known and estimated benefits and harms for patients when implementing or not implementing the technology?						
Topic: Benefit-harm balance						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	2
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	2
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	2
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	2
Clarification	<p><b>Common to all used applications</b></p> <p>Decisions concerning the implementation of new technologies generally require carefully considering the balance between benefits and harms. Examples of questions that can be answered are:</p> <p>Who is the right candidate for the technology? What is the balance between benefits and harms? For instance, is the technology estimated to improve health, health-related quality of life, quality of life and/or survival compared to alternative technologies? Can the technology harm individual patients, or any other stakeholder, in any way? How many patients might face harm in order for the technology to have a benefit for one patient? What is the extent of these benefits and harms?</p> <p>What are the perceived benefits and harms of the technology in the eyes of the patients/users themselves? It might be useful to note that the patient is often the best judge of benefits and harms for themselves.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Information from other domains (links). Literature search. Expert opinion. Stakeholder hearing</p>					
References	<p><b>Common to all used applications</b></p> <p>Autti-Rämö I and Mäkelä M, 2007 {47}</p>					
Content relations						

<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>D0001, D0029; H0001, H0004, H0005, H0006; C0008, C0005; A0010; D0017</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>D0027, D0028 D0031, D0024, D0030, D1019</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>D0024, D0030, D1019 D0027, D0028, D0031, D0024, D0030, D1019</p>
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F0011 Assessment element card

Issue: What are the benefits and harms of the technology for relatives, other patients, organisations, commercial entities, society, etc.?

Topic: Benefit-harm balance

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	3
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	3
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	3
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	3
Clarification	<p><b>Common to all used applications</b></p> <p>Examine the following: Can the technology have positive effects for others apart from the patients in question? Can the technology harm relatives, other patient groups, organisations, commercial entities, society, etc.? Some technologies have the potential to unfold unwanted or harmful effects not only on the patients that the technology is directly applied to but also indirectly on others. For example results of genetic tests may negatively interfere with the family planning and social life of not only the individual being tested but also of his or her relatives. Another example is how the caregivers' burden and well-being will be affected by the technology.</p> <p>Benefits and harms to individuals must be balanced with benefits and harms that can have impact on society as a whole (social utility, maximizing public health). These harmful effects may manifest themselves in the physical, social, financial or even other domains of life.</p> <p>Changes in the availability of new, more effective technologies may significantly alter the requirements placed on the health care system. Is the symbolic value of the technology of any moral relevance?</p> <p>Another relevant question is how the assessed technology relates to more general challenges of modern medicine (over-diagnosis, medicalization)?</p> <p>Table 1 in the process description can be used to describe benefits and harms.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Literature search. Expert opinion. Stakeholder hearing</p>					
References	<p><b>Common to all used applications</b></p> <p>Beauchamp TL, 2012 {1}; Autti-Rämö I and Mäkelä M, 2007 {47}</p>					

<b>Content relations</b>	<b>Common to all used applications</b>  G0011
<b>Sequential relations</b>	<b>Common to all used applications</b>  D0029, H0001, H0002, C0020, C0040, A0006, E0006, D0017  <b>Specific to Diagnostic Technologies (3.0)</b>  I0008  <b>Specific to Screening Technologies (3.0)</b>  I0008

F0003 Assessment element card

Issue: Are there any other hidden or unintended consequences of the technology and its applications for patients, relatives, other patients, organisations, commercial entities, society etc.?

Topic: Benefit-harm balance

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	4
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	4
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	4
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	4
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>The technology may be used for other indications (extended use) or other purposes, e.g., in combination with other technologies (unintended use). It may have side-effects in addition to those following from the intended use.</p> <p>Consider not only the consequences of the formal intended use of the technology, but also the ethical consequences of unintended and extended use. If unintended consequences are not well-known, they should be speculated and elaborated upon. Evaluate the intended purpose and uses of the technology against the likely uses and consequences of the technology in reality.</p> <p>The mode of delivery, the need for laboratory tests or clinical follow-up to ensure safe and effective dosage and the way of delivery (at home, outpatient or in-patient) may have a large impact on the health care processes, systems and on individuals. They may also change the concepts of disease and normality (e.g. change an untreatable cancer into a chronic disorder or changing the border values when the concept of normality also changes).</p> <p>New technologies tend to lead to new areas of inventions and give rise to new ethical questions (e.g., in vitro fertilisation (IVF) and development of genetic testing has led to questions of preimplantation genetic diagnostics (PGD)). As pre-symptomatic screening tests have become available, the healthcare system has to be prepared to handle moral issues raised by true positive and false negative findings.</p> <p>Another relevant question is whether or not there will be a moral obligation related to the implementation, withdrawal, or use of the technology (e.g. check-ups or alternative procedures).</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>Diagnostic technologies may also have effects on relatives. Not only genetic tests, but all diagnoses of hereditary disorders, also provide knowledge about relatives. Diagnostic information may also affect social relations (e.g. STD)'. </p>					

	<p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>Pharmaceuticals have usually been designed and studied for a specific and defined group of patients, but they may be used for a larger group (variation in age and severity of the disorder and persons with comorbidities and/or need for other pharmaceuticals). Expensive pharmaceuticals (orphan disorders, new cancer treatments) and the prescription of pharmaceuticals according to genetic profiles challenge the equal and just use of health care resources. The health care system has to be prepared to handle moral issues raised by the new, expensive possibilities to treat rare, otherwise non-treatable disorders and to prolong life in chronic disorders.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>Screening positive and being diagnosed with the disease may have effects on relatives as all diagnoses of hereditary disorders also provide knowledge about relatives. Screening results may also affect social relations.</p>
<p><b>Methodology and sources</b></p>	<p><b>Common to all used applications</b></p> <p>Literature search. Expert opinion. Stakeholder hearing</p>
<p><b>References</b></p>	<p><b>Common to all used applications</b></p> <p>Hofman B, 2005 {49}; Ogletree TW {50}</p>
<p><b>Content relations</b></p>	
<p><b>Sequential relations</b></p>	<p><b>Common to all used applications</b></p> <p>None</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>D0030, D0022, D0023, I0008, C0006</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>D0022, D0023, I0008, C0006 D0030, D0022, D0023, I0008, C0006</p>

F0104 Assessment element card						
Issue: Are there any ethical obstacles for evidence generation regarding the benefits and harms of the intervention?						
Topic: Benefit-harm balance						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	5
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	5
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	5
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	5
Clarification	<p><b>Common to all used applications</b></p> <p>When assessing benefits and harms of an intervention there may be ethical obstacles to the conduct of further research in order to strengthen the scientific basis. This concerns issues like the following:</p> <ul style="list-style-type: none"> <li>• When clinical experience shows that the intervention has an effect on a group for whom there are no treatment alternatives and it would thus be ethically unacceptable to conduct a study in which the comparative group would be denied the procedure,</li> <li>• In the case of a vulnerable group of subjects who are difficult to study,</li> <li>• Where specific integrity problems would arise if research were to be conducted.</li> </ul>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Literature search. Expert opinion.</p>					
References	<p><b>Common to all used applications</b></p> <p>Heintz E et al 2015 {51}</p>					
Content relations						
Sequential relations	<p><b>Common to all used applications</b></p> <p>D0029, F0010</p>					

F0005 Assessment element card						
Issue: Is the technology used for individuals that are especially vulnerable?						
Topic: Autonomy						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Complete	Yes	6
	Medical and Surgical Interventions (3.0)	Yes	Critical	Complete	Yes	6
	Pharmaceuticals (3.0)	Yes	Critical	Complete	Yes	6
	Screening Technologies (3.0)	Yes	Critical	Complete	Yes	6
Clarification	<p><b>Common to all used applications</b></p> <p>Clarify the right and justification to use the technology on vulnerable persons. Persons who are vulnerable could, for example, be pregnant women (in which case their unborn child needs to be protected), critically ill patients or individuals that have reduced decision-making capacity (children, persons with cognitive disabilities or patients that due to their illness/state have limited decision making capacity). Who has the right to balance the benefit against possible harm in these situations? On what grounds can these decisions be made? Is the technology so valuable, as to justify its use on people who cannot give informed consent?</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Literature search. Expert opinion. Stakeholder hearing</p>					
References	<p><b>Common to all used applications</b></p> <p>Miller BL, 2004 {52}</p>					
Content relations						
Sequential relations	<p><b>Common to all used applications</b></p> <p>C0005</p>					

F0004 Assessment element card						
Issue: Does the implementation or use of the technology affect the patient's capability and possibility to exercise autonomy?						
Topic: Autonomy						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	7
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	7
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	7
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	7
Clarification	<p><b>Common to all used applications</b></p> <p>Many technologies can alter a person's self-determination. The technology may interfere with a patient's right to autonomy, directly or indirectly, by influencing/subtracting their decisional capacity. However, patients have, in most cases, a right to autonomy, i.e. a right to be self-governing agents. This means they possess both the right to decide (not) to use/participate, and the right to receive relevant information. Drugs for sedation and surgical treatment of severely ill patients are examples where patient autonomy may be reduced.</p> <p>Technology may require users/patients to behave in a certain way (e.g. dietary restrictions for faecal blood test). In order to be able to decide autonomously, the user/receiver of the technology should understand all alternative treatments or different therapeutic paths following test results. They should be able to make informed consent at every step.</p> <p>The practical challenge with treatment technologies is that, in order to be fully autonomous, the patient should understand not just direct risks of the treatment, but also all alternatives, whether side-effects take place, and how these can affect the living quality or choices (e.g. car driving, nutrition).</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Literature search. Expert opinion. Stakeholder hearing</p>					
References	<p><b>Common to all used applications</b></p> <p>Hofman B, 2005 {49}; Miller BL, 2004 {52}</p>					
Content relations						
Sequential relations	<p><b>Common to all used applications</b></p> <p>H0013, D0012, D0013, D0016</p>					

F0006 Assessment element card

Issue: Is there a need for any specific interventions or supportive actions concerning information in order to respect patient autonomy when the technology is used?

Topic: Autonomy

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Complete	Yes	8
	Medical and Surgical Interventions (3.0)	Yes	Critical	Complete	Yes	8
	Pharmaceuticals (3.0)	Yes	Critical	Complete	Yes	8
	Screening Technologies (3.0)	Yes	Critical	Complete	Yes	8
Clarification	<p><b>Common to all used applications</b></p> <p>Focus on the following: Is the common professional practice of discussing the technology with patients enough, or is special information needed to decide on this technology? Can the technology entail special challenges/risks that the patient/person needs to be informed of? Should the patient be explicitly informed, for example, that false positive results of a test may lead to unnecessary further investigations and treatments, sometimes with serious harms? An example is screening programmes for early identification of life-threatening situations that may have life-threatening side effects, such as invasive surgery with risk of death. Technology used for off-label use may have unexpected severe side-effects (e.g. patients with comorbidities or children).</p> <p>The information should enable the user/receiver of the technology to understand the technology and its associated risks/challenges. It should be in accordance to their personal values and intellectual capacity, thereby enabling users to decide accordingly. The patient should be explicitly informed, for example, that the treatment may have serious side effects, may have an effect on personality or lead to increased need of sleep or serious weight gain. They should also be informed of when the mode of delivery or action may affect their daily life (e.g. no car driving allowed, restricted travelling).</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Expert opinion, stakeholder hearing</p>					
References	<p><b>Common to all used applications</b></p> <p>Heintz E et al., 2015 {51}</p>					
Content relations						
Sequential relations	<p><b>Common to all used applications</b></p> <p>H0013, H0007, H0008, C0008, B0014, I0002, C0005</p>					

F0007 Assessment element card						
Issue: Does the implementation or withdrawal of the technology challenge or change professional values, ethics or traditional roles?						
Topic: Autonomy						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	9
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	9
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	9
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	9
Clarification	<p><b>Common to all used applications</b></p> <p>Technologies may change the patient-physician relationship, challenge professional autonomy or otherwise interfere with professional ethics and values. The patient-physician relationship is traditionally based on mutual trust, confidentiality and professional autonomy so that individual treatment decisions can be made in the best interest of the patient. Technologies that interfere with core values and principles of medical and professional ethics challenge the professional integrity of the physicians or other healthcare professionals (e.g. screening for drug abuse when use is denied). Technologies that are aligned with professional ethics are more likely to be implemented successfully. For example, people may ask for the technology for many reasons, while the professionals may see them as unnecessary and even potentially harmful (e.g. antibiotics, sleep medicine, antidepressants, whole body MRI scans).</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Expert opinion</p>					
References	<p><b>Common to all used applications</b></p> <p>Hofmann B, 2005 {49}; Medical Professionalism Project, 2002 {53}</p>					
Content relations						
Sequential relations	<p><b>Common to all used applications</b></p> <p>G0010</p>					

F0008 Assessment element card						
Issue: Does the implementation or use of the technology affect human dignity?						
Topic: Respect for persons						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	10
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	10
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	10
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	10
Clarification	<p><b>Common to all used applications</b></p> <p>Especially those technologies that are applied to persons with reduced autonomy (children, mentally impaired, severely ill) may violate a person's dignity, i.e. challenge the idea that all human beings have intrinsic value, and should thus not be seen as means to others ends. Labelling people as result of using the technology may also threaten their dignity.</p> <p>Some technologies may cause healthy people to be labelled as sick (e.g. PSA for prostate cancer) or otherwise less worthy, abnormal, less clean, etc. For instance labelling people as needing psychiatric medication for their behavioural difficulties may threaten their dignity. People with physical disabilities may be labelled by prenatal screening programmes, which imply that their handicap is an indication for abortion.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Literature search. Expert opinion. Stakeholder hearing</p>					
References	<p><b>Common to all used applications</b></p> <p>Hofman B, 2005 {49}; Kilner JF, 2004 {54}</p>					
Content relations						
Sequential relations						

F0009 Assessment element card						
Issue: Does the implementation or use of the technology affect the patient's moral, religious or cultural integrity?						
Topic: Respect for persons						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	11
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	11
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	11
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	11
Clarification	<p><b>Common to all used applications</b></p> <p>A technology may challenge integrity by preventing (or having the possibility to prevent) patients to live according to their moral convictions, values, preferences or commitments. It may also interfere with the coherent image or identity of the user's self. This is especially important to analyse for vulnerable patient groups.</p> <p>The technology may challenge religious, cultural or moral convictions or beliefs of some groups (e.g. pharmaceuticals produced from human blood given to cultural groups that do not accept blood transfusion, pharmaceuticals used for abortion in cultural groups that do not accept abortion, and assisted reproductive technologies that have separated the concept of genetic, biological and social motherhood).</p> <p>The technology may change generally or locally accepted social arrangements by challenging traditional conceptions or social roles. For instance, ADHD medication might challenge the integrity of people who value personality, and cochlear implants may be problematic for those who do not see deafness as a disability.</p> <p>Identifying the conceptions behind the beliefs and values may help put them in perspective when considering the ethical consequences of use and the overall acceptability of the technology. When possible, considering other acceptable alternatives for the affected groups of users is important. Use of the technology can also be detrimental to integrity if it is associated with discouraging honesty or ethical conduct, e.g., systems that encourages users to lie about their health state in order to get better service/treatment.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Literature search. Expert opinion. Stakeholder hearing</p>					
References	<p><b>Common to all used applications</b></p> <p>Hofmann B, 2005 {49}; Kilner JF, 2004 {54}</p>					
Content relations						

<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>H0011, H0013</p>
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F0101 Assessment element card						
Issue: Does the technology invade the sphere of privacy of the patient/user?						
Topic: Respect for persons						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	12
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	12
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	12
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	12
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>The sphere of privacy can be invaded both virtually and physically. Describe, e.g., these issues: Does the technology affect the population's possibility to have control over personal information? Is dissemination or gathering of information regarding the individual patient or the population justified? Is cooperation and sharing of information with professional groups outside the health services needed? Is the handling of personal information reasonable, given the purpose of using the technology? Is the technology more or less invasive than the alternatives, regarding the physical body and/or the spatial sphere? Is a violation of the privacy of the patient or population necessary and reasonable to achieve desired outcomes?</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Literature search. Expert opinion. Stakeholder hearing</p>					
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Heintz E et al 2015 {51}</p>					
<b>Content relations</b>						
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>B0010, D0011, I0007, I0009, I0002</p>					

F0012 Assessment element card						
Issue: How does implementation or withdrawal of the technology affect the distribution of health care resources?						
Topic: Justice and Equity						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	13
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	13
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	13
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	13
Clarification	<p><b>Common to all used applications</b></p> <p>Many technologies imply substantial costs, sometimes covered with resources from other areas. A new technology may require re-allocation of human resources, funding and training. A large re-allocation of resources may seriously jeopardise other patient groups (e.g. new technology that requires human resources in acute care or new diagnostic technology that uncovers a large pool of unmet needs for treatment). How this reallocation affects the existing health care system has to be studied. Who will gain and who will lose? Is the prioritisation explicit or implicit?</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>Diagnostic technologies sometimes acquire significant symbolic value (e.g. foetal ultrasound, PSA) that may create demands for tests that are not justified on health grounds.</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>Pharmaceuticals may acquire abstract promise of health benefit that may create demand that is not justified. Some diagnosis may create demands for pharmaceuticals that are not always justified to be prescribed on health grounds (e.g. large variation in prescribing ADHD medication for children by various countries).</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>Screening technologies sometimes acquire significant symbolic value (e.g. foetal ultrasound, PSA) that may create demands for tests that are not justified on health grounds.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Expert opinion.</p>					
References	<p><b>Common to all used applications</b></p> <p>Hofmann B, 2005 {49}; Sterba JP, 2004 {55}; Daniels N, 2001 {56}</p>					

<b>Content relations</b>	
<b>Sequential relations</b>	<b>Common to all used applications</b> G0007, E0001,E0002, E0009

<p>F0013 Assessment element card</p> <p>Issue: How are technologies with similar ethical issues treated in the health care system?</p> <p><b>Topic: Justice and Equity</b></p>						
<b>Application-specific properties</b>	<b>Application</b>	<b>Used</b>	<b>Importance</b>	<b>Transferability</b>	<b>Core</b>	<b>Order</b>
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	14
	Medical and Surgical Interventions (3.0)	Yes	Important	Partial	Yes	14
	Pharmaceuticals (3.0)	Yes	Important	Partial	Yes	14
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	14
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Clearly presenting how technologies with similar ethical issues are treated in a healthcare system may help in adopting coherent and just health policies, either by applying past precedents to current cases, or by showing that past cases need reconsideration. Similarity is to be defined individually for each technology. The idea is to focus only on the similarities relevant for solving the ethical problems considered important for the current HTA project. The similar ethical problems can be related to similarities in the technology's medical, technological, economic, social, organisational or legal nature.</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Literature search. Expert opinion</p>					
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Hofmann B, 2005; {49}</p>					
<b>Content relations</b>						
<b>Sequential relations</b>						

H0012 Assessment element card						
Issue: Are there factors that could prevent a group or person from gaining access to the technology?						
Topic: Justice and Equity						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	None	Yes	15
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	15
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	15
	Screening Technologies (3.0)	Yes	Critical	None	Yes	15
Clarification	<p><b>Common to all used applications</b></p> <p>This issue concerns inequality in health. Investing in the reduction of health inequalities is a target of the European Commission, as it contributes to social cohesion and breaks the vicious spiral of poor health being a contributor to, and a result of, poverty and exclusion. Can the technology be applied in a way that gives equal access to those in equal need? How can this be guaranteed? Could potential discrimination or other inequalities (geographic, gender, ethnic, religious, employment, insurance) prevent access?</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Search for or conduct a literature review or, conduct a primary study for important questions that are not covered in the literature; gather evidence from patient groups.</p> <p>See also: <a href="http://ec.europa.eu/health/strategy/docs/swd_investing_in_health.pdf">http://ec.europa.eu/health/strategy/docs/swd_investing_in_health.pdf</a> for more information.</p>					
References						
Content relations						
Sequential relations	<p><b>Common to all used applications</b></p> <p>G0009, G0101, A0012, I0011</p>					
Other domains	Also in: Patients and Social aspects					

F0014 Assessment element card						
Issue: Does the implementation or use of the technology affect the realisation of basic human rights?						
Topic: Legislation						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Complete	Yes	16
	Medical and Surgical Interventions (3.0)	Yes	Critical	Complete	Yes	16
	Pharmaceuticals (3.0)	Yes	Critical	Complete	Yes	16
	Screening Technologies (3.0)	Yes	Critical	Complete	Yes	16
Clarification	<p><b>Common to all used applications</b></p> <p>The basic human rights are most notably declared in the United Nations Declaration of Human Rights (<a href="http://www.un.org/en/documents/udhr/">http://www.un.org/en/documents/udhr/</a> ). They are universal and consider the most important goods, protections and freedoms for mankind. For HTA, perhaps the most relevant are the rights to equality, non-discrimination, safety, adequate standard of living, and healthcare.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Literature search. Laws, rules and regulations. Expert opinion. Stakeholder hearing</p>					
References	<p><b>Common to all used applications</b></p> <p>Hofmann B, 2005; {49}; Marks SP, 2004 {57} in ETH</p>					
Content relations						
Sequential relations	<p><b>Common to all used applications</b></p> <p>H0012</p>					
Other domains	Also in: Legal aspects					

F0016 Assessment element card						
Issue: Can the use of the technology pose ethical challenges that have not been considered in the existing legislations and regulations?						
Topic: Legislation						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	None	No	17
	Medical and Surgical Interventions (3.0)	Yes	Important	None	No	17
	Pharmaceuticals (3.0)	Yes	Important	None	No	17
	Screening Technologies (3.0)	Yes	Important	None	No	17
Clarification	<p><b>Common to all used applications</b></p> <p>Describe whether legislation and regulation to use the technology is fair and adequate. Use of the technology may lead to ethical issues that make current regulations inadequate. Screening and diagnostic technologies are commonly regulated differently than treatments, especially medications. Ethical reflection is essential in order to assess what kind of legislation, regulation or amendments are needed.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Laws, rules and regulations. Stakeholder hearing. Expert opinion</p>					
References	<p><b>Common to all used applications</b></p> <p>Hofmann B 2005 {49}, Capron AM 2004 {58} from the ETH domain</p>					
Content relations						
Sequential relations	<p><b>Common to all used applications</b></p> <p>B0010, I0011, I0009, I0002, I0026 I0037</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>I0008</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>I0008</p>					
Other domains	Also in: Legal aspects					

F0017 Assessment element card						
Issue: What are the ethical consequences of the choice of endpoints, cut-off values and comparators/controls in the assessment?						
Topic: Ethical consequences of the HTA						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	18
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	18
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	18
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	18
Clarification	<p><b>Common to all used applications</b></p> <p>Address any risks of the chosen end-points, cut-off values or comparators/controls giving a biased description of the results of the technology.</p> <p>Clinical effectiveness should ideally be directly related to the disease under treatment. This is not always entirely possible, so other end-points may need to be used (e.g. surrogate markers for preventing a life-threatening disease). In addition, the technology may have several aims (e.g. those related to treating the disease and preventing secondary morbidity).</p> <p>The choice of cut-off values for sensitivity and specificity should be done considering the moral value of different results – for example, high specificity is required if false positives have serious consequences.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Other domains (SAF, EFF). Expert opinion, Stakeholder hearing</p>					
References	<p><b>Common to all used applications</b></p> <p>Hofmann B, 2005 {49}</p>					
Content relations						
Sequential relations	<p><b>Common to all used applications</b></p> <p>See methodological description in EFF and SAF</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>B0018, D1004, D1005, D1006</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>D1004, D1005, D1006, B0018, D1004, D1005, D1006</p>					

F0102 Assessment element card						
Issue: Are there any ethical problems related to the data or the assumptions in the economic evaluation?						
Topic: Ethical consequences of the HTA						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	19
	Medical and Surgical Interventions (3.0)	Yes	Important	Partial	Yes	19
	Pharmaceuticals (3.0)	Yes	Important	Partial	Yes	19
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	19
Clarification	<p><b>Common to all used applications</b></p> <p>Consider whether there are any ethical problems related to the data or assumptions that have been used in the economic evaluation. An example is whether or not indirect costs have been valued in a fair and adequate way.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Literature search, Expert opinion</p>					
References	<p><b>Common to all used applications</b></p> <p>Burls A et al, 2011 {9}; Heintz E et al 2015 {51}</p>					
Content relations						
Sequential relations	<p><b>Common to all used applications</b></p> <p>See methodological description in ECO</p>					

F0103 Assessment element card						
Issue: What are the ethical consequences of conducting the technology assessment at this point of time?						
Topic: Ethical consequences of the HTA						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	20
	Medical and Surgical Interventions (3.0)	Yes	Important	Partial	Yes	20
	Pharmaceuticals (3.0)	Yes	Important	Partial	Yes	20
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	20
Clarification	<p><b>Common to all used applications</b></p> <p>At what time of the technology's lifetime is the technology assessed? What are the consequences of assessing the technology with respect to prioritisation?</p> <p>Who would (not) get access to the new technology, as result of conducting HTA at this point of time? If there are methodological and ethical obstacles to fill a knowledge gap, what are the consequences for the patient group if the knowledge gap cannot be filled in the (near) future? Should the technology be made available to patients despite the inadequate scientific basis at the time of assessment?</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Expert opinion, Stakeholder hearing</p>					
References	<p><b>Common to all used applications</b></p> <p>Hofmann B, 2005 {49}; Heintz E et al 2015 {51}</p>					
Content relations						
Sequential relations	<p><b>Common to all used applications</b></p> <p>D0029, F0104</p>					

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# Organisational aspects (ORG)

## *Description*

The domain of Organisational Aspects (abbreviation: ORG) considers the ways in which different kinds of resources (e.g. material artefacts, human skills and knowledge, money, attitudes, work culture) need to be mobilised and organised when implementing a technology, and the consequences they may further on produce in the organisation and the health care system as a whole. Organisational issues include e.g. work processes and patient/participant flow, quality and sustainability assurance, centralisation, communication and co-operation, managerial structure, and acceptance of a technology.

There are three levels on which to consider organisational aspects: The first is intra-organisational (e.g. how information about a new technology is provided to the patients in the organisation), the second is inter-organisational (e.g. how the communication between different organisations occur), and lastly there is the health care system level (e.g. how to set national objectives). There are various stakeholders besides staff and patients/participants, at various levels, e.g. payers, providers and suppliers. These groups usually have different aims for and expectations of the technology.

The elements which constitute an organisation have been defined in many ways through different approaches; for example, the physical structure, social relations, technology and organisational culture. The structure of an organisation defines its assignment of tasks, reporting systems and the mechanisms of interaction and coordination. In addition, there are other elements of a society and its culture that influence an organisation and its function. There are also different types of organisations, e.g. the profit centre organisation, the matrix organisation and the network organisation. { 1 }

One challenge which assessment of organisational aspects faces is the complexity of health care systems and processes. Due to the multiplicity of objectives and criteria in organisational analysis, this assessment is less pre-determined and more variable than for example economic and clinical effectiveness analyses. In addition, the findings are normally more context-dependent and less transferable than e.g. in the effectiveness and safety domains of an HTA. The choice of assessment areas should also be guided by the information needs of HTA end users (e.g. regional health authorities' focus may differ from that of hospital managers). Furthermore, different health care systems and national rules for medicine prescription must be taken into account in order to deal with transferability issues. Since organisational aspects vary across countries, this could limit exportation of HTA information from one country to another.

### **Topics and issues in this domain**

The organisational domain includes five topics, each containing 2 to 6 issues (questions), thus resulting in a total of 15 issues (table 1). These topics and issues arguably represent the most important organisational issues, but their relevance depends on the specific technology and needs which need to be considered within each assessment. In the context of some technologies, one might identify other more relevant topics and issues, and if such are found, the Model should be amended.

The issues of the organisational domain are more generic than those of many other HTA Core Model domains. This is because organisational aspects are difficult to define in detail beforehand. For example, the issue concerning patient/participant flow asks to describe the steps of the patient path including e.g. intervention and waiting times. Therefore, one issue compiles a coherent full picture of the path instead of focusing on the details in separate issues - such an approach may be more relevant in some other domains. The content of respective issues is explained more comprehensively in the Clarification section of Assessment element table (AE table 2).

While defining the issues, an important thing to consider was that the viewpoint of the organisational domain consists of different levels of health care (micro-, meso- and macro-level).

**Table 1. Topics and issues in this domain**

Topic	Issue	Assessment element ID
Health delivery process	How does the technology affect the current work processes?	G0001
Health delivery process	What kind of patient/participant flow is associated with the new technology?	G0100
Health delivery process	What kind of involvement has to be mobilised for patients/participants and important others and/or caregivers?	G0002
Health delivery process	What kind of process ensures proper education and training of staff?	G0003
Health delivery process	What kinds of co-operation and communication of activities have to be mobilised?	G0004
Health delivery process	In What way is the quality assurance and monitoring system of the new technology organised?	G0012
Structure of health care system	How do de-centralisation or centralisation requirements influence the implementation of the technology?	G0005
Structure of health care system	What are the processes ensuring access to the new technology for patients/participants?	G0101
Process-related costs	What are the costs of processes related to acquisition and setting up the new technology?	G0006
Process-related costs	How does the technology modify the need for other technologies and use of resources?	D0023
Process-related costs	What are the likely budget impacts of implementing the technologies being compared?	G0007
Management	What management problems and opportunities are attached to the technology?	G0008

Management	Who decides which people are eligible for the technology and on what basis?	G0009
Culture	How is the technology accepted?	G0010
Culture	How are other interest groups taken into consideration during the planning/implementation of the technology?	G0011

## Why is this domain important?

In many countries, the organisational aspects have not been a visible part of HTA until a few years ago; the focus has primarily been on clinical aspects {2-4}. The growing focus on organisational issues in HTA indicates an acknowledgement that many resource allocation decisions in the provision of technologies are of crucial importance, and organisational aspects in an HTA influence the behaviour of managers and health professionals {5}. Policymakers on the national level need information on organisational aspects as well, when making decisions on the use of technologies. Organisational aspects in HTA may clarify most of the challenges and barriers in implementing health technologies and, hence, they could influence the impact of health technology assessment.

## Relations to other domains

The organisational domain is related to all other domains: health problem and current use (e.g. utilisation, management), description and technical characteristics (e.g. investments), safety (e.g. occupational safety), effectiveness (e.g. adherence), cost and economic evaluation (e.g. budget impact), ethical aspects (e.g. acceptance), patients and social aspects (e.g. patient/participant aspects), and legal (e.g. privacy). The relationships between the issues are marked in the AE table 4.

Some relationships between issues are sequential. For example the domain of Health Problem and Current Use of Technology (CUR) includes issues concerning the utilisation of a technology, the number of people including the target group and estimates of the utilisation of the technology. The results for these questions should, however, be known before answering most of the ORG domain's issues. In addition, issues concerning any required quality assurance of the technology, which is included in the domain of Description and Technical Characteristics (TEC), are important in the ORG domain. Here, the organisational domain's point of view is different from that of the CUR domain: instead of describing the content of any necessary quality assurance of a new technology, it describes the process required for organising the quality assurance.

The ORG domain is related to the Costs and Economic Evaluation (ECO) domain, as some of the information on organisational aspects can be beneficial in economic analysis. For example, the patient/participant flow of a new technology, which is described in the organisational domain, could offer information on parameters used in economic analysis. For this reason, a dialogue between the ECO domain and the ORG domain should be initiated at an early stage, so that the ECO domain understands the organisational context and can help to provide the Organisational Aspects with any relevant information.

## **Diagnostics-specific content**

Implementation of new diagnostic methods leads to necessary organisational changes which should be taken into account. The implementation of a new diagnostic test can substantially increase (or decrease) the number of patients who need to be treated, thus changing the relationships between different organisations and influencing the health care system as a whole. Some diagnostic tests are used by patients at home and patients should be taught how to use them.

## **Screening-specific content**

A screening program is a system which incorporates all necessary steps, from identifying and providing information to the eligible population, through actual screening, to diagnostic testing and treatment. The assessment of a screening technology thus implies assessing a complex organisation where organisational changes and relationships within and between organisations are considered.

The screening technology being assessed can have various objectives and thus various implications for the assessment of organisational aspects. For example, when assessing a mammography screening program, the focus can be on a new screening test (digital mammography), or on the population eligible for screening (screening for women less than 50 years old), or on varying the screening interval (1 to 3 years), or on the way to deliver the test (e.g. in colorectal cancer screening calling people to attend faecal testing versus mailing the test kit to them).

Regarding the population eligible for screening, the organisational domain finds important certain factors from other domains; namely, the extent of the use of screening as defined in the CUR domain, while in the TEC domain, these are issues concerning definitions of the screening test and further investigations (diagnostic tests). The ECO domain often benefits from determining e.g. the management of screening programmes, personnel training and patient/participant flows, which are specified in the organisational domain.

## **Pharmaceutical-specific content**

Pharmaceutical policy is a system dealing with not only registration and reimbursement, but also with the distribution, rational and safe use of pharmaceuticals in clinical practice, and the management of these. When assessing a new pharmaceutical, it is necessary to consider the impact of a single pharmaceutical on the care pathway organisation, and the interaction of the pharmaceutical with pre-existing health technologies.

# *Methodology*

## **Process for answering research questions**

The organisational aspects process of assessment starts with defining the relevant scope of analysis, as well as relevant topics and issues for the technology that is being assessed. After this, one must choose a theoretical perspective that is appropriate for the co-production. When identifying the research problems and questions, it has to be taken into account that organisational analysis deals with the overall policy questions and with the organisational set-up.

The first step is to make a systematic literature search with a focus on organisational aspects. If there are no systematic reviews available, primary studies and other sources of information (e.g. guidelines) should be used. If there are no relevant studies, one's own research should be conducted, e.g. in the form of surveys or interviews. If there are no resources or time for personal research, health care professionals or content experts should at least be consulted.

The researchers working in this domain should consider their basic approach early on in the project, as several other domains (e.g. ECO domain) depend on the answers produced by this domain. Sometimes it could be sensible to make a joint survey with the technology description and current use domains early in the project as a pragmatic approach in finding answers to key questions. Other domains could contribute to the survey questions by providing useful information for everyone, in all domains. A common survey has to be considered carefully, as it may prove time consuming and requiring lot of resources.

Qualitative research plays a significant role when assessing organisational aspects. Qualitative research can assist in understanding how patients perceive health and make decisions related to health service usage, and in understanding the culture of communities in relation to implementing changes and overcoming barriers.

If the researchers of this domain decide to make a full systematic literature review to answer one or more questions in this domain, they should also consult the EUnetHTA Guideline [Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness](http://www.eunethta.eu/eunethta-guidelines), available at <http://www.eunethta.eu/eunethta-guidelines>. Although focusing on effectiveness, the guideline may provide useful advice for work within other domains as well.

## **Gathering information**

### *Where to find information?*

Several sources of information are necessary in order to find answers to questions of the ORG domain. To reduce publication bias, it is recommended that a wide range of sources of information be utilised {6}. The sources should include published literature, as well as grey literature, hand searching of journals, contacting experts, and scanning reference lists of relevant papers. In addition, own research is often an important source of information. The information retrieved for the ORG domain may often be rather general in nature and not necessarily disease-or product-specific.

## Databases and search strategies

Some important databases and other sources of information possibly useful for performing analysis in this domain are listed below. The list is extensive and researchers within each HTA project should carefully consider which sources best match the needs of their project. We recommend also using the Summarized Research in Information Retrieval for HTA (SuRe Info, available at <http://vortal.htai.org/?q=sure-info>) which provides research-based information related to the information retrieval aspects of producing health technology assessment.

The databases needed for the organizational domain depend on the topic of assessment. Usually, the most used databases are MEDLINE/Pubmed, CRD DARE, Cinahl, Cochrane Library and GIN.

### **Bibliographic databases on published literature:**

- Health sciences:
  - MEDLINE (published by the United States National Library of Medicine) / Pubmed (<http://www.ncbi.nlm.nih.gov/pubmed/>)
  - EMBASE (Excerpta Medica published by Elsevier) (<https://www.embase.com/>),
  - Cochrane Library (<http://www.thecochranelibrary.com/view/0/index.html>)
  - CRD Databases
    - DARE (Centre for Reviews and Dissemination / Database of Abstracts of Reviews of Effects)
    - HTA (Health Technology Assessment)
    - NHS EED (National Institute for Health Research / Economic Evaluation Database)
  - Cinahl (Cumulative Index to Nursing and Allied Health Literature)
  - PsycInfo (literature in behavioral sciences and mental health)
- Social Science databases: Sociological Abstracts, Social Services Abstracts, Social Care on line / Caredata and SocINDEX, ASSIA (Applied Social Sciences Index and Abstracts)
- Administrative studies: General science publishers' databases such as Emerald Library, Science Direct and Ebsco Academic Search Elite, Pub Med Central (PMC) and Bio Med Central (BMC), ProQuest Health Management
- Educational database: ERIC (Education Recourses Information Center)

### Other databases:

- GIN (Guideline International Network) at <http://www.g-i-n.net/>
- Experience of organisations e.g. NHS Technology Adoption Centre <http://www.technologyadoptionhub.nhs.uk/>
- The EUnetHTA pool of structured HTA information will be a pertinent source of information on e.g. disease incidence, at <http://www.corehta.info>
- HTAi Vortal includes information for conducting HTA at <http://vortal.htai.org/>
- The Joanna Briggs Institute Library at <http://www.joannabriggslibrary.org/jbilibrary/>
- Ongoing research databases, e.g.
  - EUnetHTA POP database at <http://eunethta.dimdi.de/PopDB/>
  - ClinicalTrials.gov at <http://www.clinicaltrials.gov/>
  - Prospero (International prospective register of systematic reviews) at <http://www.crd.york.ac.uk/PROSPERO/>
- Horizon scanning databases and web sites, e.g. EuroScan at [www.euroscan.org.uk](http://www.euroscan.org.uk) BIOSIS (life sciences database) <http://science.thomsonreuters.com/training/biosis>
  - Includes patents, journals, conferences, books, review articles etc.
- Institute of Health Economics (IHE) ‘Health technology assessment on the net’ report (<http://www.ahfmr.ab.ca>) can provide a useful starting point (see also other sources in Appendix 1).
- Databases of international organisations, e.g. the WHO, OECD
- Regulatory bodies’ databases
- Grey literature:
  - Dissertational Abstracts, conference proceedings (Web of Science database);
  - OAIster (including open access collections)

### Registers and statistics:

- Technology and procedure registers (in Appendix 1)
- Disease registers (in Appendix 1)
- Birth defect registries
- National screening registries
- Routinely collected statistics and administrative data (e.g. DRG, discharge databases, reimbursement claims databases)

- Pharmaceutical registers (Rote Liste, Vidal, DrugDex)

**Web sites:**

- Scientific specialist associations' web sites
- Clinicians' web sites
- Patient associations' web sites
- Manufacturers' web sites
- Marketing authorisation and other regulatory institutions' web sites (in Appendix 1).
  - The SPC (Summary of Product Characteristics) includes information on the marketing authorisation status of a pharmaceutical [https://en.wikipedia.org/wiki/Summary\\_of\\_Product\\_Characteristics](https://en.wikipedia.org/wiki/Summary_of_Product_Characteristics)
  - EPARs (European Medicines Agency/European Public Assessment Reports)
  - National health services' web sites
  - Regional/local governments' health departments' web sites
  - Benefits and sickness funds' web sites
  - Technology developers' and manufacturers' web sites
  - Various sources through using internet search engines

**Other sources:**

- Hand-searching the reference lists of key papers
- Grey literature (e.g. working papers from research groups or committees, white papers, or preprints)
- Conference proceedings
- Market research reports
- Manufacturers' handbooks and direct contacts
- Industry
- Expert opinions: Contacts or interviews with appropriate experts and agencies
- National and regional guidelines
- National and regional norms and regulations

## Own primary research

One's own research is needed in situations where adequate information cannot be found through a literature search, as well as in the case of a specific need for information on a particular geographic area (if the information is not found in the literature). As the organisational domain is in multiple ways related to other domains, it may be helpful to co-operate with the other domains while conducting one's own research. Relationships, especially sequential ones (e.g. with the ECO domain) need to be taken into account before starting one's own research.

Some aspects to bear in mind when considering own research:

- Own qualitative research might be the only way to assess real practice use and misuse.
- Useful information can be received from:
  - Discussions with experts or officials
  - Expert surveys or interviews
  - Research using administrative databases
  - Register-based research
  - Industry

If resources available for the assessment project do not allow carrying out one's own primary research, it can be useful to consult health care professionals or other content experts in a less formal manner.

When starting primary research, the aim of the research needs to be clarified. The list of assessment elements is there to help specify the aim and content of the research. The research questions will then influence the choice of research design (quantitative or qualitative). Quantitative research could be descriptive (survey or case series) or analytical (observational or experimental), while qualitative research uses inductive reasoning and could be used together with quantitative research designs (mixed method). There are several possible study methods to choose from, e.g. interviews, questionnaires, observation or analysis of written material, among others. The target group(s) of one's own research has(have) to be planned carefully. For example, tailored questionnaires for or interviews with different groups of professionals may be needed in order to acquire information about work processes.

It will usually prove difficult to isolate and measure the output effects of given organisational initiatives. A more realistic option is to describe the various dimensions of the process in the relationship between a technology and organisational behaviour. The natural starting point when analysing a change in processes is to map the current work processes and patient-flow. Therefore, the data collection methods involve qualitative methods such as interviews or observations, or quantitative methods such as surveys. { 1 }

## ***What kind of information is required?***

Evaluating public health interventions is usually a complex affair, as multiple interventions, outcomes, participants, settings and stakeholders are often necessary components. Because of this complexity, no single research method is likely to be appropriate and a range of different study designs need to be used. There has been a proposal for a framework which offers guidance for the various phases of the design and assessment of complex interventions . These include establishing the theoretical basis (mechanisms of action) for the intervention, as a sound theoretical base is considered vital to the design of complex interventions and the providing an explanation for likely success mechanisms. However, in practice, many interventions and assessments lack explicit theoretical underpinning. {7}

In a complex system such as health care, the boundaries are typically indistinct, and activities of different agents are not predictable. Multiple approaches to assessment are needed in these kinds of systems {8}. It is possible to understand how various organisational functions operate by looking at different theoretical frameworks.

One approach to addressing health care systems is to divide them into the micro-level (patient interaction), meso-level (health care organization and community) and macro-level (health policy). All these levels have been taken into account while defining organisational domain issues. Most of the issues are relevant at all levels (e.g. approval of a new technology), but some mostly on one level, (e.g. issues related to the staff, which affect mostly the hospital level). There are issues related to the patients/participants in nearly all topics.

The relationship between technology and organisation can be tackled in different ways. At least two different and incompatible views on causality and transferability can be distinguished with regards to organisational issues: the diffusion model and the translation model, see Appendix 2 {1, 9}.

The definition of organisational analysis in this document is based on the loose approach called co-production of technology and its context and especially on the translation model. The main thesis of the definition is that a technology needs a context or a network to function. In addition to the translation model, other approaches that form the co-production approach are, for example, constructive technology assessment {10, 11}, the systems approach {12} and social construction of technology {13}.

Both the organisational and the administrative perspective can be used in an organisational analysis {14} Administrative analysis uses a managerial perspective (e.g. decision making, co-ordination and managerial tools) , while organisational analysis deals with changes in relation to the executing /producing function (e.g. organisational conditions, change processes).

## **Study types, design, outcome measures**

A wide range of disciplines need to be applied when researching the organization and delivery of health services {15}. It can be challenging for researchers from various disciplines to think outside their own paradigms {4}. Multidisciplinary research is nevertheless a key element in the organisational domain, and qualitative study is the mostly used study type. (Table 2). In this kind of research approach, the scope of relevant evidence is not known in advance and the search method is therefore usually iterative. The information collected by the iterative search can be systematic only if the search steps have been documented carefully.

There are several ways of formulating the research question of organisational aspects. Within quantitative research, the review question is usually based on PICO (Patient, Interventions, Control, Outcomes). On the other hand, within qualitative evidence synthesis the more appropriate methods for formulating a research question would be SPICE (Setting, Perspective, Intervention/Interest, Comparison, Evaluation) {16} or PICO (Population, phenomena of Interest, Context) {17}.

The choice of study design that gives the most reliable answer to a research question depends on the question itself. Both quantitative and qualitative studies and their synthesis are essential in the organisational domain. Although the most important sources of information are observational and qualitative studies, it is also relevant to check if there are controlled or quasi-experimental studies available. Other types of relevant information for organisational issues can be found in national and international guidelines, statistics and registers and handbooks.

**Table [2]: Types of information required in this domain**

Topic	Study type	Quality assessment	Systematic vs other	Synthesis
Health delivery process	Guidelines, observational, mostly qualitative, partly quantitative, RCT or systematic reviews of RCTs	AGREE, or other methods to evaluate guideline quality, tools for qualitative and quantitative (RCT)study appraisal.	Not necessarily systematic, some are systematic (RCT, guidelines)	narrative, meta-analysis for most commonly evaluated intervention, narrative for less common and complex interventions
Structure of health care	Guidelines, observational, mostly qualitative. Health Information Databases (DRG etc.)	Not relevant, tools for qualitative study appraisal, AGREE	not necessarily systematic, systematic for guidelines	narrative
Process-related costs	Guidelines, producer technical handbooks, Costing and budget impact analyses,	Not relevant, Tools for the evaluation of economic studies	systematic at least for technical requirements	narrative
Management	Guidelines, observational studies mostly qualitative, consensus, protocols	Not relevant, tools for qualitative study appraisal, AGREE	not necessarily systematic, systematic for national and regional reports	narrative
Culture	Observational, mostly qualitative. Scientific societies websites	Not relevant, tools for qualitative study appraisal	not necessarily systematic, systematic for national and regional reports	narrative

## ***Inclusion and exclusion criteria: principles and tools***

The inclusion and exclusion criteria of the studies should be clearly defined *a priori*. The eligibility criteria used should specify the patients, interventions or exposures, and outcomes of interest. In many cases the type of study design will also be a key component of the eligibility criteria.

## **Tools for critical appraisals**

Quality assessment of information retrieved in the organisational domain may be difficult, as there is often no standard way of doing it, and 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 source (see table 2) and type of information requested (quantitative or qualitative; registers, administrative data etc.).

There are different study types used in gathering information for the organisational domain, and the range of quality assessment and appraisal instruments available to assess studies is therefore wide. Some of the appraisal instruments are generic and others targeted to specified contexts.

For quantitative studies, assessment of quality is clearer than for qualitative studies. It has been claimed that a qualitative study's quality cannot be determined by prescribed instruments {18}. Therefore, the use of checklists or scales in order to assess the quality of observational or qualitative studies in particular is not always relevant.

The Canadian CADTH has reviewed quality assessment tools and provides useful insights into the topic and details beyond what is included in this chapter {19}. Relevant guidance about critical appraisal of quantitative and qualitative studies is available in the Cochrane Handbook for Systematic Reviews of Interventions in part 2, Chapter 8 (Assessing risk of bias in included studies) [www.cochrane-handbook.org](http://www.cochrane-handbook.org).

## ***Critical Appraisal of Quantitative and Qualitative Evidence***

There is a range of study designs that may be incorporated within quantitative reviews. A common approach is to state a preferred hierarchy of study types: Experimental (e.g. randomised controlled trials (RCTs)), quasi-experimental (e.g. non-randomised controlled trials), observational (correlational) (e.g. cohort, case control studies), observational (descriptive) (e.g. case series and case study) and expert opinion. By also stating the level of evidence, the quality of evidence would be more appropriately assessed. An example of such an approach is the JBI Levels of Evidence classification, available at <http://joannabriggs.org/jbi-approach.html#tabbed-nav=Levels-of-Evidence>

## **Quality Assessment of Trials**

The RCT (Randomized Controlled Trials) and quasi-RCT represent one of the most frequent research study types, where one can find quantitative data on the results of applying a certain health technology. The quality of this information should be assessed using aspects such as: random assignment of patients, blinded allocation of patients, blinded evaluation of outcomes, similar control and treatment groups, confounders, outcomes measurement, statistical analysis etc. Relevant

guidance is in the Cochrane handbook (Part 2, 8.4 Introduction to sources of bias in clinical trials) [www.cochrane-handbook.org](http://www.cochrane-handbook.org).

### **Quality Assessment of Epidemiologic studies**

Different fields in epidemiology have varying levels of validity. One way to assess the validity of findings is to observe the ratio of false-positives (claimed effects that are not correct) to false-negatives (studies which fail to support a true effect).

Several checklists or scales exist for the critical appraisal of observational studies, but no consensus exists about using them. In choosing the checklist, it has to be considered how easy the scale is to use and how long it takes to complete each instrument. The most appropriate scales are Newcastle Ottawa Scale\*, the checklist of AHQR (System to Rate the Strength of Scientific Evidence) and checklist of STROBE\*\* on reporting observational studies.

The EUnetHTA guideline for classifying evidence and assessing risk of bias for non-randomised studies recommends the ACROBAT-NRSI (A Cochrane Risk of Bias Assessment Tool) as primary RoB tool for the assessment of non-randomised studies, available at <http://www.eunethta.eu/eunethta-guidelines>.

*\*Newcastle Ottawa scale, available through [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) may not be appropriate in the quality assessment of studies examining disease prevalence or burden of disease. It is more appropriate for studies assessing the link between diseases and risk factors.*

*\*\*STROBE check list ([www.strobe-statement.org/index.php?id=available-checklists](http://www.strobe-statement.org/index.php?id=available-checklists)) can be used as a check list for study quality, although it is an instrument meant for assessing the quality of reporting.*

### **Quality Assessment of case-control or cohort studies**

Case-control or cohort studies can be used to identify effectiveness of the benefits observed in randomised trials across broader populations in clinical settings, and to provide information on adverse effects and risks. Relevant guidance is available in Joanna Briggs Institute's Reviewer's Manual, 2014, particularly Appendices V and VI {17}.

### **Quality Assessment of observational studies**

Much like for epidemiological studies, there are several checklists or scales on the critical appraisal of observational studies, but no consensus about using them. In choosing a checklist, it had to be taken into account how easy the scale is to use and how long it takes to complete each instrument. Some of the most appropriate scales are Newcastle Ottawa Scale, the checklist of AHQR (System to Rate the Strength of Scientific Evidence) and checklist of STROBE on reporting observational studies.

### **Quality Assessment of guidelines**

AGREE (<http://www.agreetrust.org/>) is a tool for assessing quality of clinical practice guidelines. Grading the quality of evidence and the strength of recommendations can be done with GRADE (<http://www.gradeworkinggroup.org/>).

### **Quality Assessment of manufacturers' data**

The information provided by manufacturers might be limited due to issues of confidentiality and marketing. This kind of source can be useful in answering questions concerning the requirements for use of the technology, the development status or forthcoming innovations of the technology. Manufacturers may also provide information about on-going research and on scientific literature not yet published. Scientific information provided by manufacturers needs to be evaluated for validity and applicability. 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.

### **Quality assessment of expert opinion**

If there is not enough time to perform a primary study, health care professionals and content experts or other stakeholders can be consulted for their opinion. However, one needs to be aware that the amount of knowledge or the respondents' views may be limited, as it reflects the willingness of the participants to listen and speak. Even when speaking, the participant's information output is influenced by the positions and power relations of the professionals and patients, knowledge asymmetry, patient's dependency on the doctor's good will, and time constraints. Stakeholders may represent the patient's perspective, but the evaluator should be critical to any political agenda.

While establishing validity, it is not possible to focus on limiting bias in the appraisal of quantitative studies, especially when dealing with text and opinion. In appraisal of text, one needs to consider the opinions being raised are vetted, the credibility of the source investigated, the motives for the opinion examined, and the global context in terms of alternate or complementary views. The validity in this context therefore relates to what is being said, the source, his/her credibility and logic, and consideration of the overt and covert motives at play.

### **Quality assessment of registers, statistics and routinely collected data**

**Registers:** When one or more quality-assured registers exist, as is the case for example for many organized screening programs or medical implants, the information can be highly reliable.

The relevance and quality of registers should be appraised carefully, considering the following questions:

- How representative is the register? (European, national, regional, local?)
- What kind of information has been coded?
- What are the inclusion/exclusion criteria for the data entered?
- What is the quality of information?
- How complete is the coverage?

Data access is an important aspect when working with registers. It may be impossible for institutions other than the ones managing the register to analyse the raw data. However, some registers conduct customized analyses.

**Statistics and routinely collected data:** Routinely collected administrative data (e.g. DRGs, discharge databases, reimbursement claims databases) can be useful, when available. For example sickness funds collect large amounts of information which could be used to analyse the utilisation of a technology. By definition, this data has been collected for purposes other than research and

they cannot be used to answer scientific questions without previous processing. An analysis of this kind of data might be very time-consuming, since data needs to be “prepared” before analysis, and hence the data may not be feasible for use within an HTA project. The use of routinely collected statistics has several limitations. The reliability of the diagnosis varies and it is usually not possible to differentiate between different stages of the disease. Even the validity of the coding of death causes may be variable, and in some countries it is known to be very limited. There are several national and international sources of statistics which can be used to assess the incidence, prevalence, mortality, or burden of disease. These statistics are usually in aggregated form and increasingly available online.

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. Researchers of this domain should be aware of the *Policy for HTA Core Model and core HTA information*(<http://www.corehta.info/PoliciesAndTerms.aspx>) that defines specific rules for using non-public data.

## ***Critical Appraisal of Qualitative Evidence***

A variety of checklists and tools to assess qualitative studies is available. These tools use a series of criteria that can be scored and the decision to include a study can be made based on whether it meets a pre-determined proportion of all criteria, or certain criteria. Some tools use weighted scores to evaluate different criteria. An example of a checklist for critical appraisal of qualitative research is available within the CASP (Critical Appraisal Skills Programme) Checklists at <http://www.casp-uk.net>.

Appraisal should consider appropriateness of research method(s), sampling, data collection and analysis. Although there are several available quality assessment instruments, disagreement still exists about which criteria is appropriate for the critical appraisal of qualitative research, and whether quality assessment should be done at all.

For example, within a Cochrane Intervention review, a critical appraisal of qualitative studies is considered an essential step. According to Cochrane guidance, critical appraisal involves (1) filtering against minimum criteria, involving adequacy of reporting detail on the data sampling, collection and analysis; (2) technical rigour of the study elements indicating methodological soundness and (3) paradigmatic sufficiency, referring to researchers’ responsiveness to data and theoretical consistency. When choosing an assessment instrument, the review team needs to how appropriate their choice is in the context of their review, and to be aware that whether or not a study meets the standard might depend on the instrument used. {20}.

## **Analysing and synthesizing evidence**

### ***Data extraction***

There are several issues defined in the HTA Core Model, in this domain particularly, where systematic data retrieval is not necessary (see Table 1). Unsystematic information gathering from books, surveys, introduction sections of reviews and articles, registers and the internet (until saturation is reached) may be enough. However, in the case of insufficient or selective inclusion of information sources and data, one should beware of selection bias and duly reflect the possible limitations in the domain's discussion chapter.

When using systematic data retrieval, the approach to data extraction must be appropriate with regards to the review question, the type of review and the available evidence. The data extraction needs to be systematic and transparent. The design of these forms should be undertaken carefully, as it can be a subjective process {7}. The amount of information to be extracted should be directly related to the questions posed and it must balance detail with usefulness (overly inclusive/minimalist data extraction form).

In reviews of qualitative studies, data extraction is typically a more iterative process. Review authors may move between reading primary papers, data extraction and synthesis/interpretation in several cycles as key themes and questions emerge from the synthesis. {21}

Key components of data extraction (especially of quantitative studies) include: identifying features of the study (title, authors, journal, publication details); population characteristics and care setting; methodological quality; interventions; outcomes: length of follow-up: drops-outs: missing data; data of the results: effect measures, and notes. A different form may be necessary if there are findings from qualitative studies. The Cochrane handbook has aggregated different kinds of extraction forms of qualitative studies {21}. Relevant guidance is available also through the Joanna Briggs Institutes' Reviewer's Manual {17} and the SUMARI (System for the Unified Management, Assessment and Review of Information), available at <http://joannabriggs.org/sumari.html>. SUMARI is designed to assist researchers and practitioners in fields such as health, social sciences and humanities to appraise and synthesis evidence of feasibility, appropriateness, meaningfulness and effectiveness; and to conduct economic evaluations of activities and interventions.. It is composed of several modules, which e.g. facilitate critical appraisal, data extraction and meta-aggregation of the findings of qualitative studies.

### ***Biases, confounding factors, level of evidence***

Triangulation is a way to reduce bias in research, and thus should be recommended when assessing organisational issues. Triangulation compares the results from two or more different methods of data collection (for example, interview and observation) or two or more data sources (for example, interviews with members of different interest groups). The researcher looks for patterns of convergence to develop or corroborate an overall interpretation. Triangulation can be seen as a way of ensuring comprehensiveness and encouraging a more reflexive analysis of data than as a pure test of validity. {22}

## ***Evidence tables***

Evidence tables may include information such as study design attributes, patient characteristics, patient outcomes, and derived summary statistics.

Until now the HTA Core Model has not contained any standard tables for summarizing the evidence supporting the answers to research questions. Provision of table templates will be explored in collaboration with Work Packages 4 and 5 of the EUnetHTA Joint Action 2.

The following resources provide useful insights into presenting data in tabular format:

- The Cochrane Handbook for Systematic Reviewers of Interventions, <http://www.cochrane.org/training/cochrane-handbook> and <http://handbook.cochrane.org>
  - particularly chapter 11.5 ‘Summary of findings tables ‘
- Guidelines International Network: Evidence Tables Working Group <http://www.g-i-n.net/activities/etwg>
- Sign 50: A Guideline Developer’s Handbook <http://www.sign.ac.uk/guidelines/fulltext/50/index.html> , example at <http://www.sign.ac.uk/guidelines/fulltext/50/compevidence.html>
- NICE: The Guidelines Manual 2012, appendices J-K, <http://publications.nice.org.uk/the-guidelines-manual-appendicies-jk-pmg6c>
- HTA 101: V. Appraising the evidence, <http://www.nlm.nih.gov/nichsr/hta101/ta10107.html>
- GRADE: The Grading of Recommendations Assessment, Development and Evaluation <http://www.gradeworkinggroup.org/index.htm>

## ***Meta-analysis***

Meta-analysis is rarely used in the organisational domain because most of the studies are qualitative or otherwise not suitable for meta-analysis.

## ***Synthesis of qualitative research***

Synthesizing qualitative evidence entails a process of combining evidence from individual qualitative studies in order to create new understanding. This is done by comparing and analysing concepts and findings from different sources of evidence with a focus on the same topic of interest. The synthesis can be an aggregative or interpretive process which requires authors to identify and extract evidence, categorizing the evidence, and combine categories so as to develop synthesized findings. It is important to understand why people feel or behave in certain ways rather than just to make a description of it {23}.

There is a range of methods available for synthesizing diverse forms of evidence; for example, meta-ethnography, grounded theory, thematic synthesis, narrative synthesis, realist synthesis and content analysis. Some of these methods maintain the qualitative form of the evidence (such as

meta-ethnography) and some involve converting qualitative findings into a quantitative form (such as content analysis). {7}

Synthesis methods are classified in different ways, and it has been argued whether it is acceptable to conduct syntheses of qualitative evidence at all, and if it is acceptable to synthesize qualitative studies derived from different traditions. {7, 24, 25}

Qualitative and quantitative findings could be synthesized in two ways: multilevel synthesis (separate and combined synthesis) and parallel (separate and juxtaposed synthesis) {23}. Quantitative and qualitative studies can be synthesized together; one example is a systematic review on teenage pregnancy and social disadvantage {20}.

## Reporting and interpreting

Transparency in information retrieval is crucial when reporting core HTA information; for each issue, one should explicitly state the sources and methods of information retrieval, whether they are systematic or not, and what the quality assessment criteria was (also when missing).

A reader of core HTA information might be interested in knowing the incidence of the condition and the extent of use of the technology in other countries, particularly when there is no information available from one's own country. Therefore, both European and national-level data may be of importance, and can thus be reported. Tables, graphs and figures make for abundant numerical information, e.g. trends in epidemiology, more digestible.

Overview of guidelines synthesizing the main recommendations on management practises would be illustrative.

The transferability of research identified in the literature searches will have to be assessed very carefully, since this domain is generally considered to be highly context-specific. It is possible that the results from the literature review can be considered hypothesis-generating and useful for planning primary research in one's own context.

## Screening-specific content

Policy measures such as the choice between organised and opportunistic screening, or the reimbursement/funding strategies, are implemented at the macro-level and are likely to be assessed more appropriately by observational/qualitative studies. The organisation of delivering screening services at the institutional (meso-level) can be studied using qualitative research designs, but experimental studies may also offer valuable and crucial information. Similarly, at the micro-level of the provider-patient interaction, both experimental and qualitative evidence are important when assessing screening technology. Of course, there are interactions moving across the three levels, and different actors may be involved at more than one level (i.e. the provider is involved both at the meso- and at the micro-level).

## **Pharmaceutical-specific content**

Pharmaceuticals can be used at home or in the hospital, and this to some extent determines the success of treatment. In the hospital, a pharmaceutical is administered by trained and skilled personnel. At home, and at events that take place during the hospital stay, pharmaceuticals are administered by the patient himself, by their relatives, or in some cases by ambulatory trained personnel. It is necessary to evaluate whether patients are able to administer the prescribed treatment at home, read labels, understand dose instructions, and open containers or packaging.

## Assessment elements

G0001 Assessment element card						
Issue: How does the technology affect the current work processes?						
Topic: Health delivery process						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	1
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	1
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	1
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	1
Clarification	<p><b>Common to all used applications</b></p> <p>Describe current tasks and work processes. This helps illustrate the whole process as well as the continuity of care across professional and organisational boundaries. Who is doing what in the process?</p> <p>There are many actors at different levels (intra-organisational, inter-organisational and health care system level) in the process. Continuity should be ensured so that there will be no gaps between the steps of the process.</p> <p>Explain what kind of changes a new technology could have: it might replace or reduce some activities. In addition, the new technology may have an impact on current pathways of care (e.g. shift towards community care or inpatient care).</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>The implementation of a new diagnostic test can substantially increase (or decrease) the number of patients in need of treatment thus changing the relationships between different organizations and influencing the health care system as a whole.</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>Specify the differences in work processes between the new medicine and the comparator. For example, the new medicine does not need routine laboratory unlike the comparator.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>Describe how the screening process has been organised, e.g. (1) how the target population is chosen; (2) how and by whom the invitation is carried out (open/fixed invitation, announcement/personal invitation letter); (3) how and by whom the information for consent is given; (4) how, where and by whom the test is executed, 5) how, where and by whom the further investigations and treatment are carried out; (6) how, when, and by whom the follow up services are carried out (e.g. notification of results, recalls, reminders).</p> <p>It's important to describe all steps needed in the screening process for the economic evaluation.</p>					

<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Literature search, guidelines, annual reports and statistics, reports and own study (e.g. questionnaires and interviews of different actors)</p>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Kristensen FB et.al, 2001 {1}; Kristensen FB et al., 2007 {14}</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>A0007, A0011, A0023, A0024; B0004, C0063; D0010, D0020, D0021, D0023; F0001, F0007; I0002, I0009</p>
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>E0001</p>

G0100 Assessment element card						
Issue: What kind of patient/participant flow is associated with the new technology?						
Topic: Health delivery process						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	2
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	2
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	2
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	2
Clarification	<p><b>Common to all used applications</b></p> <p>This issue deals with the path of the patient/participant from their own point of view. Describe the patient's path step by step. This also includes waiting times for diagnosis and/or treatment and waiting times for the analysis of the technology.</p> <p>Take into account all preparations that patients/participants need to make before and after (e.g. diet before bariatric surgery), as well as the need for self/home monitoring.</p> <p>In addition, take into account the impact of the technology on current pathways of care. It may e.g. shift towards community care or inpatient care.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Literature search, guidelines, annual reports and statistics, reports and own study (e.g. questionnaires and interviews of different actors)</p>					
References	<p><b>Common to all used applications</b></p> <p>Kristensen FB et.al, 2001 {1}; Kristensen FB et al., 2007 {14}</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>A0010, H0003</p>					
Sequential relations	<p><b>Common to all used applications</b></p> <p>E0001</p>					

G0002 Assessment element card						
Issue: What kind of involvement has to be mobilized for patients/participants and important others and/or caregivers?						
Topic: Health delivery process						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	None	No	3
	Medical and Surgical Interventions (3.0)	Yes	Important	None	No	3
	Pharmaceuticals (3.0)	Yes	Important	Partial	Yes	3
	Screening Technologies (3.0)	Yes	Critical	None	Yes	3
Clarification	<p><b>Common to all used applications</b></p> <p>This issue concerns the role of patients/participants. A new technology may require task distribution among the people involved in treatment and care. Patients/participants and their important others and/or caregivers may be more actively involved in their own care and treatment, or otherwise, tasks they used to carry out may be taken over by health professionals.</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>Some diagnostic tests are used by patients at home, and patients should be taught how to use them.</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>The way in which the patient administers the medicine and how he is involved in the follow-up (monitoring by patients/participants or by their important others and/or caregivers).</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>The screening needs to be organised in such a way that the test and further investigations are easily attainable; e.g. mobile mammography.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Literature search, annual reports and statistics reports, hospital documents and own study: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory, participants).</p>					
References	<p><b>Common to all used applications</b></p> <p>Kristensen FB et al., 2007 {14}</p>					

<b>Content relations</b>	<b>Common to all used applications</b> A0007; B0014; H0003, H0010, H0006, H0007, H0008, H0009, H0013
<b>Sequential relations</b>	<b>Common to all used applications</b> H0002

G0003 Assessment element card						
Issue: What kind of process ensures proper education and training of staff?						
Topic: Health delivery process						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	4
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	4
	Pharmaceuticals (3.0)	Yes	Important	Partial	Yes	4
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	4
Clarification	<p><b>Common to all used applications</b></p> <p>A new technology may require new kinds of professionals or new tasks for existing personnel. This issue deals with how the organisation can ensure proper education. Take into account the effect of training on the management and effectiveness</p> <p>Implementing a technology can change the nature of the work and thus have influence on job satisfaction.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>When implementing new screening technologies, proper staff education has to be ensured. For example, when implementing a screening for foetal abnormalities, it takes time to educate nurses and develop their competence in operating the ultrasound.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Literature search, guidelines, reports and hospital/hospital district documents, as well as and own research: interview or questionnaires of different actors of the process.</p>					
References	<p><b>Common to all used applications</b></p> <p>Kristensen FB et.al, 2001 {1}; Kristensen FB et al., 2007 {14}; Busse R et al., 2002 {26}</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>B0013, B0012: C0063; D0023; E0001, E0002, F0007</p>					
Sequential relations	<p><b>Common to all used applications</b></p> <p>E0003</p>					

G0004 Assessment element card						
Issue: What kind of co-operation and communication of activities have to be mobilised?						
Topic: Health delivery process						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	5
	Medical and Surgical Interventions (3.0)	Yes	Important	Partial	Yes	5
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	5
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	5
Clarification	<p><b>Common to all used applications</b></p> <p>Co-operation and communication is crucial in order to achieve a fluent patient pathway. Implementing a technology can demand new co-operation and communication in and outside the organization, e.g. with other hospitals, pharmacies and manufactures. Therefore structure of co-ordination is important. Also, interaction and communication with patients/participants and their important others and/or caregivers could change. Adaptation of self/home monitoring needs close co-operation and fluent communication.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>Screening needs close co-operation and fluent communication between all actors involved in the screening process in all steps (e.g. screening unit, laboratory, hospital, registry, participants). There are actors at different levels which make the communication and co-operation challenging, especially when developing a new screening. The information must be fluent, and electronic communication (software) is crucial. Adequate communication with participants and their important others and/or caregivers must be taken into account.</p> <p>Different kinds of "patient information" could be defined for screening. For example: (1) "promotional/educational information" with the aim of involving the target population and promoting participation; (2) "screening related information" to communicate with participant the "phase related information" in the different phases of the process (e.g. sending invitation; communicating the test results etc.).</p> <p>Information strategies should be tailored to the specific subgroup of the target population (depending on socio-economic status, cultural background, epidemiological features, etc.). Risk families need special information.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Literature search, guidelines, reports and documents of hospitals and hospital districts, guidelines, own research: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory, participants).</p>					

<b>References</b>	<b>Common to all used applications</b> Kristensen FB et.al, 2001 {1}; Kristensen FB et al., 2007 {14}; SMM, 2003 {27}
<b>Content relations</b>	<b>Common to all used applications</b> B0014, B0015; C0063; D0023; E0001; H0010, H0007, H0008, H0009, H0013; I0002
<b>Sequential relations</b>	

G0012 Assessment element card

Issue: In what way is the quality assurance and monitoring system of the new technology organised?

Topic: Health delivery process

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	6
	Medical and Surgical Interventions (3.0)	Yes	Important	Partial	Yes	6
	Pharmaceuticals (3.0)	Yes	Important	Partial	Yes	6
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	6
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>A new technology usually affects current quality assurance not only inside the organization but also outside in different health care levels. To assure quality, a monitoring system with standards and indicators is needed; it is also possible for there to be variation in how the quality assurance and monitoring system is implemented. Take into account who the responsible person for quality assurance and for the monitoring system is, and how any follow up has been arranged.</p> <p>Additionally, consider how quality assurance and the monitoring system affect management and effectiveness.</p> <p>Other international, national, regional and/or (cross) organisational demands for quality assurance (e.g. quality standards and monitoring) and for registration could also be in place, and this is another thing to keep in mind.</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>Describe what information has to be gathered (clinical indicators, special patient groups, laboratory results).</p> <p>There are national standards for Pharmacovigilance of pharmaceuticals. Some countries legally oblige physicians to report the adverse events. In most countries, manufacturers are required to submit all the reports of adverse events they receive from healthcare providers to the national authority. A specific monitoring system may be necessary for innovative pharmaceuticals.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>Screening involves asymptomatic participants and quality control is therefore crucial. Quality control needs to be systematic at every step of the screening process and throughout the screening programme. Specify the acceptable delay between screening test to test positive result and finally to treatment. Pay special attention to the control in cases where the programme is provided by several entities (e.g. a combination of private and public health care organisations) and when test and further investigations are separated.</p>					

<b>Methodology and sources</b>	<b>Common to all used applications</b>  Literature search, annual reports and statistics reports of hospitals and own study: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratories). Information from manufacturers.
<b>References</b>	<b>Common to all used applications</b>  Kristensen FB et al., 2007 {14}
<b>Content relations</b>	
<b>Sequential relations</b>	

G0005 Assessment element card

Issue: How do de-centralisation or centralisation requirements influence the implementation of the technology?

Topic: Structure of health care system

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	7
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	7
	Pharmaceuticals (3.0)	Yes	Important	Partial	Yes	7
	Screening Technologies (3.0)	Yes	Critical	None	Yes	7
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>The setting (primary - secondary - tertiary care) can vary between different countries depending on the health care system. (De)centralisation could have some economic and qualitative benefits. Centralisation could make the technology more difficult to access. Usually, expensive technologies are centralised to tertiary care units with special educated staff.</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>Report in what health care level the medicine is implemented.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>Sometimes, a screening test (for example, a maternal ultrasound) needs specifically trained personnel; this is possible after education/training and a sufficient amount of patients/participants. Centralisation could make screening or further investigation more difficult to access. For example, in foetal screening, timing is important. Decentralisation makes screening more attainable but its quality can weaken.</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Literature search, guidelines, reports and documents of hospital and hospital districts, health information databases (DRG etc.), own study: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory, participants).</p> <p>Literature search, guidelines, reports and documents of hospitals- and hospital districts, health information databases (DRG etc.), own research: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory, participants).</p>					

<b>References</b>	<b>Common to all used applications</b>  Kristensen FB et.al, 2001 {1}; Kristensen FB et al., 2007 {14}; Busse R et al., 2002 {26}; SMM, 2003 {27}
<b>Content relations</b>	<b>Common to all used applications</b>  B0004; E0001; F0012
<b>Sequential relations</b>	

G0101 Assessment element card						
Issue: What are the processes ensuring access to the new technology for patients/participants?						
Topic: Structure of health care system						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	8
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	8
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	8
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	8
Clarification	<p><b>Common to all used applications</b></p> <p>Access to care is often measured in terms of utilisation. There are different viewpoints: individual, population-specific and health system factors. Access to care is related to e.g. social, cultural, economic, organisational, relational or geographical factors.</p> <p>Access to care by wide definition includes availability, accessibility, accommodation, affordability and acceptability.</p> <p>This issue is related to the issue of acceptability of new technology (G0010)</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Literature search, guidelines, reports and documents of hospitals and hospital districts, health information databases (DRG etc.), own research: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory, participants).</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>H0012</p>					
Sequential relations						

G0006 Assessment element card						
Issue: What are the costs of processes related to acquisition and setting up the new technology?						
Topic: Process-related costs						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	9
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	9
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	9
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	9
Clarification	<p><b>Common to all used applications</b></p> <p>Implementing the required changes in e.g. hospital premises may be costly for organisations. Starting costs or running costs of a new technology could be very high. High costs can influence the decision on whether to introduce the new technology. Costs can be divided if some organisation(s) is(are) responsible for the acquisition costs and others for the running costs. Take into consideration any investments at all stages of the process.</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>This includes e.g. devices, special room and software needed for the new medicine.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>When constructing a new screening programme, there is a need for many investments (e.g. equipment, education and implementation support, training). Take into account e.g. screening program management requirements and sample types which could have critical economic implications. In addition, patient's preferences and social aspects can influence the compliance rate and thus may have an impact on ECO domain.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Literature search, guidelines, reports and documents of hospitals and hospital districts and manufacturers (e.g. producer handbook), own research: questionnaires and interviews of different actors of the screening process (monitoring authorities, hospitals, hospital districts, laboratory)</p>					
References	<p><b>Common to all used applications</b></p> <p>Kristensen and Sigmund, 2007{14}</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>B0007, B0008, B0009; E0001, E0002, E0009; G0007</p>					

Sequential relations						
<p>D0023 Assessment element card</p> <p>Issue: How does the technology modify the need for other technologies and use of resources?</p> <p><b>Topic: Process-related costs</b></p>						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	10
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	10
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	10
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	10
Clarification	<p><b>Common to all used applications</b></p> <p>New (less invasive) interventions may reduce the need for surgical interventions. Some treatments require ongoing monitoring and healthcare visits, including hospitalisation.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>Screening tests may cause further diagnostic testing and different treatment due to having detected the disease at an earlier stage.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Trials and pharmaco-economic studies, guidelines on utilisation of resources. Observational studies, statistics</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>B0013, E0001, E0002, E0009, F0003, G0001, G0003, G0004, G0007</p>					
Sequential relations	<p><b>Common to all used applications</b></p> <p>G0001, G0003, G0007</p>					
Other domains	Also in: Costs and economic evaluation					

G0007 Assessment element card

Issue: What are the likely budget impacts of implementing the technologies being compared?

Topic: Process-related costs

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	None	Yes	11
	Medical and Surgical Interventions (3.0)	Yes	Critical	None	Yes	11
	Pharmaceuticals (3.0)	Yes	Critical	None	Yes	11
	Screening Technologies (3.0)	Yes	Critical	None	Yes	11
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Whenever a technology is introduced, there will be an impact on health care budgets. It is possible to undertake a budget impact analysis which attempts to examine the likely impact of introducing a technology on finances or budgets from e.g. the perspective of different payers. Different payers include: government-level institutions; regions; municipalities; employers; insurance companies and patients/participants. The relevant perspective from which to estimate budget impact may change during different phases of the management process, and incentives are connected to this issue.</p> <p>For example: What kind of incentives does the budget impact impose on different actors? How might this potentially impact on each organisation? What is the estimated net financial (e.g. annual) cost of introducing the technology? Budget impact analysis provides data to inform an assessment of the affordability of a technology. It also provides a service planning tool to inform decisions about taking the technology into use.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>The relevant 'payer' can change during the screening process (e.g. a municipality pays for the screening test but then a hospital district pays for further investigations). Screening is usually free of charge for people, but sometimes participants have to pay e.g. a hospital fee for further investigations. Note that when initiating a new screening programme, initial cost outlays may be necessary.</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Literature searches, reports questionnaires and interviews of different actors of the screening process (monitoring authorities, hospitals, hospital districts, laboratories), as well as information from manufacturers.</p>					
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Kristensen and Sigmund, 2007 {14}; Sullivan et al., 2014 {28}, both from the ORG domain</p>					

<b>Content relations</b>	<b>Common to all used applications</b> A0011; B0007, B0009, B0012; D0023; F0012
<b>Sequential relations</b>	
<b>Other domains</b>	Also in: Costs and economic evaluation

G0008 Assessment element card						
Issue: What management problems and opportunities are attached to the technology?						
Topic: Management						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	12
	Medical and Surgical Interventions (3.0)	Yes	Important	Partial	Yes	12
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	12
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	12
Clarification	<p><b>Common to all used applications</b></p> <p>The issue concerns the administrative/managerial questions of technology: management of resources (e.g. investments), co-ordination (in relation to different levels and different steps of the process), establishment of objectives, monitoring and control (how quality assurance affects management or effectiveness), evaluation and sanctioning. Take into account the relevant data/information management systems connected to each of these points.</p> <p>This issue also includes risk management and safety issues (e.g. safety of personnel).</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Literature search, guidelines, reports and documents of hospitals, own research: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory).</p>					
References	<p><b>Common to all used applications</b></p> <p>Sullivan SD et al., 2014 {28}; Weinstein MC et al., 2003 {29}; Kristensen FB et al., 2007 {14}</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>A0011, A0012, A0015, A0016, A0025; B0010, B0020; C0063; D0021; H0009, I0009</p>					
Sequential relations						

G0009 Assessment element card

Issue: Who decides which people are eligible for the technology and on what basis?

Topic: Management

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	13
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	13
	Pharmaceuticals (3.0)	Yes	Important	Partial	Yes	13
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	13
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Provide information on the key actors who decide on the use of the technology. Do most important decisions take place on the national level (e.g. population screening) or are they, for example, made by individual professionals (e.g. surgical method for a specific disease)? How is the decision made – are there some documented criteria?</p> <p>Information about the possible variations on the decision level and decision criteria has ethical implications.</p> <p>This issue may be especially important in the context of rare diseases.</p> <p>This issue is related to the issue of work processes (G0001).</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>Companion diagnostics (tests or measurements) assist physicians in making treatment decisions for their patients by elucidating the efficacy and/or safety of a specific pharmaceutical or a class of pharmaceuticals for a targeted patient group or sub-groups. Specify and explain how companion diagnostics should be used to identify eligible patients.</p> <p>Specify the criteria for higher risk groups of patients such as the elderly and children.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>Decisions about people eligible for screening are made in the beginning of the screening. Usually, the decisions have been made nationally or regionally (in municipalities) but also locally (by employers). In systematic screening, the screening unit does not make decisions about who is eligible for screening. The management of positive test results needs systems to guarantee proper follow-up and, sometimes, case specific evaluation. In this topic responsibilities should be identified.</p>					

<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Literature search, guidelines, documents of hospitals, own research: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory).</p>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>KristensenFB et al. 2007 {24} from the CUR domain</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>A0011, A0012; B0004, B0016; D0021; I0012; H0012, F0012; G0001</p>
<b>Sequential relations</b>	
<b>Other domains</b>	<p>Also in: Health Problem and Current Use of the Technology</p>

G0010 Assessment element card						
Issue: How is the technology accepted?						
Topic: Culture						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	14
	Medical and Surgical Interventions (3.0)	Yes	Important	Partial	Yes	14
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	14
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	14
Clarification	<p><b>Common to all used applications</b></p> <p>Look at acceptance from the perspectives of organisation, personnel, and patients/participants. The organisational view can be separated into the intra-organisational (primary care), inter-organisational (secondary care) and health care system level. Acceptance can vary on different levels and with different actors. Alternative ways to introduce a new technology into an organisation could cause problems such as resistance among staff and dysfunction of processes.</p> <p>Acceptability is related to access to care.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>Acceptance may vary even within one specific screening process; for example, in foetal screening someone might accept an ultrasound but not a chromosomal (serum) test. When describing organisational acceptance, an example would be how sometimes screening may consist of elements which are not suitable for the image of the organisation.</p> <p>Screening is voluntary, and for persons who are eligible for screening there is no wrong decision, regardless of whether they decide to participate or not. Giving comprehensible information on pros and cons of screening is important, and the staff's communicational skills may influence a patient to accept screening.</p> <p>A patient's/participant's preferences on screening could influence the compliance rate and thus may have impacts on ECO domain.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Literature search, own research: questionnaires and interviews of different actors of the screening process (monitoring authorities, hospitals, hospital districts, screening units, laboratory, staff, participants).</p>					
References	<p><b>Common to all used applications</b></p> <p>Kristensen FB et al., 2007 {14}</p>					

<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>A0011, A0012; F0007; H0006, H0007, H0011, H0012</p>
<b>Sequential relations</b>	

<p>G0011 Assessment element card</p> <p>Issue: How are the other interest groups taken into account in the planning/implementation of the technology?</p> <p><b>Topic: Culture</b></p>						
<b>Application-specific properties</b>	<b>Application</b>	<b>Used</b>	<b>Importance</b>	<b>Transferability</b>	<b>Core</b>	<b>Order</b>
	Diagnostic Technologies (3.0)	Yes	Critical	None	Yes	15
	Medical and Surgical Interventions (3.0)	Yes	Critical	None	Yes	15
	Pharmaceuticals (3.0)	Yes	Important	None	No	15
	Screening Technologies (3.0)	Yes	Important	None	No	15
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>It may be useful to know who the possible stakeholders are, as well as what kind of co-operation exists and what kind of interaction is needed. The stakeholders could e.g. be the pharmaceutical industry and companies offering technologies for screening, authorities national or regional, registries, administrative parties, municipalities, policy makers/decision makers, staff groups, GPs/primary care physicians and patient organisations. One may also ask: Has the patient organisation taken part into the evaluation process? Has it been involved from the beginning (in the planning) or in the later stages, for example as commentator?</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Literature search, reports and documents of hospitals, own research: questionnaires and interviews of different actors involved in the screening process (monitoring authorities, hospitals, hospital districts, screening units, laboratory, manufacturers, registry, participants).</p>					
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Kristensen FB et.al, 2001 {1}; Kristensen FB et al., 2007 {14}; SMM, 2003 {27}</p>					
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>B0015, F0003, F0011</p>					
<b>Sequential relations</b>						

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# Patients and Social aspects (SOC)

## *Description*

The Patients and Social Aspects (SOC) domain takes patients or individuals in whose care a health technology is used as a point of reference in an HTA. **Patients Aspects** relate to issues relevant to *patients, individuals and caregivers*. *Patient* refers to a person who receives (or has received) and uses (or used) health technologies and health services in the healthcare sector. The term *individual* is sometimes used synonymously with 'patient', but it can also refer to a healthy individual, who receives health technologies, e.g. a person taking part in a screening programme. The term *caregivers* (sometimes referred to as carers) refers to family, friends and other persons from the patient's/individual's social network, who provide care to the patient and are in other ways involved during the course of the disease. It excludes those paid to give care, such as healthcare professionals. **Social Aspects** are related to *social groups*, that is specific groupings of patients or individuals that may be of specific interest in an HTA, such as older people, people living in remote communities, people with learning disabilities, ethnic minorities, immigrants etc.

Patients, caregivers or individuals can provide unique perspectives about experiences, attitudes, preferences, values and expectations concerning health, illness, service delivery and treatments that can inform HTA. Patients, caregivers and individuals will have a range of perspectives and an HTA should seek to gather as much evidence as possible to understand these wide ranging views. There may be some social groups that are particularly important to consider for a specific health technology or for which there is a policy imperative for special consideration (such as those with disabilities) or in which the value of the technology may be different (such as ethnic minorities) and these may need to be specified. Hence social groups are also important consideration in HTA.

A technology may be implemented in a hospital, primary care or at home. However, implications for patients may extend far beyond the original setting of the technology. Patients and caregivers attribute specific meaning and significance to health technologies, to which they may attach feelings of hope, fear, perhaps uncertainty, as well as societal values {1-5}. The assessment which looks at patients, individuals, caregivers and social groups is thus interested in all the above mentioned aspects. Since the focus of this domain is the patients and caregivers the views of citizens (that is citizen using health services but not having the condition under study) is not included in the Patients and Social Aspects domain, but will be covered in the Ethical and Legal domain of the Core Model.

Awareness of how valuable patients' perspectives are within healthcare services grew in the 1970s with a WHO declaration stipulating that health is not defined solely by absence of disease, but also includes physical, physiological and social wellbeing of the individual. Although this definition has been debated, it nevertheless draws attention to the importance of individuals' perceptions and experiences during the course of diseases and in their use of health technologies. Since the 70s, patients' perspectives have gained an increasing role in policy, planning and decision-making in health service delivery internationally, and should therefore present an integral part of HTA {6}. In recent years, HTA has focused only on the clinical effectiveness and cost-effectiveness of the health technology being studied. This has often been because patients' views have been presented in an ad hoc, unscientific manner. For this reason, it is essential that patients' perspectives are studied in

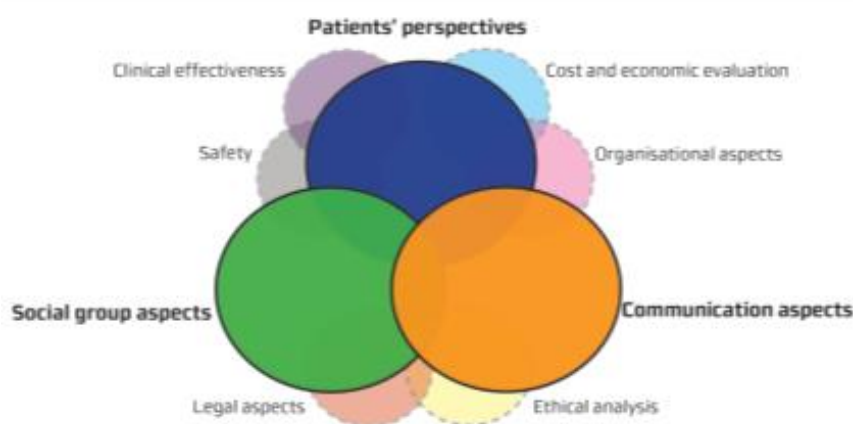
HTA using a systematic and methodologically robust process and they should be seen as an essential part of the evidence base that is integral to the interdisciplinary process of an HTA {7, 8}

The Patients and Social Aspects domain should seek to identify evidence from the **patients, individuals, care-givers** and **social groups** about

- The burden of living with the condition being studied
- Experiences of current health technologies
- Experiences with and expectations of the health technology being studied (in particular what would be valued most from the technology and issues regarding managing technology administration and side-effects).

In addition to these issues it is recognised that there are underlying issues of **communication** related to the effective use of a health technology by individual patients or social groups and so these are studied separately. Communication topics e.g. about the use and implication of a technology, the meaning of results for a wider diagnosis pathway, communication on diagnostic tests, e.g. genetic test, or regarding training for self administered devices are thus important for the decisions about and effective use of the technology.

Figure 1 shows the different themes that contribute to the Patients and Social Aspects domain in terms of the topics of **patients** (including individuals and care-givers), **social groups** and **communication** as well as it's relation to other domains of HTA-Core Model. (See also the paragraph below: 'Relation to other domains').



**Figure 1. Relevant themes of Patients and Social Aspects domain and the relation to other domains of HTA.**

The scope of analysis for the Patients and Social Aspects domain (and thus the choice of methodological and analytical approach) is based on what issues are relevant for a given technology.

The SOC domain contains eight issues, which are in turn related to the three topics of the patients' perspectives, social groups' aspects and communication aspects as indicated in Figure 1. Table 1 below shows the topics and issues of the domain.

**Table 1: Topics and issues in the SOC domain**

Topic	Issue	Assessment element ID
Patients' perspectives	What are the experiences of living with the condition?	H0200
Patients' perspectives	What expectations and wishes do patients have with regard to the technology and what do they expect to gain from the technology?	H0100
Patients' perspectives	How do patients perceive the technology under assessment?	H0006
Patients' perspectives	What is the burden on care-givers?	H0002
Social group aspects	Are there groups of patients who currently don't have good access to available therapies?	H0201
Social group aspects	Are there factors that could prevent a group or person from gaining access to the technology?	H0012
Communication aspects	How are treatment choices explained to patients?	H0202
Communication aspects	What specific issues may need to be communicated to patients to improve adherence?	H0203

## Why is this domain important?

Patients' perspectives on their illnesses and the technology under study provide a unique insight into the influence and impact of the technology. The patients – and potentially caregivers – are the only ones who have personal experience and knowledge of a disease, its course and use of a technology, and they thus are able to value the quality and usefulness of the technology and its impact on every day life {9}.

The patient is not just a passive target for interventions in health care. He or she is also a person with different roles – a family member, a citizen, an employee, a consumer, etc. {1}. The person may have many different spheres to the life: everyday life, homes, schools, workplace, health services, etc. The use of the technology may place a burden on the patient (e.g. administering the treatment) or may change their abilities in their life spheres in both negative and positive ways and so can affect all the spheres of the patient's and the caregiver's everyday life. It is therefore essential to take into consideration issues of power, empowerment and stigmatisation {10-13}.

A technology is not effective in isolation. Social analysis reveals that, in order to achieve satisfactory results, resources are needed in an individual's daily activities. The use of a health technology requires the user to mobilise some type of resource in his or her daily activities (for example, some kind of action from him or herself or support from other people) in order to achieve satisfactory results with the technology. An assessment of patient aspects both in and outside the clinical encounter is therefore necessary. The analysis of patients' and caregivers' perspectives should reveal the resources needed for patients, individuals and caregivers when using a technology effectively. The use of a technology always produces certain changes or consequences in different spheres of life, and these should also be anticipated. The changes can be positive or negative, expected or unexpected {14-16}. In addition, the different meanings individuals give to a technology, as well as the implications of its use are important to recognise {17, 18}.

The European Union has formulated a policy about social investment in order to support citizen participation in employment and social life, and among other arenas social and patients aspects has been identified as a special target for health investments {19}. Investing in people's health as human capital helps improve the health of the population in general and reinforces employability. This, in turn, makes active employment policies more effective, helps secure adequate livelihoods and contributes to growth. It is important to stress that investing in health in order to secure and improve livelihoods should be a population-based target – in this way, assessing the value of individuals in society would include paid (employed) as well as unpaid (unemployed) people, e.g. young and older people, disabled persons, stay at home mothers etc.

## Relations to other domains

The SOC domain focuses on topics and issues related to patients' and caregivers' experiences, expectations, values, opinions related to the health technology being studied, their experiences of living with the condition being studied, the consequences (e.g. effect and efficiency) for everyday life when using the technology being studied. These topics are underlined in Figure 1.

Patient perspectives can be present in several other domains of the HTA-Core Model:

- Costs and Economic Evaluation (ECO) domain
- Organisational Aspect (ORG)
- Ethical Analysis (ETH) domain
- Legal Aspects (LEG) domain
- Clinical Effectiveness (EFF)
- Safety (SAF) domains

This could be the case if patient related issues are discussed and estimated at a societal level, for example issues related to the socio-economic benefits at a societal level could be covered in the ECO domain, or issues about provision of health care and equitable allocation of resources could be covered in the Organisational Aspect (ORG). Patients' perspectives on ethical and/or political topics could also be discussed in the Ethical Analysis (ETH) domain or Legal Aspects (LEG) domain, or patient perspectives on biological/physical/psychological topics could be discussed in the Clinical Effectiveness (EFF) and Safety (SAF) domains, However, patients aspects would in

such cases often be a minor part of the overall estimation. In addition the methods to collect evidence can be domain specific and as such different from SOC domain. This could entail a risk of treating patients' perspectives in an unsystematic and fragmented way. It is therefore important not to exclude Patients and Social Aspects when patients' issues are part of other domain analysis.

The information from SOC can guide other domains in, for example defining important endpoints for assessment. Coordination is needed across all domains in order to exchange information and to avoid overlap when producing a core HTA.

## **Screening-specific content**

Access equity is essential for a person's participation in the screening and, consequently, for the success of the screening programmes. The consideration of the behaviours and attitudes of social groups will be important as will issues of communication such as the delivery modes of the screening. Self-sampler devices, being able to mail a sample instead of visiting a clinic and the possibility of telephone reminder messages can affect participation, as can mass media campaigns.

Furthermore, correct and balanced information and communication on the benefits and harms of screening are essential for an individual to be able to make an informed decision about participating in screening.

## **Pharmaceutical-specific content**

In the cases where pharmaceuticals replace a more invasive self-limiting treatment such as a radical cystectomy, the pharmaceuticals may have a large impact on patients' social life (e.g. social interaction, employment, independence, and stigma). An individual's perception and views on certain pharmaceuticals, as well as the consequences these may have for their social life, can influence patterns of use of pharmaceuticals, whether they are used correctly or not.

# *Methodology*

## **The research paradigm**

The analysis of the SOC domain is both theoretically and empirically complex and demanding. Hence, advanced skills in social science are required from the person conducting this part of the HTA coming from any of the following fields:

- Medical Anthropology
- Medical Decision-Making
- Medical Sociology
- Science and Technology Studies
- Governance of Innovation Studies
- Medical Ethics
- Social Psychology
- Communication science
- Health Services Research
- Health Sociology

It is anticipated that much of the relevant research will be qualitative research, which is intended to provide in-depth (thick) descriptions of analysed themes and/or to address particularities {20}. Quantitative studies (such as surveys, PROs etc.) also provide important insights into patients and social aspects. Their critical appraisal and analysis is similar to that present in EFF domain and so the focus of this section will be on qualitative research.

Qualitative research can be used in an exploratory manner to understand issues which arise for patients. This is an iterative process which provides insights important for informing value judgments in HTAs. Qualitative studies apply logical analysis and documentation. The analysis results are theoretically generalisable, that is, one generalises in relation to the theory of their study, which data analysis can strengthen, weaken or clarify. The results of the analysis can thus be extended to cases other than the ones under study, depending on the assessment of the study's character and evidence.

Qualitative studies often involve generating evidence in the form of certain themes, concepts and trends. Therefore, it is possible to use thematic mapping, i.e. mapping out relevant sub-themes, and the assessment of the quantity and quality of existing literature related to them. The applicability of published information depends on its ability to give insight into social processes. Examples of sub-themes are: how illness or risk perceptions change family relations, roles, people's interaction with technology, unforeseen and unintended social consequences, risk management. It is also important to define the questions that cannot be answered on basis of the existing literature.

An assessment of patient and caregiver aspects should not be a separate process within an HTA. Co-operation and interaction between the HTA team members is essential due to the complexity of the patients and caregivers analysis. Relevant patient issues for a technology could be identified when considering, for example ethical and organisational aspects {21}. Some issues may also be studied as patient-related outcomes (PRO), and may as such be related to EFF and SAF. When these issues are brought into the SOC analysis, the focus is on exploring the interrelation between biological, individual, social and cultural aspects. Patient-related outcomes can result in central thematic issues or topics which can have a major impact on the content and conclusions of an HTA report. For example, does a given technology have patient related consequences other than the intended ones?

Overall, the scope of patient related HTA analysis can be very wide. During the practical work in designing an HTA, one must single out those topics that are of particular relevance for the technology under assessment and adjust the work in the SOC domain to the work being done within the affiliated domains. The assessment elements table contains more specific issues on this topic. To be able to judge what issues are relevant to a given technology, a preliminary analysis is required:

1. Define the relevant scope of the analysis:

- What is the extension of the technology nationally as well as internationally? How widely is the technology already being used or practiced? Information provided by the Health Problem and Current Use of the Technology domain (CUR) may provide valuable information.

2. Define the relevant set of research elements:

- Decide which topic(s) and issues in the SOC domain are relevant for the technology in question (see Figure 1 and Table 1: Assessment elements).

3. Choose the relevant methodological approach:

- Decide whether the central questions can be answered based on existing studies or whether there is a need for new primary studies (e.g. evidence collection from patient groups). You may need to conduct some preliminary literature searches.
- Decide upon the theoretical perspective for the analysis.
- Change the relevant assessment elements to precise study questions on the basis of the chosen theoretical perspective. (Note this may need to be done in an iterative manner as relevant patient issues emerge from the literature search).

When the scope of the SOC analysis, exact research questions, and relevant methodologies are clear, write a study plan describing the different phases and strategies of the assessment process.

## Gathering information

The following phases may need to be addressed in the following order to find answers to the relevant issues:

1. Search for published qualitative systematic reviews and if there isn't one available conduct one and/or
2. Conduct (a) primary study(ies) on specific issues not covered in the literature and/or
3. Consult patient groups for their perspectives on living with the condition, experiences and expectations of current and new technologies.

As indicated the above mentioned phases are not mutually exclusive. Thus you can do primary studies and consult patient groups even if literature review is available or you do your own because there might be issues relevant for answering the study questions that are not covered in existing literature.

Throughout these processes, good practice suggests that patient representatives should be involved to help focus the research and interpret the findings {22, 23}

### *Literature reviews*

It is advised to search for published syntheses of research concerning the patient and social issues in question. Although research into patients' perspectives has increased over the past decade, there is still relatively limited published research compared to that available on effectiveness and so it may be necessary to conduct your own synthesis of evidence {24, 25, 26}.

### *Literature searching*

The search process is similar to that for a quantitative systematic review practice (see EFF), except that studies with different research paradigms are considered, including qualitative, quantitative and mixed-methods research.

Some important databases and other sources of information which could prove useful for SOC analysis are listed below. We recommend also using the Summarised Research in Information Retrieval for HTA (SuRe Info, available at <http://vortal.htai.org/?q=sure-info>), which provides research-based information relating to the information retrieval aspects of producing health technology assessment.

- Psychological/sociological databases such as:
  - ASSIA (Applied Social Sciences Index and Abstracts)
  - Eric
  - ISI Web of Science / Scopus
  - Psycinfo
  - Social Care Online/Caredata

- Social Services Abstract
- SocINDEX
- Sociological Abstracts
- Medical databases such as:
  - Cinahl
  - Cochrane Library
  - Embase
  - Medline
  - Pubmed
  - Web of Science
- Euroethics (European Database Network on Ethics in Medicine), including:
  - Biogea (Italy)
  - Cendibem (Spain)
  - CRIB (Belgium)
  - ETHINSERM (France)
  - ETHMED (Austria, Germany, Switzerland)
  - EUROETHIK (Germany)
  - MIKS (Sweden)

Examples of relevant scientific journals:

- Anthropology and Medicine
- Culture, Medicine and Psychiatry
- Health Expectations
- International Journal of Qualitative Methods
- Medical Anthropology Quarterly
- Medical Care
- Medical Decision-making
- Patient education and counselling
- Patient preference and adherence
- Qualitative Health Research

- Social Science and Medicine
- Sociology of Health and Illness
- The Patient: Patient Centred Outcomes Research
- Values in Health

Suggested search terms include: ‘patient experience of’, ‘patient expectations of’, ‘patient attitude to’, ‘patient outcome assessment’, ‘quality of life’, ‘social aspects of’, ‘medical decision-making process’, ‘patient education’, ‘everyday lives’, ‘psychological aspects’ etc. depending on the research question.

## Tools for critical appraisals

All studies should be quality-evaluated before inclusion in a synthesis. For qualitative research quality assessments should evaluate the following {6, 8}:

- Purpose of the study and its relevance to the study question
- Context (population/setting/values)
- Appropriateness of methods and theoretical framework
- Transparency of data generation, analysis and interpretation (avoidance of bias)
- Connection between research question and conclusions (internal consistency in relation to the theoretical framework of the study)
- Account of the knowledge generated given the methods (relevance for practice)

To assess these aspects it is advisable to use tools which have been specifically developed for critical appraisal of qualitative studies. Some acknowledged tools are:

- CASP {27}
- Guidance recommended by the Cochrane Qualitative Research Methods Group {28}
- Quality framework {29}

Guidelines for standards on qualitative research vary and are currently debated and developed. For further guidance see, e.g. {24, 30, 31, 32, 33, 34, 35, 36}.

Assessment of the quality of quantitative studies should follow guidelines relevant for those, see e.g. EFF.

The literature review should identify what questions can be answered on the basis of existing literature, after which it should be considered how the included studies can be utilised, what their weaknesses are and any important gaps that may require primary research.

## ***Data extraction table***

When a systematic review of qualitative research is performed, a standard template for data extraction should be used as follows.

Publication details: First author, year
Patient, social group or communication issue(s): to be categorised by the reviewer
Nature of the study: aims/objectives, user/caregivers involvement in the design/conduct of study, country, site (setting, key characteristics of the context), details of theory/conceptual model.
Methods: study type and design, study date and duration, sampling/recruitment, methods of data collection, data collector, used research tools (if any), analysis methods
Participant characteristics: gender, age, ethnicity, types of patients, individuals, practitioners or policy makers, country of study, healthcare setting
Features of the studied intervention (when applicable): aim of the intervention, intervention process (description of how the intervention/service was delivered)
Outcomes and results: outcome measures, details of findings, strengths/limitations of the study, author's conclusions in relation to their research question.
Reviewers' comments: e.g. remarks on quality issues such as relevance to HTA research questions

## ***Qualitative synthesis***

The synthesis of qualitative studies can be done according to different methods, such as meta-ethnography, meta-synthesis {37} or narrative analyses {38}. Guidance for making a synthesis of qualitative literature can be found in the following:

- The framework approach {39}
- The Cochrane Qualitative Review Methods Group {40}
- JBI system for qualitative synthesis {41}
- Synthesising qualitative research in HTAs {42}

Guidance can also be found in method books {43, 44, 45, 46}. A critical interpretive synthesis of literature considering access to healthcare by vulnerable groups provides one example {47}.

## ***Primary studies***

If no relevant studies are identified, it could be worthwhile to carry out own primary studies concerning the issue(s) relevant for the specific technology under assessment. In this case, it must always be taken into consideration whether the need is for a primary HTA study, or whether the need for new knowledge has dimensions that speak for a larger research project rather than an HTA. The study design should be based on the ideas which correspond to those described in the domain description.

HTAs of patient and caregiver issues do not have a hierarchy of study methods which serves as a starting point. The study design has to be structured individually in every primary assessment study, in a way fitting to the studied research questions. Every kind of research technique can be used: various types of interviews, surveys, observation, participant observation, analysis of written material and documents, etc. {48, 49, 50, 51}.

The timing of the study of the social and patients' aspects of the technology must be considered thoroughly. Depending on the specific technology studied, the appropriate endpoint for assessing the patient experience will differ. Both ethical and practical considerations must be taken into account when deciding whether to study people before or during the application/use of technology, or to ask them about their experience afterwards. This choice may have considerable significance for the results. Any intervention has an influence on practice, and it must be clear from the study whether the effects of the intervention are part of the specific context in which the people being studied behave, or whether the study reflects daily practice.

## **Sampling and generalisability of the results**

In qualitative studies, sampling is done purposefully since the aim of the sampling and the analysis of the data is description and explanations – that is to say, it is important to include informants with a position (e.g. knowledge, experience, sex, age, social status etc.) relevant to the subject being studied.

Guidelines for qualitative research standards vary, and are currently being debated and developed. For further guidance, see e.g. {30} or {31}. Other tools can be found in {50} and in {51}.

If there is not enough time to perform a primary study, stakeholders representing patient perspective, such as patient associations, could be consulted. In order to distinguish such data collection from formal consultation of a stakeholder advisory group, it is necessary to gather the information in a systematic way. Patient groups may be asked to provide information from their networks about specific issues. Use of structured templates {52, 53} could be helpful and they should be given support to contribute.

Other sources of patient perspectives could be:

- WHO, OECD, ILO, UNESCO homepages and databases
- Patient (virtual) forums

## Reporting and interpretation

For transparency purposes, when reporting it is very relevant to clearly divide facts from interpretation. This is especially true for the SOC domain, as relevant issues could be subject to interpretation from various parties and perspectives.

It is therefore also very relevant to clearly state whose perspectives is taken on the issue, e.g. the patient, the healthcare professional, family/social environment, the individual, public health authorities or the healthcare system. See {54, 55} for further guidance.

## Assessment elements

H0200 Assessment element card						
Issue: What are the experiences of living with the condition?						
Topic: Patients' perspectives						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	1
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	1
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	1
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	1
Clarification	<p><b>Common to all used applications</b></p> <p>This issue concerns the patient's everyday life living with the disease, e.g. familiar, social and work related roles, ability to manage relationships with other people in a socially appropriate manner in major areas of life, ability to take care of one self etc. It includes:</p> <ul style="list-style-type: none"> <li>• Illness and treatment burden</li> <li>• Limitations to activities of daily living: work, family, social life, ability to care for oneself, leisure activities</li> <li>• Psychological issues: stigma, anxiety, fear, social acceptance</li> <li>• Financial implications, aids needed to support daily living</li> </ul>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Search for or conduct a literature review or, conduct a primary study for important questions that are not covered in the literature; gather evidence from patient groups.</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>CUR, ETH</p>					
Sequential relations						

H0100 Assessment element card						
Issue: What expectations and wishes do patients have with regard to the technology and what do they expect to gain from the technology?						
Topic: Patients' perspectives						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	2
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	2
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	2
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	2
Clarification	<p><b>Common to all used applications</b></p> <p>This issue concerns what patients and care-givers expect to gain from the technology; it includes e.g.:</p> <ul style="list-style-type: none"> <li>• Improved survival, delayed progression?</li> <li>• Improvement of specific symptoms (e.g. fatigue, incontinence, diarrhoea, mobility etc.)?</li> <li>• Improvements/changes related to implications of daily living, social and psychological issues by using the current technology</li> <li>• What size of effect is important?</li> </ul>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Search for or conduct a literature review or, conduct a primary study for important questions that are not covered in the literature; gather evidence from patient groups.</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>EFF, ETH, SAF</p>					
Sequential relations						

H0006 Assessment element card						
Issue: How do patients perceive the technology under assessment?						
Topic: Patients' perspectives						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	3
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	3
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	3
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	3
Clarification	<p><b>Common to all used applications</b></p> <p>This issue is about the patients' attitudes, perceptions, preferences, satisfaction and expectations to the technology. This covers whether any positive or negative issues arise as a consequence of using the technology e.g. feelings of unity or empowerment, existential experiences (e.g. insecurity, worries, hope, anxiety, stigmatisation, social status, courage to face life, satisfaction, changes in self-conception). It includes:</p> <ul style="list-style-type: none"> <li>• What understanding do patients have of the technology?</li> <li>• What implications – positive and negative – does the technology have regarding activities of daily living, social life, psychological issues, financial implications, support and resources (practical, physical, emotional) and requirement in order for the patient to use the technology with satisfactory results?</li> <li>• Can the technology be used/taken easily?</li> <li>• What treatment benefits could be improved?</li> <li>• What side effects are most difficult to manage?</li> </ul>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Search for or conduct a literature review or, conduct a primary study for important questions that are not covered in the literature; gather evidence from patient groups.</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>ETH, LEG, ORG</p>					
Sequential relations						

H0002 Assessment element card						
Issue: What is the burden on care-givers?						
Topic: Patients' perspectives						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	4
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	4
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	4
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	4
Clarification	<p><b>Common to all used applications</b></p> <p>Describe who the important other people are that are involved in the use of the technology, in addition to the patients (parents, children, friends, people at work place etc.). What kind of support (practical, physical, emotional, financial, nurturing, personal) do care-givers mobilize? It includes e.g.:</p> <ul style="list-style-type: none"> <li>• What challenges do care-givers face when supporting patients to manage their condition and receive care?</li> <li>• How do care-givers perceive the new technology; what challenges and benefits might it offer?</li> <li>• What support and resources need to be mobilised in order for the patient to use the technology satisfactorily?</li> </ul> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>E.g. the results of screening or genetic and prenatal testing, may affect relatives.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Search for or conduct a literature review or, conduct a primary study for important questions that are not covered in the literature; gather evidence from patient groups.</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>ETH, LEG</p>					
Sequential relations						

H0201 Assessment element card						
Issue: Are there groups of patients who currently don't have good access to available therapies?						
Topic: Social group aspects						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	No				
	Medical and Surgical Interventions (3.0)	No				
	Pharmaceuticals (3.0)	No				
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	5
Clarification	<p><b>Common to all used applications</b></p> <p>This issue concerns inequality in health. Investing in the reduction of health inequalities is a target of the European Commission, as it contributes to social cohesion and breaks the vicious spiral of poor health being a contributor to, and a result of, poverty and exclusion. It includes e.g.: Do available therapies give rise to inequality in access and use of the health care? Are there special groups discriminated, e.g.:</p> <ul style="list-style-type: none"> <li>• Children, older people, certain age groups</li> <li>• People with a specific genetic mutation, people with disabilities</li> <li>• People living in remote areas, ethnic groups etc.</li> <li>• People with a certain type of the disease</li> </ul>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Search for or conduct a literature review or, conduct a primary study for important questions that are not covered in the literature; gather evidence from patient groups.</p>					
References	<p><b>Common to all used applications</b></p> <p>European Commission: Social investment package, 2013, available at <a href="http://ec.europa.eu/health/strategy/docs/swd_investing_in_health.pdf">http://ec.europa.eu/health/strategy/docs/swd_investing_in_health.pdf</a></p>					
Content relations	<p><b>Common to all used applications</b></p> <p>CUR, ETH, ORG, TEC</p>					
Sequential relations						

H0012 Assessment element card						
Issue: Are there factors that could prevent a group or person from gaining access to the technology?						
Topic: Social group aspects						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	None	Yes	5
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	5
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	5
	Screening Technologies (3.0)	Yes	Critical	None	Yes	6
Clarification	<p><b>Common to all used applications</b></p> <p>This issue concerns inequality in health. Investing in the reduction of health inequalities is a target of the European Commission, as it contributes to social cohesion and breaks the vicious spiral of poor health being a contributor to, and a result of, poverty and exclusion. Can the technology be applied in a way that gives equal access to those in equal need? How can this be guaranteed? Could potential discrimination or other inequalities (geographic, gender, ethnic, religious, employment, insurance) prevent access?</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Search for or conduct a literature review or, conduct a primary study for important questions that are not covered in the literature; gather evidence from patient groups.</p> <p>See also: <a href="http://ec.europa.eu/health/strategy/docs/swd_investing_in_health.pdf">http://ec.europa.eu/health/strategy/docs/swd_investing_in_health.pdf</a> for more information.</p>					
References						
Content relations						
Sequential relations	<p><b>Common to all used applications</b></p> <p>G0009, G0101, A0012, I0011</p>					
Other domains	Also in: Ethical analysis					

H0202 Assessment element card						
Issue: How are treatment choices explained to patients?						
Topic: Communication aspects						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	6
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	6
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	6
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	7
Clarification	<p><b>Common to all used applications</b></p> <p>This issue is about patient participation, incl. what support or limit use of the technology in relation to communication aspects. It includes e.g.:</p> <ul style="list-style-type: none"> <li>• Do patients with the condition have good information sources to explain the condition and treatment options to them?</li> <li>• Are there good decision aids available to help shared decision making between patients and doctors and/or other health personnel?</li> <li>• Do patients feel themselves involved in a sufficient and appropriate way?</li> </ul>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Search for or conduct a literature review or, conduct a primary study for important questions that are not covered in the literature; gather evidence from patient groups.</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>ETH</p>					
Sequential relations						

H0203 Assessment element card						
Issue: What specific issues may need to be communicated to patients to improve adherence?						
Topic: Communication aspects						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	7
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	7
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	7
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	8
Clarification	<p><b>Common to all used applications</b></p> <p>This issue is about communication and how it influences the use of the technology, e.g.:</p> <ul style="list-style-type: none"> <li>• Preparation in advance of intervention, dosage instructions, side effects etc.</li> <li>• Is there information which patients would need that are not usually available?</li> </ul>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Search for or conduct a literature review or, conduct a primary study for important questions that are not covered in the literature; gather evidence from patient groups.</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>EFF, ETH, SAF</p>					
Sequential relations						

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# Legal aspects (LEG)

## *Description*

### What is this domain about?

The objective of the Legal Aspects (LEG) domain is to assist the HTA doers in detecting rules and regulations which need to be taken into consideration when evaluating the implications and consequences of implementing a health technology. Rules and regulations have been established to protect the patient's rights and societal interests. The rules and regulations may be a part of patient rights legislation, data protection legislation, or health care personnel's provisions, rights and duties in general. The market access authorisation or -regulation processes have not been the direct focus of HTA earlier, but this may be subject to change in the future.

**Table 1. Topics and issues in this domain**

Topic	Issue	Assessment element ID
Autonomy of the patient	What kind of legal requirements are there for providing appropriate information to the user or patient and how should this be addressed when implementing the technology?	I0002
Autonomy of the patient	Who is allowed to give consent for minors and incompetent persons?	I0034
Privacy of the patient	Is there a possibility that the use of the technology produces additional information that is not directly related to the current care of the patient and may violate their right to respect for privacy?	I0007
Privacy of the patient	What do laws/binding rules require with regard to informing relatives about the results?	I0008
Privacy of the patient	What do laws/binding rules require with regard to appropriate measures for securing patient data and how should this be addressed when implementing the technology?	I0009
Equality in health care	What do laws/binding rules require with regard to appropriate processes or resources which would guarantee equal access to the technology?	I0011

Equality in health care	What are the consequences of various EU-level and national regulations for the equal access to the technology?	I0012
Ethical aspects	Does the implementation or use of the technology affect the realisation of basic human rights?	F0014
Ethical aspects	Can the use of the technology pose ethical challenges that have not been considered in the existing legislations and regulations?	F0016
Authorisation and safety	What authorisations and register listings does the technology have?	I0015
Authorisation and safety	What do laws/binding rules require with regard to the safety of the technology and how should this be addressed when implementing the technology?	I0017
Ownership and liability	What should be known about the intellectual property rights and potential licensing fees?	I0019
Ownership and liability	What should be known about the legal or binding rules regarding the width, depth and length of the manufacturers guarantee?	I0021
Regulation of the market	What kind of legal price control mechanisms are there that are relevant to the technology?	I0023
Regulation of the market	What kind of regulation exists for the acquisition and use of the technology?	I0024
Regulation of the market	What legal restrictions are there for marketing the technology to the patients?	I0025
Regulation of the market	What should be known about the legal issues in cases of new technologies where the current legislation is not directly applicable?	I0026
Regulation of the market	Are there relevant concerns about conflicts of interest regarding the preparation of binding rules and their implementation?	I0037

## Why is this domain important?

Proper knowledge of relevant legal questions has significant consequences for decision-making, which is often perceived as part of the so called socio-legal issues {1, 2}. Legal issues in HTA will be increasingly important as norms of professional ethics are continuously codified into statutes, and European Union is producing ever more health-technology-related legislation. The rapid innovation processes of new technologies put the policy and decision-makers in situations where they need to know the legal implications of implementing and not implementing a technology, and the roles and responsibilities of different actors, e.g. patients, providers and payers. The perspective should include levels of international, EU and national legislations, keeping in mind the national characteristics which limit the transfer of legal information from one country to another. The LEG domain helps in identifying the legal barriers which hinder the export and import of HTA results {3, 4, 5, 6}. It gives insight into the areas of healthcare legislation in need of harmonisation, and provides tools for legislative and policy reforms.

## Relations to other domains

There are two elements shared with the Ethical Analysis (ETH) domain. Content relations are identified with Health Problem and Current Use of the Technology (CUR), Description and Technical Characteristics of the Technology (TEC), Safety (SAF), ETH, Organisational Aspects (ORG), and Patients and Social Aspects (SOC) domains. Most of the relations are also sequential, meaning that results of some issues are needed before a particular issue in legal domain is answered. The relations are described in the assessment elements table.

## *Methodology*

### Process for answering research questions

The aim within LEG is not, and indeed cannot be, to give or even propose a binding legal solution to a given question. Instead, the aim is to guide the HTA doers in recognising the relevant legal questions they need to consider when evaluating the technology and providing advice for decision-makers. For each relevant question identified in the Model, there should be an answer which helps the national HTA doer to adapt the information to their local context. Some issues may be similarly regulated in all countries, while other issues, e.g., those guided by EU directives, may imply more national variability which the HTA Core Model user can not address fully when providing the answer. What is most important is that the level of transferability of the information is clearly stated in the result card.

# Gathering information

## *What kind of information is required*

Relevant directives, treaties and recommendations by the European Union and the European Council provide the HTA doers with a basic framework for responding to the questions in the legal domain. Helpful documents on interpretation of laws are e.g. preparatory acts of legislation and judgments of courts. These primary sources of legal information often need to be complemented by various so-called soft law instruments, agreements and documentation by the technology supplier, and legal scientific literature.

There are three levels of legislation to consider: international, European Union and national legislations.

**1. International law**, particularly that generated by the Council of Europe The Council of Europe is an international organisation promoting co-operation between all countries of Europe in the areas of legal standards, human rights, democratic development, the rule of law and cultural co-operation. It is an entirely separate body from the European Union (EU). The conventions of the Council of Europe are not statutory acts of the Organisation; they owe their legal existence to the consent of those Member States that sign and ratify them.

In 1950, for instance, the Council of Europe established the *European Convention for the Protection of Human Rights and Fundamental Freedoms* (ECHR), commonly known as the *European Convention of Human Rights*, which is currently ratified and thus binding for all 47 member countries of the Council of Europe, among them all 28 member states of the EU. The most important document in the field of medicine is the *Human Rights and Biomedicine Convention* with its *Additional Protocols* (e.g., privacy and information rights are governed by its Article 10, which supplements the right to know with its counterpart, the right 'not to know'.)

[The Council of Europe Treaty Series](#) groups together all the conventions concluded within the organisation since its foundation in 1949. [The recommendations of the Committee of Ministers](#) since 1978 cover several issues of health policy. However, these have not been ratified by all European countries, so their applicability needs to be checked in each respective case. In addition, it may be necessary to investigate whether the [European Court of Human Rights](#) (ECtHR) has given a relevant decision on the matter based on the *European Convention on Human Rights*. ECtHR provides a refuge when all applications by national jurisdictions have been unsuccessful and no other internationally binding rules of law, such as those of the EU, apply. In the field of privacy, for instance, the ECtHR confirms the fundamental importance of the strict protection of personal medical data. The European Patent Convention and World Trade Organisation's *Agreement on Trade Related Aspects of Intellectual Property Rights* (TRIPS) may be useful sources when dealing with issues related to intellectual property rights. Knowledge of these need to be updated regularly as new judgments arise in a constant manner.

## 2. The level of the European Union. European Union Law contains Regulations and Directives

- **EU directives** lay down certain end results that must be achieved in every Member State. National authorities have to adapt their laws to meet these goals, but are free to decide how to do so.
- **EU Regulations** are legal acts that become immediately enforceable as laws in all member states simultaneously.

Relevant regulations and directives have been listed in the table below, in particular those regarding, e.g., patient safety, public health issues, and free movement of goods, patients and personnel. Regulations related to free markets and competition law may become relevant in, e.g. public procurement.

Judgments of the European Court of Justice (ECJ) are particularly relevant when interpreting EU legislation. Whereas national courts in the EU member states are responsible for ensuring proper application of EU law, the EU case-law is made up of judgments from the ECJ, which interpret EU legislation. Case law (known also as common law) is law developed by judges through decisions of courts and similar tribunals, as opposed to statutes adopted through the legislative process. ECJ also exercises proceedings on failure to fulfil obligations, actions for annulment, actions for failure to act, and direct actions). The ECJ case law (EUR-Lex, CURIA) is considered a supplementary source of law.

<b>Major European Union legislation</b>
<b>Human rights, patients' rights</b>
<ul style="list-style-type: none"> <li>• Charter of fundamental rights of the European Union (OJ 2010/C 83/02)</li> <li>• Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare</li> <li>• Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.</li> </ul>
<b>Medical devices</b>
<ul style="list-style-type: none"> <li>• Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007 amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to <b>active implantable medical devices</b></li> <li>• Directive 2001/104/EC of the European Parliament and of the Council of 7 December 2001 amending Council Directive 93/42/EEC concerning <b>medical devices</b>.</li> <li>• Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000 amending Council Directive 93/42/EEC as regards <b>medical devices incorporating stable derivatives of human blood or human plasma</b>.</li> <li>• Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on <b>in vitro diagnostic medical devices</b>.</li> </ul>
<b>Medicinal products</b>
<ul style="list-style-type: none"> <li>• Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on <b>advanced therapy medicinal products</b> and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.</li> <li>• Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to <b>medicinal products for human use</b>.</li> <li>• Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the <b>authorisation and supervision of medicinal products</b> for human and veterinary use and establishing a European Medicines Agency</li> </ul>

<ul style="list-style-type: none"> <li>• Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the <b>implementation of good clinical practice in the conduct of clinical trials</b> on medicinal products for human use.</li> </ul>
<ul style="list-style-type: none"> <li>• Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on <b>orphan medicinal products</b>.</li> </ul>
<ul style="list-style-type: none"> <li>• Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems.</li> </ul>
<p><b>Health care professionals</b></p>
<ul style="list-style-type: none"> <li>• Directive 2013/59/Euratom laying down basic safety standards for <b>protection against the dangers arising from exposure to ionising radiation</b>, and repealing Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom</li> </ul>
<ul style="list-style-type: none"> <li>• Directive 2004/18/EC of the European Parliament and of the Council of 31 March 2004 on the coordination of procedures for the award of <b>public works contracts, public supply contracts and public service contracts</b>.</li> </ul>
<p><b>Product safety</b></p>
<ul style="list-style-type: none"> <li>• Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.</li> </ul>
<ul style="list-style-type: none"> <li>• Directive 2001/95/EC of the European Parliament and of the Council of 3 December 2001 on <b>general product safety</b>.</li> </ul>
<p><b>International Treaties and recommendations from the Council of Europe</b></p>
<p>This is a selection of the important <a href="#">treaties</a> and <a href="#">recommendations</a> for HTA doers. More can be found from the web page of <a href="#">the Council of Europe</a></p>
<ul style="list-style-type: none"> <li>• Convention for the Protection of Human Rights and <b>Fundamental Freedoms</b> CETS No. 005.</li> </ul>
<ul style="list-style-type: none"> <li>• Convention for the protection of Human Rights and <b>dignity</b> of the human being with regard to the application of biology and medicine: Convention on Human Rights and Biomedicine CETS No.: 164.</li> </ul>
<ul style="list-style-type: none"> <li>• Additional Protocol to the Convention on Human Rights and Biomedicine concerning <b>Genetic Testing</b> for Health Purposes, CETS No.: 203.</li> </ul>
<ul style="list-style-type: none"> <li>• Additional Protocol to the Convention on Human Rights and Biomedicine, concerning <b>Biomedical Research</b> CETS No.: 195.</li> </ul>
<ul style="list-style-type: none"> <li>• Additional Protocol to the Convention on Human Rights and Biomedicine concerning <b>Transplantation of Organs and Tissues</b> of Human Origin CETS No.: 186.</li> </ul>
<ul style="list-style-type: none"> <li>• Recommendation R (97) 5 of the Committee of Ministers to Member States on the <b>protection of medical data</b>.</li> </ul>
<ul style="list-style-type: none"> <li>• Recommendation R (2006) 18 of the Committee of Ministers to Member States on <b>health services in a multicultural society</b>.</li> </ul>

**3. The level of national legislation.** As EU Directives allow member states a certain amount of flexibility, member states adapt the directives while taking into account the differing national situations. Much of the healthcare-related EU legislation is given as minimum directives and hence a stricter national control may apply. It may also be necessary to investigate judgments, especially precedents of national Supreme Courts.

# Gathering information

## *Databases and search strategies*

Laws, preparatory acts of legislation and judgements of courts can be consulted directly in international databases (presented below) and in respective national sources. For identifying scientific literature, articles can be searched for in Medline, combining the term 'legal' with the medical search terms. Library electronic databases can be further used to search for relevant international and national monographs as well as articles on the issue in question. Journals such as the *European Journal of Health Law, Health Economics, Policy and Law, Medical Law International, Medical Law Review* and *Medicine and Law* may be scrutinised.

## **Databases and useful web sites of the European Union and the European Council**

- [EUR-Lex](#): EU law and other public EU documents.
  - **Hints for searching:** EUR-Lex provides free access to EU law, in the 24 official EU languages. You can search for documents or procedures using the search widget on homepage or quick, advanced or expert search. The simplest way to search from the database is to search by words or by document number with the search widget on homepage. For example by using the 'Simple search'-option, and a search combination 'diagnostic\*' and 'medical', one is lead to a long list of the community legislation and also soft law material.

One must bear in mind that the legal nature of these instruments varies to great extent. In EU law, only Regulations, Directives and Decisions form the legally binding framework. In addition, there are recommendations, guidelines and communications - soft law that aim to specify some aspects, to harmonise practices and to assist and help different stakeholders.

If you have the document reference, e.g. a directive number, use the 'By document reference' option. After a search, you can use the clickable facets in the left-hand menu to narrow your search results by domain, year of document, author, etc. For example 'Legislation' subdomain is useful when searching the legally binding Regulations, Directives, Decisions, and EU court cases.

Once you have a search results list, click on the title of the document or legislative procedure you wish to consult. There are up to five views available presented as tabs: About this document, Text, Procedure, Linked documents, All. Via the text tab you can access all available languages and formats of an item.

If you want to compare texts in different languages you can use the multilingual function. Via the linked documents tab you can access e.g. the amendments of the document and the latest consolidated version. Consolidation consists of the integration in a legal act of its successive amendments and corrigenda. Several legal texts published in different issues of the *Official Journal of the European Union* (OJ) are combined as a 'consolidated family' in one easy-to-read document. This is particularly helpful when the document has been amended many times. However, if you use a consolidated version you should be aware that consolidated texts are intended for use

as documentation tools and the institutions do not assume any liability for their content and that those texts have no legal value.

- EUR-Lex also offers an interface to databases on national law ([N-Lex](#)). For more detailed help use the [site's Help page](#)
- [CURIA](#): Case law database of the European Court of Justice
  - Terms such as ‘state aid’, ‘marketing authorisation’, ‘personal data’, ‘essentially similar product’, ‘advertising’, ‘free movements of services’, ‘medicinal products’ and ‘medical device’ may be of relevance.
- [HUDOC](#): Case law database of the European Court of Human Rights
- [EudraLex - Volume 1](#) ‘The rules governing medicinal products in the European Union’ compiles the body of European Union legislation (directives and recommendations) in the pharmaceutical sector for medicinal products for human use.
- [EU-legislation of medical devices](#) – includes also other amending or implementing legislation, guidance, consensus statements and interpretative documents.
  - [Proposal for a regulation of the European Parliament and of the Council on in vitro diagnostic medical devices 2012](#).

## Other websites

- [European Medicines Agency's Human medicines regulatory information](#)
- [treSS –Database](#) on EU Coordination regulations on Social Security including case-law
- [European Data Protection Supervisor](#) – Opinions delivered by the EDPS
- [Non-binding ISO standards related to health](#): The International Standards Organisation (ISO) has developed more than 1,200 norms and technical specifications in the field of health. While they are not legally binding, they may be used as international reference measures with a substantial impact on the development of rules and regulations.

## Patents

- [The European Patent Convention](#) - European patent system's founding treaty, including the implementing regulations.
- [European Patent Register](#) - The European Patent Register contains all the publicly available information on European patent applications as they pass through the grant procedure.
- [TRIPS](#) - trade-related aspects of intellectual property rights, patents, and pharmaceuticals and public health — including discussions in the WTO's TRIPS Council.
- World Intellectual Property Organisation (WIPO) [WIPO Lex](#). Electronic database which provides access to intellectual property (IP) laws and treaties of the Members of WIPO, the World Trade Organisation (WTO) and the United Nations (UN).

- PATENTSCOPE (<http://patentscope.wipo.int/search/en/search.jsf>). A WIPO with more than 32 million patent documents including international patent applications submitted under the Patent Cooperation Treaty (PCT).

## Reporting and interpreting

In each result card, the results should be preferably reported in the order of the legal sources' power of influence. The authors should make a reasonable effort to produce a result which is beyond the interest of one's own country. General or EU-level information is therefore preferred, but national information can also be useful to other jurisdictions, as long as the sources are transparently reported and the generalisability or transferability of the result considered.

## Assessment elements

I0002 Assessment element card						
<p>Issue: What kind of legal requirements are there for providing appropriate information to the user or patient and how should this be addressed when implementing the technology?</p> <p><b>Topic: Autonomy of the patient</b></p>						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	1
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	1
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	1
	Screening Technologies (3.0)	Yes	Critical	None	Yes	1
Clarification	<p><b>Common to all used applications</b></p> <p>Describe the rules and recommendations for what patients should know about the implications of using or not using the technology. The right of the patient not-to-know may also be important, as well as the patient's right to complain.</p> <p>These rules are likely to be helpful for the persons involved in implementing the technology to prepare proper information and counselling. This information may be particularly important with technologies carrying high risks of harm, technologies with the potential to provide information that is not directly relevant to the condition being tested, and in emergency situations in which the patient does not usually have sufficient time to consider the treatment decision.</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>As screening programs target symptom-free and healthy people, it is particularly important that the individuals are aware of the potential benefits and harmful consequences of attending a screening test. The information provided for individuals attending screening should therefore not be persuasive.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Convention on Human Rights and Biomedicine CETS No: 164 (including the Explanatory report to Biomedicine convention).</p> <p>Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare, National laws specially on patients' rights.</p> <p>Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes, CETS No. 203.</p>					

<b>References</b>	<b>Common to all used applications</b> EU Charter of fundamental rights (2000/C 364/01) Art 3; Biomedicine Convention Art 5
<b>Content relations</b>	<b>Common to all used applications</b> B0014, B0015, C0002, C0005, C0007, C0008, F0004, F0006, F0010, F0016, G0004
<b>Sequential relations</b>	<b>Common to all used applications</b> B0014, B0015, C0002, C0005, C0007, C0008, F0004, F0010, G0004

I0034 Assessment element card						
Issue: Who is allowed to give consent for minors and incompetent persons?						
Topic: Autonomy of the patient						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	None	No	2
	Medical and Surgical Interventions (3.0)	Yes	Important	None	No	2
	Pharmaceuticals (3.0)	Yes	Important	None	No	2
	Screening Technologies (3.0)	Yes	Critical	None	Yes	2
Clarification	<p><b>Common to all used applications</b></p> <p>According to law, a minor is a person under a certain age, usually the age of majority, which legally demarcates childhood from adulthood. The age of majority depends upon jurisdiction and application, but is generally 18. An incompetent person may be defined as one whose mind is unsound, deranged, or impaired in function, such as a slow I.Q., deterioration, illness or psychosis. What do laws/binding rules require when considering informed consent in these groups? See also I0002.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Convention on Human Rights and Biomedicine CETS No.: 164 (including the Explanatory report to Biomedicine convention).</p> <p>National laws on patients' rights.</p> <p>Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes, CETS No.: 203.</p> <p>Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data, OJ 1995 L 281/31.</p>					
References	<p><b>Common to all used applications</b></p> <p>Convention on Human Rights and Biomedicine, Art 6 and 7</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>F0005, I0002</p>					
Sequential relations	<p><b>Common to all used applications</b></p> <p>F0005, I0002</p>					

I0007 Assessment element card

Issue: Is there a possibility that the use of the technology produces additional information that is not directly related to the current care of the patient and may violate their right to respect for privacy?

Topic: Privacy of the patient

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	3
	Medical and Surgical Interventions (3.0)	Yes	Important	Partial	Yes	3
	Pharmaceuticals (3.0)	Yes	Important	Partial	Yes	3
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	3
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>The protection of sensitive personal data is secured at the EU level. Privacy protection is a modern expression of the ancient ethical principle of confidentiality in doctor-patient relationship. The use of computerised patient record databases and modern genetic diagnostics entail certain challenges to this principle. For example, in Z vs. Finland (ECHR February 25, 1997) there was a case of an HIV infected person whose HIV positive test was an incidental finding, not related to her healthcare intervention at the time.</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Case laws, medical case reports. Z vs. Finland (ECHR February 25, 1997); M.S. vs. Sweden (ECHR August 28, 1997); national legislation; legal literature.</p>					
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Directive 95/46/EC, EU FR Charter Art 8, Biomedicine Convention Art 10, CM Recommendation R (97) 5. European Convention on Human Rights CETS No.: 005 art. 8</p>					
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>B0012, C0006, D0022, F0101</p>					
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>C0006, D0022, F0101</p>					

I0008 Assessment element card						
Issue: What do laws/binding rules require with regard to informing relatives about the results?						
Topic: Privacy of the patient						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	4
	Medical and Surgical Interventions (3.0)	No				
	Pharmaceuticals (3.0)	No				
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	4
Clarification	<p><b>Common to all used applications</b></p> <p>A test result may indicate that the relatives of a patient may have a medical condition that would need to be addressed. If this can be foreseen, appropriate procedures, complying with the existing legislation, must be considered beforehand – is the information to be revealed to, or withheld from the relatives in question? Describe on what conditions (if any) the privacy of the original patient can be broken in order to inform the relatives of their situation.</p> <p>There may be situations, e.g. when treatment malpractice is suspected after the death of the patient, when (closest) relatives demand the results. Similar cases could occur in sudden, unexpected deaths and in some cases of highly infectious diseases.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.</p> <p>Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes, CETS No.: 203.</p> <p>Convention on Human Rights and Biomedicine CETS No.: 164 (including the Explanatory report to Biomedicine convention).</p> <p>National laws specially on patients' rights and data protection.</p> <p>Z vs. Finland (ECHR February 25, 1997); M.S. vs. Sweden (ECHR August 28, 1997).</p>					
References	<p><b>Common to all used applications</b></p> <p>Directive 95/46/EC</p> <p>Convention on Human Rights and Biomedicine Art 10</p>					

<b>Content relations</b>	<b>Common to all used applications</b> B0014, F0011, G0004, H0002
<b>Sequential relations</b>	<b>Common to all used applications</b> B0014, F0011, H0002

I0009 Assessment element card

Issue: What do laws/binding rules require with regard to appropriate measures for securing patient data and how should this be addressed when implementing the technology?

Topic: Privacy of the patient

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	5
	Medical and Surgical Interventions (3.0)	Yes	Important	Partial	Yes	4
	Pharmaceuticals (3.0)	Yes	Important	Partial	Yes	4
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	5
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Provide an overview of the legal requirements regarding policies and procedures, as well as examples of: practical local solutions; securing the kind of patient data that will be generated when using of the technology.</p> <p>Who is allowed to save and store the patient-data, where is it saved, for how long, and who can have access to it? Does the use of the technology produce some additional (i.e. diagnostically or therapeutically irrelevant) information on the patient that could be relevant for, e.g., health insurance, marketing studies, or safety authorities and how should data protection be handled in these cases? Is it possible that legal data protection requirements have adverse consequences to the quality of care, e.g. by complicating the transfer of patient data in a screening process, and how should this be addressed?</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.</p> <p>Convention on Human Rights and Biomedicine CETS No.: 164 (including the Explanatory report to Biomedicine convention).</p> <p>Recommendation R (97) 5 of the Committee of Ministers to Member States on the protection of medical data.</p> <p>National laws specially on patients' rights and data protection.</p> <p>Z vs. Finland (ECHR February 25, 1997); M.S. vs. Sweden (ECHR August 28, 1997).</p>					

<b>References</b>	<b>Common to all used applications</b> Directive 95/46/EC Convention on Human Rights and Biomedicine Art 10
<b>Content relations</b>	<b>Common to all used applications</b> B0010, F0101, F0016
<b>Sequential relations</b>	<b>Common to all used applications</b> B0010, F0101, F0016

I0011 Assessment element card

Issue: What do laws/binding rules require with regard to appropriate processes or resources which would guarantee equal access to the technology?

Topic: Equality in health care

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	6
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	5
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	5
	Screening Technologies (3.0)	Yes	Critical	None	Yes	6
<p><b>Clarification</b></p>	<p><b>Common to all used applications</b></p> <p>In general, equality in health care is stipulated in the EU Charter of Fundamental Rights and it is also one of the central principles of the Biomedicine Convention. Moreover, in many national constitutions, equality of citizens also covers access to health care. However, there may be experiences on a national level of some specific difficulties in equal access to the technology, and there may probably also be proposed solutions, which could be helpful for decision-makers in other countries as well.</p>					
<p><b>Methodology and sources</b></p>	<p><b>Common to all used applications</b></p> <p>Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare.</p> <p>Recommendation R (2006) 18 of the Committee of Ministers to Member States on health services in a multicultural society.</p> <p>National laws.</p> <p>Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes, CETS No.: 203.</p> <p>Case law: S.H. and others vs. Austria (ECtHR April 1, 2010).</p> <p>Gillberg vs. Sweden (ECtHR November 2, 2010).</p> <p>Commission vs. France (ECJ C-512/08) of October 5, 2010.</p> <p>R.R. vs. Poland (ECtHR May 26, 2011)</p> <p>Panaitescu vs. Romania (ECtHR April 10, 2012).</p> <p>Costa and Pavan vs. Italy (ECtHR August 28, 2012)</p>					

<b>References</b>	<b>Common to all used applications</b> EU FR Charter Art 35, Biomedicine Convention Article 3, CM RecommendationR (2006) 18
<b>Content relations</b>	<b>Common to all used applications</b> F0012, F0014, F0016, G0009, G0101, H0012
<b>Sequential relations</b>	<b>Common to all used applications</b> F0012, F0014, F0016, G0009, G0101, H0012

I0012 Assessment element card						
Issue: What are the consequences of various EU level and national regulations to the equal access to the technology?						
Topic: Equality in health care						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Partial	Yes	7
	Medical and Surgical Interventions (3.0)	Yes	Important	Partial	Yes	6
	Pharmaceuticals (3.0)	Yes	Important	Partial	Yes	6
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	7
Clarification	<p><b>Common to all used applications</b></p> <p>The possible consequences of the EU Directive of cross border health care could be considered here. There may be nationally legally defined processes, including reimbursement and pricing, determining the implementation of and level of access to a technology. This information may give useful insight also beyond one's own country.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare.</p> <p>National laws.</p>					
References	<p><b>Common to all used applications</b></p> <p>Charter of Fundamental Rights of the European Union (2000/C 364/01). Art 35</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>A0021, B0004, F0012, F0013, G0009, G0101, H0012, H0015</p>					
Sequential relations	<p><b>Common to all used applications</b></p> <p>A0021, B0004, F0012, F0013, G0009, H0012, H0015</p>					

F0014 Assessment element card						
Issue: Does the implementation or use of the technology affect the realisation of basic human rights?						
Topic: Ethical aspects						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Complete	Yes	8
	Medical and Surgical Interventions (3.0)	Yes	Critical	Complete	Yes	7
	Pharmaceuticals (3.0)	Yes	Critical	Complete	Yes	7
	Screening Technologies (3.0)	Yes	Critical	Complete	Yes	8
Clarification	<p><b>Common to all used applications</b></p> <p>The basic human rights are most notably declared in the United Nations Declaration of Human Rights (<a href="http://www.un.org/en/documents/udhr/">http://www.un.org/en/documents/udhr/</a> ). They are universal and consider the most important goods, protections and freedoms for mankind. For HTA, perhaps the most relevant are the rights to equality, non-discrimination, safety, adequate standard of living, and healthcare.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Literature search. Laws, rules and regulations. Expert opinion. Stakeholder hearing</p>					
References	<p><b>Common to all used applications</b></p> <p>Hofmann B, 2005; {49}; Marks SP, 2004 {57} in ETH</p>					
Content relations						
Sequential relations	<p><b>Common to all used applications</b></p> <p>H0012</p>					
Other domains	<p>Also in: Ethical analysis</p>					

F0016 Assessment element card						
Issue: Can the use of the technology pose ethical challenges that have not been considered in the existing legislations and regulations?						
Topic: Ethical aspects						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	None	No	9
	Medical and Surgical Interventions (3.0)	Yes	Important	None	No	8
	Pharmaceuticals (3.0)	Yes	Important	None	No	8
	Screening Technologies (3.0)	Yes	Important	None	No	9
Clarification	<p><b>Common to all used applications</b></p> <p>Describe whether legislation and regulation to use the technology is fair and adequate. Use of the technology may lead to ethical issues that make current regulations inadequate. Screening and diagnostic technologies are commonly regulated differently than treatments, especially medications. Ethical reflection is essential in order to assess what kind of legislation, regulation or amendments are needed.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Laws, rules and regulations. Stakeholder hearing. Expert opinion</p>					
References	<p><b>Common to all used applications</b></p> <p>Hofmann B 2005 {49}, Capron AM 2004 {58} from the ETH domain</p>					
Content relations						
Sequential relations	<p><b>Common to all used applications</b></p> <p>B0010, I0011, I0009, I0002, I0026 I0037</p> <p><b>Specific to Diagnostic Technologies (3.0)</b></p> <p>I0008</p> <p><b>Specific to Screening Technologies (3.0)</b></p> <p>I0008</p>					
Other domains	Also in: Ethical analysis					

I0015 Assessment element card						
Issue: What authorisations and register listings does the technology have?						
Topic: Authorisation and safety						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Complete	Yes	10
	Medical and Surgical Interventions (3.0)	Yes	Critical	Complete	Yes	9
	Pharmaceuticals (3.0)	Yes	Important	Complete	Yes	9
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	10
Clarification	<p><b>Common to all used applications</b></p> <p>Describe the register listings, both at EU level and national level, which might be relevant when implementing the technology and planning, e.g., local authorisation, monitoring or evaluation functions, as well as qualification and quality control. Examples include technology registers, registers for marketing authorisation, certification of safety and reimbursement. However, some of the registers, e.g. the one for medical devices (EUDAMED), are not open for HTA doers. Register listings information may be particularly relevant for the technologies which can be used off-label or as investigational intervention outside clinical trials (so-called expanded access or compassionate use).</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.</p> <p>Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices.</p> <p>National laws.</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use</p>					
References	<p><b>Common to all used applications</b></p> <p>In vitro diagnostic directive (98/79/EC); EUDAMED; FDA; EMA</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>A0020, B0010, C0002, C0007, C0060</p>					

<b>Sequential relations</b>	<b>Common to all used applications</b> A0020, B0010, C0002, C0007, C0060
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I0017 Assessment element card						
Issue: What do laws/binding rules require with regard to the safety of the technology and how should this be addressed when implementing the technology?						
Topic: Authorisation and safety						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Complete	Yes	11
	Medical and Surgical Interventions (3.0)	Yes	Critical	Complete	Yes	10
	Pharmaceuticals (3.0)	Yes	Critical	Complete	Yes	10
	Screening Technologies (3.0)	Yes	Critical	Complete	Yes	11
Clarification	<p><b>Common to all used applications</b></p> <p>List the legal requirements for safety of the technology and quality of care. Does the technology fulfil these requirements, and what should be done to ensure that the legal requirements maintain fulfilled when implementing the technology? Consider the findings of the SAF and ORG domains here, in the light of relevant European or national safety regulations. See also I0015.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Results from the Safety domain.</p> <p>Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.</p> <p>Directive 2001/95/EC of the European Parliament and of the Council of 3 December 2001 on general product safety.</p> <p>Council Directive 93/42/EEC of 14 June 1993 concerning medical devices.</p> <p>National laws.</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products</p>					
References	<p><b>Common to all used applications</b></p> <p>Directive 93/42/EEC</p> <p>Directive 2001/95/EC</p>					

<b>Content relations</b>	<b>Common to all used applications</b> B0002, B0003, B0008, C0002, C0020, C0040, C0062, C0063, C0064, G0012, I0015
<b>Sequential relations</b>	<b>Common to all used applications</b> B0002, B0003, B0008, C0002, C0020, C0040, C0062, C0063, C0064

I0019 Assessment element card						
Issue: What should be known about the intellectual property rights and potential licensing fees?						
Topic: Ownership and liability						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Important	Complete	Yes	12
	Medical and Surgical Interventions (3.0)	Yes	Important	Complete	Yes	11
	Pharmaceuticals (3.0)	Yes	Important	Complete	Yes	11
	Screening Technologies (3.0)	Yes	Important	Complete	Yes	12
Clarification	<p><b>Common to all used applications</b></p> <p>This information is important because infringement of intellectual property rights can reduce the use of the technology and have implications for the wording of the acquisition contract of a new technology, and possibly also licencing fees.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions.</p> <p>Directive 2004/18/EC of the European Parliament and of the Council of 31 March 2004 on the coordination of procedures for the award of public works contracts, public supply contracts and public service contracts.</p> <p>National laws.</p> <p>Patent data bases.</p> <p>Manufacturer's information.</p> <p>C-317/05 (ECJ)</p>					
References	<p><b>Common to all used applications</b></p> <p>2004/18/EC on public contracts.</p> <p>European patent convention (EPC), Directive 98/44/EC, national legislation</p>					
Content relations						
Sequential relations						

I0021 Assessment element card						
Issue: What should be known about the legal or binding rules regarding the width, depth and length of the manufacturers guarantee?						
Topic: Ownership and liability						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Complete	Yes	13
	Medical and Surgical Interventions (3.0)	Yes	Critical	Complete	Yes	12
	Pharmaceuticals (3.0)	Yes	Optional	Complete	No	12
	Screening Technologies (3.0)	Yes	Optional	Complete	No	13
Clarification	<p><b>Common to all used applications</b></p> <p>This issue may help the decision-maker to be aware of their legal rights when considering the manufacturer's guarantee. The user guide plays a part in determining the manufacturer's liability.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Manufacturer's information</p> <p>Sales/purchase contract</p>					
References	<p><b>Common to all used applications</b></p> <p>National laws about manufacturer guarantee</p>					
Content relations						
Sequential relations						

I0023 Assessment element card						
Issue: What kind of legal price control mechanisms are there that are relevant to the technology?						
Topic: Regulation of the market						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	14
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	13
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	13
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	14
Clarification	<p><b>Common to all used applications</b></p> <p>Describe the adopted economic measures for controlling public health expenditures when adopting technologies. This information, although not transferable, gives insight to decision-makers in other countries too.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Directive 2004/18/EC of the European Parliament and of the Council of 31 March 2004 on the coordination of procedures for the award of public works contracts, public supply contracts and public service contracts.</p> <p>Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems.</p> <p>National laws.</p> <p>C-317/05 (ECJ), T-179/00 (ECJ)</p>					
References	<p><b>Common to all used applications</b></p> <p>Directive 1989/105/EEC</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>G0007</p>					
Sequential relations	<p><b>Common to all used applications</b></p> <p>G0007</p>					

I0024 Assessment element card						
Issue: What kind of regulation exists for the acquisition and use of the technology?						
Topic: Regulation of the market						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	15
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	14
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	14
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	15
Clarification	<p><b>Common to all used applications</b></p> <p>Expensive technology and dangerous pharmaceuticals are typically subject to acquisition regulation.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Directive 2004/18/EC of the European Parliament and of the Council of 31 March 2004 on the coordination of procedures for the award of public works contracts, public supply contracts and public service contracts.</p> <p>National law.</p> <p>Case law: Commission vs. Poland (ECJ C-185/10) of March 29, 2012.</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use</p>					
References	<p><b>Common to all used applications</b></p> <p>Directive 2004/18/EC</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>G0006, G0007</p>					
Sequential relations	<p><b>Common to all used applications</b></p> <p>G0006, G0007</p>					

I0025 Assessment element card						
Issue: What legal restrictions are there for marketing the technology to the patients?						
Topic: Regulation of the market						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	16
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	15
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	15
	Screening Technologies (3.0)	Yes	Critical	Partial	Yes	16
Clarification	<p><b>Common to all used applications</b></p> <p>Describe general legal principles of the restrictions placed on the marketing of health technologies to lay people.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices.</p> <p>Directive 93/42/EEC of 14 June 1993 concerning medical devices.</p> <p>Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices.</p> <p>National laws</p> <p><b>Specific to Pharmaceuticals (3.0)</b></p> <p>Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use</p>					
References	<p><b>Common to all used applications</b></p> <p>Directive 1989/105/EEC</p> <p>Directive 2001/83/EC</p>					
Content relations						
Sequential relations						

I0026 Assessment element card						
Issue: What should be known about the legal issues in cases of new technologies where the current legislation is not directly applicable?						
Topic: Regulation of the market						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	17
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	16
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	16
	Screening Technologies (3.0)	No				
Clarification	<p><b>Common to all used applications</b></p> <p>Novel technologies may not always be unambiguously covered by existing legislation. Sometimes, an otherwise restricted technology can be used in clinical trials or as 'compassionate use', i.e. in extended use outside clinical trials. Important questions, such as 'How are the liability issues solved according to existing legislation?', or, 'Is the voluntary participation of patients guaranteed properly?' may be important to consider. If the current law does not provide a straightforward answer to the liability issues it may be advisable to consult a legal expert on the interpretation of the existing provisions with regard to the technology in question. Sometimes even new legislative measures are needed.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Consulting legal expert(s), possibility of analogical interpretation of law, court decisions, literature</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>B0002, B0003; F0003, F0016</p>					
Sequential relations	<p><b>Common to all used applications</b></p> <p>B0002, B0003, F0003, F0016</p>					

I0037 Assessment element card						
Issue: Are there relevant concerns about conflicts of interest regarding the preparation of binding rules and their implementation?						
Topic: Regulation of the market						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (3.0)	Yes	Critical	Partial	Yes	18
	Medical and Surgical Interventions (3.0)	Yes	Critical	Partial	Yes	17
	Pharmaceuticals (3.0)	Yes	Critical	Partial	Yes	17
	Screening Technologies (3.0)	Yes	Important	Partial	Yes	17
Clarification	<p><b>Common to all used applications</b></p> <p>Relevant concerns of partiality or conflicts of interest with regard to binding guidance may give useful insight to decision-makers about the importance of implementing a technology.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Literature</p>					
References	<p><b>Common to all used applications</b></p> <p><a href="#">Decision No 1926/2006/EC of the European Parliament and of the Council</a> of 18 December 2006 establishing a programme of Community action in the field of consumer policy (2007-2013) (2.4.2014)</p> <p><a href="#">Directive 2001/20/EC of the European Parliament and the Council</a> of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (especially (4), (6), Art 13 (1., 3a, 3b). (2.4.2014).</p> <p><a href="#">World medical association declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects</a>, (especially A5) (2.4.2014)</p> <p>Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research Strasbourg, 25.I.2005.</p> <p><a href="#">The Treaty of Lisbon amending the Treaty on European Union and the Treaty establishing the European Community</a> entered into force on 1 December 2009. , especially Chapter III Article 12) (2.4.2014).</p>					
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# Appendices

## ***Appendix Intro-ETH: Ethical considerations within HTA process***

Every HTA process should be performed considering the following ethical issues:

- The driving forces (and valued interests) to perform the assessment at this stage should be identified, including the stakeholders and the whole HTA organisation. *Are there particular interests that make this technology subject to assessment (pressure from producers, patient groups or professionals, costs)?*
- The morally relevant reasons for performing / not performing a HTA on this topic should be identified. *Is the topic a significant public health issue? Is the technology likely to benefit public health? Are HTA resources wisely spent on this topic? Is the topic a priori morally contentious? Is there fear of presenting unpopular results? Has the technology already been implemented without proper, objective evaluation? Is the technology being used beyond its actual target group? Have the costs exceeded the resources?*
- The interests of the producers of the technology should be identified. *Developers and producers are interested in promoting their technology which influences the distribution and use of technologies. What are the financial interest in respect to 'well doing'.*
- It should be identified whether there are related technologies that are morally contentious, or if the technology is a novel, innovative mode of care. *It is important to identify, from the beginning, whether there are ethically relevantly similar technologies in use. They may provide useful casuistic background for the ethical analysis. On the other hand, novel, innovative technologies may pose unexpected ethical problems and value conflicts, which may justify extra emphasis placed on ethical analysis.*
- The interests of the content expert group should be discussed openly so that the work can be conducted in an objective and independent way. *It is morally important to evaluate the relationship between professionals and the industry with respect to the development and use of the technology in question. What are their final interests? Is the technology of relevance for the professional identity and development?*
- The choice of endpoints in the assessment has to be carefully considered. *The choice of endpoints leads to questions that are of moral relevance. What is the aim of the technology - to reduce mortality, increase functional status, improve quality of life, lengthen disease-free time, save money? Are there other stakeholders with possible gains or losses that should be evaluated? The decision on endpoints has also an impact on the inclusion criteria of original studies and thus may not reflect the entire existing literature on the technology in question.*

- The morally relevant issues related to the selection of meta-analysis and studies to be included in the HTA have to be identified. *The choice of endpoint affects the inclusion criteria for original studies to be accepted. What to do when the quality criteria are not filled by any existing studies or when no RCT studies exist - especially when the technologies are already being used? When is it necessary to continue with the HTA even if no RCTs are available?*
- The scope of the HTA and choice of research methods (e.g. inclusion of other aspects of assessment than effectiveness in the literature searches). *The literature searches focused only on the effectiveness of the technology in question seldom give access to articles relevant to other domains of assessment (e.g. the ethical, social or organisational analysis). Ethically relevant issues may be identified during the entire HTA process and the literature searches are thus possible first after their identification. The literature search should cover other related technologies with similar ethical challenges. The detailed presentation of questions and experiences related to a (ethically relevantly) similar technology are important, as they may help decision-makers identify relevant issues and adopt coherent policies.*

## ***Appendix Intro-Scr: Screening technologies***

Depending on background and training, people may give different meaning to the word 'screening'. The following observations and definitions were agreed on originally for version 1.0 of the screening application and retained for version 2.0.

### **Why do we need a dedicated Model application for screening technologies?**

Screening involves testing to identify people at high risk of having a specific disease (diagnosis). As there is already a HTA Core Model application for diagnostic technologies that covers testing procedures, why do we need additional application for screening? The following properties of screening were identified that justify the need of a dedicated application of the HTA Core Model.

- As preventive or early diagnostic intervention, screening is targeted to a large number of healthy or asymptomatic people – in contrast to diagnostics where people typically already have some symptoms or signs of illness.
- Screening tests are usually applied in a population with low disease prevalence, i.e. mostly healthy people. Therefore, the diagnostic tools often perform very differently from clinical settings (i.e. very low positive predictive value). The same technology has different performance when used in diagnosis than in screening.
- Effectiveness depends on participation rate of the target population.
- Screening issues usually benefit from careful ethical and legal considerations, due to the risk of false positives and false negatives, the consequences related to the under-or overdiagnosis and -treatment, and earlier diagnosis in cases where prognosis improvement is negligible. Equity of access is always an issue in screening programs.
- There are several organisational issues specific for screening as it
  - involves active contact of the target population by the health service
  - is multidisciplinary and involves multiple providers
  - requires quality control and a continuous monitoring system.
- There are many specific characteristics and methodological issues which have to be taken into account when evaluating economic impact of a screening programme. For example, most of the costs of a screening programme are incurred within a relatively short time period and the benefits (e.g. life years gained) further in the future. This means that decisions about whether to discount the future costs and effects or not, and which discount rate(s) to use, need to be carefully considered.

## Multiple definitions for screening

There are **two main streams** of considering screening as a public health intervention.

- The first, mostly adopted in Europe, considers screening as a programme in which
  - the target population and adequate screening interval are determined in advance;
  - all individuals in a certain category (e.g. all women of a certain age) are involved;
  - the health services contact systematically and actively the target population; and
  - a standard process is determined for further diagnostic examinations subsequent to the screening test, as well as for treating those with the diagnosed condition.
  - This approach is also referred to as universal screening, mass screening, population screening, or community screening.
- The second stream, mostly adopted in the USA, considers screening to be spontaneous, or so called opportunistic screening, in which the practitioners recommend the test to their (asymptomatic) patients more or less systematically and according to their attitudes and knowledge. This kind of screening lacks systematic identification and contacting of the target population. Instead it is dependent on the activity of the individuals themselves, their health service providers, and funding arrangements (health insurance package). The process for further examinations and treatment is not standardised.

There are **additional uses** of the word screening in medicine

- ‘Screening’ may be performed during a regular patient visit, on an asymptomatic patient, to exclude or confirm diagnosis (e.g. bone density measurement).
- Surveillance screening involves testing of a sample of the population to survey the prevalence of a disease or an exposure, without the aim of improving prognosis in diseased individuals.
- Toxicological screening involves testing of environmental or clinical samples to identify toxic substances.
- Molecular screening is a phase in the selection of active molecules in pharmacology.

More related concepts

- Case finding: Involves a smaller group of people based on the presence of risk factors (e.g. when a family member has been diagnosed with a hereditary or communicable disease). ‘Case finding’ is also used in the context of screening a single patient who consults the doctor on a problem not directly related to the disease being screened. An example of this is cervical cancer screening during a consultation for other gynaecological problem.
- Routine safety checks (e.g. related to anaesthesia)
- Baseline value assessment (e.g. liver enzymes before medication)
- Check-up, periodic health examinations often involve a number of screening elements

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## *Appendix 1: Information sources*



## *Appendix 2: Shared methodologies*

