



# eunetha

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

**JOINT ACTION 2 - WORK PACKAGE 8**

**The HTA Core Model<sup>®</sup>**

**Version 2.1 PUBLIC DRAFT**

**29 Oct 2014**

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

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

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

The contents of version 2.1 were originally published online (at [www.corehta.info](http://www.corehta.info)) on the 29<sup>th</sup> of October 2014 as separate model applications. This pdf document combines the contents of the four applications and was published on the 6<sup>th</sup> of November 2014.

This version 2.1 contains a new version of the legal domain (which was not updated in version 2.0). Additionally, some changes have been made to the ontology, see the chapter Introduction for more information. All other contents remain as they were in 2.0.

The Model is developed by an international expert group. See chapter “Contributors” in this document for details.

The application for rapid relative effectiveness of pharmaceuticals, produced by EUnetHTA WP5, is not included in this document. It is available as a separate PDF document.

All HTA Core Model applications are available through [www.corehta.info/BrowseModel.aspx](http://www.corehta.info/BrowseModel.aspx).

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**Cite this document as:**

EUnetHTA Joint Action 2, Work Package 8. HTA Core Model<sup>®</sup> version 2.1 PUBLIC DRAFT (Pdf); 2014. Available from <http://www.corehta.info/BrowseModel.aspx>.

1	<b>Contents</b>	
2	Introduction.....	5
3	About the HTA Core Model® and its utilisation .....	5
4	HTA Core Model 2.1 .....	11
5	HTA Core Model 2.0 .....	12
6	Ethics of HTA.....	15
7	Value judgments.....	16
8	Contributors.....	17
9	References .....	22
10	Health Problem and Current Use of the Technology .....	24
11	Description.....	24
12	Methodology .....	28
13	Assessment elements .....	41
14	References .....	64
15	Description and technical characteristics of technology.....	66
16	Description.....	66
17	Methodology .....	68
18	Assessment elements .....	77
19	References .....	104
20	Safety.....	105
21	Description.....	105
22	Methodology .....	111
23	Assessment elements .....	120
24	References .....	139
25	Clinical Effectiveness .....	142
26	Description.....	142
27	Methodology .....	146
28	Assessment elements .....	167
29	References .....	205
30	Appendices .....	212
31	Costs and economic evaluation.....	213
32	Description.....	213
33	Methodology .....	216
34	Assessment elements .....	240

1	References .....	251
2	Ethical analysis.....	257
3	Description.....	257
4	Methodology .....	264
5	Assessment elements .....	276
6	References .....	302
7	Organisational aspects .....	305
8	Description.....	305
9	Methodology .....	309
10	Assessment elements .....	322
11	References .....	342
12	Social aspects.....	345
13	Description.....	345
14	Methodology .....	349
15	Assessment elements .....	356
16	References .....	378
17	Legal aspects.....	381
18	Description.....	381
19	Methodology .....	384
20	Assessment elements .....	390
21	References .....	412
22	Appendices .....	414
23	Appendix Intro-Eth: Ethical considerations within HTA process .....	414
24	Appendix Intro-Scr: Screening technologies .....	415
25	Appendix Intro-2.1: Changes in the ontology.....	418
26	Appendix 1: Information sources .....	436
27	Appendix 3. Shared methodologies .....	444

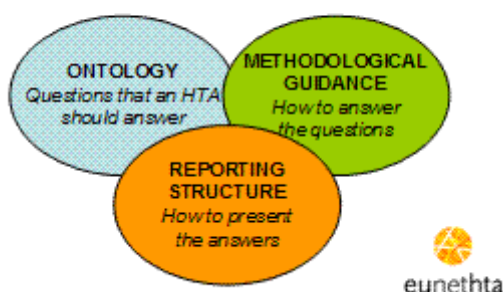
## 1 **Introduction**

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

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

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

### The HTA Core Model



10

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

12 Normally a health technology assessment (HTA) contains a vast amount of information. All  
13 potential contents of HTAs are referred to here as “HTA information”. The content, focus, quality  
14 and reporting of HTAs vary a lot; this makes finding and transferring the information into local  
15 contexts difficult. The HTA Core Model tackles this problem, in particular. The Model defines the  
16 content elements to be considered in an HTA and enables standardized reporting. The aim is to  
17 improve the applicability of HTA information in other (e.g. national or regional) HTA projects, and  
18 to enable actual collaboration between HTA agencies by providing a common framework for HTA  
19 production.

20 The HTA Core Model<sup>®</sup> is a registered trademark. Its utilisation is subject to *Terms of Use* available  
21 at [www.corehta.info](http://www.corehta.info). Two licenses are available in this document, one for non-commercial use and  
22 another for commercial use.

23 The HTA Core Model divides HTA information into standardized pieces referred to as *assessment*  
24 *elements*. An assessment element defines a piece of information that is relevant for the HTA. The  
25 elements that are most likely to be useful for international sharing of information are defined as  
26 *core elements*. Each assessment element contains a question that one should consider including and  
27 answering within a specific assessment project.

28 The HTA Core Model Online, available at [www.corehta.info](http://www.corehta.info), provides a computerized interface to  
29 the Model. Any HTA information produced using the Model and published through the database

1 within the HTA Core Model Online is referred to as *core HTA information*. The information in the  
 2 database is organized in *collections*, each containing a number of *result cards* and other material  
 3 (e.g. an introduction and summary). The result cards contain the answers to the questions defined by  
 4 the ontology.

5 A *core HTA* is one type of collection within the HTA Core Model Online. Each core HTA provides  
 6 the answers to all relevant core elements for a specific technology, considers the findings per  
 7 domain in "domain discussions", and summarizes the most important findings. Users can also  
 8 define their collection themselves and pick a free selection of elements to be answered. One could,  
 9 for example, consider sharing certain pieces of information from a national HTA project within  
 10 other European HTA agencies by including them in the pool of core HTA information.

11 The HTA Core Model builds on earlier work of projects EUR-ASSESS {1}, HTA Europe {2} and  
 12 ECHTA/ECAHI {3, 4} as well as on other theoretical guidance referenced in relevant locations. It  
 13 attempts to be loyal to the definitions of HTA that emphasize the multidisciplinary nature of  
 14 assessments. It employs the nine domains that were originally identified in the EUR-ASSESS  
 15 project (Table 1).

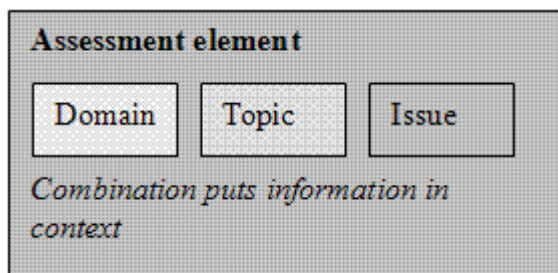
## 16 Table 1. Domains of an HTA

- 17 1. Health problem and current use of technology (CUR)
- 18 2. Description and technical characteristics of technology (TEC)
- 19 3. Safety (SAF)
- 20 4. Clinical effectiveness (EFF)
- 21 5. Costs and economic evaluation (ECO)
- 22 6. Ethical analysis (ETH)
- 23 7. Organisational aspects (ORG)
- 24 8. Social aspects (SOC)
- 25 9. Legal aspects (LEG)

26 The HTA Core Model was originally developed through *applications* that each focused on a  
 27 specific type of technology. Two first applications, one for medical and surgical interventions {5}  
 28 and the other for diagnostic technologies {6}, were created by Work Package 4 (WP4) of the  
 29 EUnetHTA Project 2006-08. An application for screening technologies was developed within WP4  
 30 of EUnetHTA Joint Action 2010-2012 {7}. A fourth application to enable rapid relative  
 31 effectiveness assessment (REA) of pharmaceuticals was developed by WP5 of EUnetHTA Joint  
 32 Action {8}. The current Model version 2.0 has been produced within WP8 of EUnetHTA Joint  
 33 Action 2 (2012-2015) and the development continues until the end of JA2. It is a major overhaul of  
 34 the applications on interventions, diagnostics and screening, supplemented by a new application for  
 35 full assessment of pharmaceuticals. The application for rapid REA of pharmaceuticals will be  
 36 updated separately by WP5 of Joint Action 2.

## 37 The ontology

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



1

## 2 **Figure 2. An assessment element**

3 Assessment elements define the standardized pieces of HTA information. Each assessment element  
4 is defined in more detail in an *element card*, which provides further information on the element and  
5 its relations to other elements. An element card may also provide advice on how to answer the  
6 question defined by the element. Two characteristics of an element, its importance and  
7 transferability (both defined in the element card) define whether an element is a "core element" or a  
8 "non-core element" (see below).

9 The relevance of the generic questions defined by the assessment elements should be evaluated  
10 within each HTA project, considering the technology that is the object of assessment as well as the  
11 project's aims and resources. When producing a collection of core HTA information, there may be  
12 specific requirements set for some collection types. Relevant questions are included in the  
13 collection, translated into practical research questions and answered during the project. When  
14 producing a core HTA, all core elements must be included in the collection. If some question is not  
15 relevant for the technology under assessment, an explanation of why it is not relevant must be  
16 included in the collection.

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

22

1 **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 Used</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 has to do with significance from the viewpoint of HTA. It is not always the same as "relevance" in a particular policy context. Three categories are used: 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. Three categories are used: Complete (Data/findings are context-independent); Partially (Data/findings are not directly transferable from one setting to another. Adjustments are needed.); Not (Data/findings are not transferable from one setting to another without serious difficulties.) <i>Core</i> defines whether the element is a core element. This is based on the importance and transferability of the element in each model application. See further details below in chapter "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 nr 1 is the first element of a domain.
<b>Clarification*</b>	A more detailed description of what the issue is about.
<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 that are likely to provide useful information when answering the questions made of this element. This information can be used when defining projects and the order of answering various research questions.
<b>Other domains</b>	Some elements are included in more than one domain. This field contains a list of other domains where this element is included (if relevant).
* 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".	

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

3 Dividing the assessment elements into core elements and non-core elements is an attempt to focus  
4 on research questions that are likely to be most useful to share in the international context. The  
5 inclusion of an element in the core is a function of two basic characteristics of the element: its  
6 importance and transferability. If the information is fully or partly transferable, it may provide  
7 valuable input beyond its original production location. Transferability is low for information that is  
8 very specific to a particular context (e.g. region, country or health care system) and is most likely  
9 not useful as such in other settings. On the other hand even non-transferable information may be  
10 useful beyond its production location. For example Italian incidence data on cardiovascular  
11 mortality is applicable not only to a regional HTA in Italy, but also to all Italian HTAs assessing



cardiovascular technologies, or Swedish data on the current use of some technology may provide researchers in another country useful benchmark data when considering possible over-or underuse of the technology in their own country.

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

The inclusion in 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>
<b>Transferability</b>	<i>3 Complete</i>	Not core	Core	Core
	<i>2 Partially</i>	Not core	Core	Core
	<i>1 Not</i>	Not core	Not core	Core

It should be emphasized that the inclusion (exclusion) of an element in (from) the core is driven by usability of the information across national borders or in other contexts. Not belonging to the core does not mean that an element would be unimportant, insignificant or not worth considering in an HTA. On the contrary, important but non-transferable assessment elements 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 other research.

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

## Methodological guidance

Methodological guidance exists in the Model on three levels. This introduction contains some model-level, or whole-HTA -level guidance in the form of ethical principles to steer all HTA projects that utilise the Model. Most guidance, on the domain level, is included in the methodology chapters of the nine domains. Further, more detailed guidance may be available at the level of individual element cards, to assist in finding answers to specific questions.

## Common reporting structure

The answers to questions defined by the assessment elements are recorded as structured pieces of information in their respective *result cards*. These are organized into collections that each form a coherent package of information, including text and other materials and metadata that enables effective use of the cards in the database of core HTA information.

Currently only one reporting template has been defined in detail for all core HTA information collections. It was designed originally for one collection type, the core HTAs. Such collections contain an extensive analysis of a health technology through all nine domains and all core elements. The same structure is very likely applicable to other types of collections as well, and can be used in any collection type. It may, however, be more feasible to define further standard collection templates to cater for the specific needs of, for example, rapid assessments.

For core HTAs the information is organised as follows:

- **Collection Summary** Contains an overview of all findings in the collection. No recommendation regarding the technology can be included in core HTA information collections. A standard table is included summarizing the consequences of using or not using the technology and its comparator(s), see below.
- **Collection Methodology** Indicates the process and overall methods used for producing the collection.
- **Collection Introduction** Provides an overview to the collection, including the reasons why, and in which context the collection was produced.
- **Scope** A structured scope for the project providing a well-defined starting point for analysis within different domains. Ensures the coherence of analysis within different domains.
- **Domain-specific sections (one for each domain included in the collection)**
  - **Introduction of domain** Indicates the specific features of the technology that are noteworthy from the viewpoint of this domain as well as the motivation of 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) Can be used if the methodology used for answering the question(s) defined by an assessment element differs from the overall domain methodology, or if the domain methodology does not provide a detailed enough description.
    - **Result** Answer to the research question(s) defined by one assessment element, with a focus on evidence or facts whenever feasible. Answers should respect 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 discussion chapter of journal articles, but focused on the question(s) included in one card.
  - **Discussion** Similar to discussion chapter of journal articles, focusing 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 more than one domain's content.

A summary table of the consequences of using or not using the technology that is the target of assessment is available to be used in the summary of the collection.

1

2 **Table 4. Consequences table.**

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

3 **HTA Core Model 2.1**

4 **Updated content**

5 The HTA Core Model version 2.1 is an improved version of 2.0. It is not an equally significant  
6 upgrade to the earlier version as 2.0 was, but contains some substantial changes described here.

7 The contents of the legal domain were not updated when version 2.0 was developed (see below),  
8 due to difficulties in finding suitable experts available for the work at that time. The new legal  
9 domain is now included in version 2.1.

10 Additionally, WP8 and WP5 have jointly revised the ontology so that model applications for both  
11 core HTAs and rapid HTAs could draw from the same pool of questions (assessment elements). In  
12 that process we have also aimed at reducing redundant overlap in the various assessment elements.  
13 This revision of the ontology applies to the following domains: CUR, TEC, SAF and EFF. One  
14 question in the ETH domain has been edited as well.

15 The table 1 in the first chapter of each domain (“Description”) lists all topics and issues in that  
16 domain. These tables have been updated to match the new ontology.

17 The changes in the ontology have been indicated in further detail in Appendix Intro2.1: Changes in  
18 the ontology.

19 In the version 2.0 the order of assessment elements was displayed incorrectly in the following  
20 domains: TEC, CUR, EFF and SOC. This was due to a technical error. Users of the HTA Core  
21 Model Online have fortunately been able to change to order to match their preferences in HTA  
22 projects. The order of assessment elements has been now reviewed in all domains and errors have  
23 been corrected.

24 **Work process**

25 A team of researchers from Finland and Austria updated the legal domain contents during the first  
26 months of 2014. A draft was sent for review by EUnetHTA member agencies and the WP8  
27 Stakeholder Advisory Group. The team revised the contents based on the feedback and the final  
28 version was published in June 2014 as a PDF document at [www.corehta.info](http://www.corehta.info). The contents of the  
29 legal domain are made fully available for projects in the HTA Core Model Online through version  
30 2.1.

1 The ontology changes were discussed and agreed on by an international expert group with  
2 representatives from WP4, WP5, WP7 and WP8. The agreed-on changes were still reviewed and  
3 approved by several of the primary investigators involved in developing version 2.0 (see chapter  
4 “Contributors” below).

5 The order of assessment elements was reviewed and revised by a researcher of THL and changes  
6 were approved by the primary investigators of respective domains.

7 The new versions of “table 1s” were compiled automatically after the ontology update.

8

## 9 HTA Core Model 2.0

10 Since version 2.1 builds heavily on version 2.0, this chapter has been included unchanged in the  
11 documentation of 2.1.

## 12 Work process

13 The HTA Core Model version 2.0 is a major overhaul of the previous model applications.  
14 Additionally an application for full assessment of pharmaceuticals was added. The new version was  
15 built by several international working groups, each working on one "domain cluster" consisting of  
16 three domains. The division of domains was as follows:

**Cluster 1: CUR-TEC-ORG** Health problem and current use of technology (CUR) Technical characteristics of technology (TEC) Organisational aspects (ORG)

**Cluster 2: SAF-EFF-ECO** Safety (SAF) Clinical effectiveness (EFF) Costs and economic evaluation (ECO)

**Cluster 3: SOC-ETH-LEG** Social aspects (SOC) Ethical analysis (ETH) Legal aspects (LEG)

17 Each working group was led by a team of three *primary investigators* (PI), each responsible for one  
18 of the three domains of the cluster. One or more *investigators* (I) supported actively the work of PIs  
19 within each domain. Several *internal reviewers* (IR) participated throughout the process by  
20 providing comments to draft documents and feedback on issues and challenges the working group  
21 encountered.

22 The primary investigators together with the coordinators formed an Editorial Team (ET) that  
23 discussed and agreed on matters common for all working groups. The overall model development  
24 contained a large amount of remote work, but also three international workshops in Helsinki during  
25 year 2013.

26 The update contains one important aspect that makes version 2.0 quite different from the earlier  
27 model applications. All content in the earlier applications was specific to the application, meaning  
28 that there were several versions of all content, distributed across different applications. For  
29 example, earlier there were three or four different versions of “domain description” of effectiveness,  
30 or slightly different questions as the same assessment element in different applications. In version  
31 2.0 the technology-independent content has been separated to be “common” for all technologies and  
32 technology-specific content has been included in separate, technology-specific sections. Users of

the HTA Core Model should always utilise the common content and the content relevant to the technology they are assessing. Users of the HTA Core Model Online will automatically see only the content relevant to their technology.

The developers used the five existing model applications for interventions, diagnostics, screening, as well as the rapid and draft full REA of pharmaceuticals as their starting points. The following were the more specific tasks for the clusters:

#### **Content outside the assessment elements:**

1-1. Division between generic and technology/use-specific content

1-2. Bringing the content up-to-date

1-3. Completeness of content

#### **Content inside the assessment elements**

2-1. Harmonise and update the domain-topic-issue structure and clarification field of assessment elements

2-2. Consider whether assessment elements have been assigned to all relevant domains and whether some elements should be merged, removed or added

2-3. Identify relations between assessment elements

2-4. Consider which assessment elements belong to each model application (i.e. is applicable to a specific technology type or use

2-5. Harmonise, expand and update methodological guidance

2-6. Check and harmonise the importance and transferability values

2-7. Harmonise and update references

Consequently, the current version 2.0 is much better harmonised and up-to-date across different technology types (and model applications). Updating the HTA Core Model will also be easier in the future, since the total amount of material has been reduced through removal of redundancies across applications.

During the update process the order of domains was slightly adjusted. Whereas the health problems and current use was originally the first in order of domains, it was now moved to the second place. The description and technical characteristics of technology domain was moved to be the first domain, as it was perceived to be most feasible to first describe the technology under assessment.

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

### 2 *Medical and surgical interventions*

3 When producing the original application for medical and surgical interventions, no specific  
4 definition for “interventions” was used. Since the initial pilot {9} was made on drug eluting stents,  
5 the concept was definitely not limited to surgical procedures only. The overall aim was more to  
6 capture a variety of *therapeutic* interventions. For example preventive, population-based  
7 interventions were not discussed and hence the application is probably not fully equipped for such  
8 contexts. Likewise, all features of pharmaceuticals were not considered when developing the model  
9 application.

10 Developers of version 2.0 continued with similar general perception of “interventions”, for the  
11 purposes of further development, the following explicit definition was agreed on:

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

### 14 *Diagnostic technologies*

15 As with medical and surgical interventions, no explicit definition of diagnostic technologies was  
16 included in the version 1.1 of the original diagnostic application.

17 The following was agreed on as definition for further development of the diagnostic application:

18 Diagnostic technology is any technology or procedure that is used to confirm, exclude or classify  
19 disease, or to monitor progress of the disease or the response to therapy. {10}

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

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

27 The first pilot testing of the application was made assessing multi-slice computed tomography  
28 (MSCT) coronary angiography {11}.

### 29 *Screening technologies*

30 The producers of core HTA information should be aware of the multitude of uses of the word  
31 'screening', and the fact the 'HTA Core Model on screening technologies' is not applicable to  
32 assessing everything that is called screening. The primary target is the **full population screening**  
33 **program** with the following components:

- 34
- It involves a test or an examination or a series of tests or examinations, AND

- is provided either systematically to the whole target population (i.e. in a screening program) , or unsystematically for asymptomatic people, e.g. in the form of locally provided health promotion or case finding programs, AND
- is done in order to make a statement regarding the possibility of having a certain disease or risk factor, AND
- 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 program; e.g. the effects of replacing the conventional mammography device with a digital one in a breast cancer screening program. In this case a relevant subset of the HTA Core Model of screening technologies is likely to be applicable.

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

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

See Appendix Intro-Scr for more information on screening.

The screening application was originally pilot tested by assessing the screening of abdominal aorta aneurysms { 12 }.

## **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, has also 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 beneficial uses of technologies, 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.
- The morally relevant reasons for performing / not performing a HTA on this topic should be identified.
- The interests of the producers of the technology should be identified.
- It should be identified whether there are related technologies that are morally contentious.
- The interests of the content expert group should be discussed openly so that the work can be conducted in an objective and independent way.
- The choice of end points in the assessment has to be carefully considered.
- The morally relevant issues related to the selection of meta-analysis and studies to be included in the HTA have to be identified.
- The scope of the HTA and choice of research methods (e.g. inclusion of other aspects of assessment than effectiveness in the literature searches).



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

## 2 **Value judgments**

3 Multiple value judgments are made – either explicitly or implicitly – in the HTA process and in  
4 subsequent healthcare decisions. According to Strech {13-16}, value judgments occur in four  
5 instances when producing evidence (be it HTA or clinical systematic review, etc.):

- 6 • Value judgements in the selection of evaluation criteria
- 7 • Value judgements in the specification of evaluation criteria
- 8 • Value judgements about the validity of the results
- 9 • Value judgements in the weighting of results

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

## 17 **Benefit-risk balance**

18 Balancing benefits and risks of technology use – or benefit-risk assessment – is a common part of  
19 regulatory processes. Similar weighing of positive and negative consequences of technology use (or  
20 non-use) often takes place within HTA processes. In this version of the Model, related  
21 considerations are included in some assessment elements of the clinical effectiveness, safety, costs  
22 and economic analysis and the ethical analysis domains, but we refrained from adding such  
23 considerations to the common reporting structure as collection-level chapter. The reasoning behind  
24 this choice was that such value judgments typically take place at the local (national or regional)  
25 level and are not a central part of core HTA information, which focuses primarily on evidence and  
26 facts. Instead, we decided to include a table in the collection summary that lists the consequences of  
27 using either the technology that is being assessed or its comparator.



## 1 Contributors

### 2 HTA Core Model update – Version 2.1

## 3 Legal domain

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

5 Investigators: Iris Pasternack, Summaryx Ltd (subcontracted by THL, Finland)

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## 8 Ontology Update

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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)

1 **HTA Core Model update – Version 2.0**

2 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
Primary Investigators	THL, Finland	NSPH, Romania	THL, Finland	UMIT, Austria	UTA, Estonia	THL, Finland	CFK, Denmark	SBU, Sweden	Not updated
	Kristian Lampe	Nona Chiriac & Marius Ciutan	Ulla Saalasti-Koskinen	Petra Schnell-Inderst & Gaby Sroczynski	Rainer Reile	Neill Booth  FIMEA, Finland  Piia Peura	Lene Mosegaard Søbjerger	Sophie Werkö & Emelie Heintz	
	CVZ, Netherlands (limited to full pharma model application) Iris pasternack								
Investigators	NSPH, Romania	UTA, Estonia	CFK, Denmark	SBU, Sweden	THL, Finland	THL, Finland	THL, Finland	CVZ, Netherlands	Not updated
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## Introduction

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	NCHTA, Russia		FIMEA, Finland			NSPH, Romania	NCHTA, Russia	CFK, Denmark	
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			NCHTA, Russia	<i>Vesa Kiviniemi</i>	<i>Nikolai Mühlberger</i>			UMIT, Austria	
			<i>Maria Avxentyeva</i>	NCHTA, Russia	NCHTA, Russia	FIMEA, Finland		<i>Magdalena Flatscher-Thöni</i>	
				<i>Olga Rebrova</i>	<i>Olga Rebrova</i>	<i>Vesa Kiviniemi</i>			
Internal Reviewers	Finland, THL and FIMEA			Austria, UMIT			Austria, UMIT		
<b>WHOLE CLUSTER</b>	Russia, NCHTA			Finland, THL and FIMEA			Denmark, CFK		
				Romania, NSPH			Finland, THL		
				Russia, NCHTA			Russia, NCHTA		

1 **Version 2.0 builds on the following earlier Model applications:**

- 2       • HTA Core Model for Medical and Surgical Interventions – Version 1.0R (2008)
- 3       • HTA Core Model for Diagnostic Technologies – Version 1.0R (2008) and Version 1.1 (2009)
- 4       • HTA Core Model for Screening Technologies – Version 1.0 (2012)
- 5       • HTA Core Model on Rapid Relative Effectiveness Assessment of Pharmaceuticals – Version 3.0 (2013)

6 Several people have contributed to the earlier model applications. A list including all investigators is available in the Screening Model 1.0 (PDF

7 document, page 15), available at [www.corehta.info/BrowseModel.aspx](http://www.corehta.info/BrowseModel.aspx).

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4 Clinical Epidemiology. 2008;61(6):521-4.

5

# 1 ***Health Problem and Current Use of the Technology***

## 2 **Description**

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

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

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

16 **Current management** patterns of the condition should be described, including the technology as  
17 such and its alternatives, and recommended policies for determining the target population. It should  
18 also be specified whether the technology is intended to replace or supplement another technology in  
19 the management chain. Anticipated problems in the use, e.g. inappropriate extension of indications  
20 (off-label use), participation rate or compliance, over-diagnosis and misuse are to be discussed, as  
21 well as the alternatives to the technology and agreed policies on whom to treat as patients or target  
22 group.

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

32



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

Topic	Issue	Assessment element ID
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 differences in the management for different stages of the disease or health condition?	A0017
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	What is the phase of development and implementation of the technology and the comparator(s)?	B0003
Utilisation	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?	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

1

## 2 Why is this domain important?

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

7 During the analysis within this domain, one might also find out that the current management  
8 practice of a health condition actually differs from evidence-based guidelines. In such situations  
9 improving compliance to the guidelines regarding existing technology might be more appropriate  
10 than introducing new technology that may be more costly and not necessarily more effective than  
11 existing technology. Consequently, the analysis within this domain aims at giving the “big picture”  
12 where the technology is supposed to be used.

13 Often health technologies are not used for a single purpose only. An HTA report often considers a  
14 single technology for a single purpose, e.g. ultrasound for diagnostics of gallstones. The analysis of  
15 this domain should provide a wider view on the possible other uses of the same technology, as  
16 introducing a technology for single use may lead into a process where it is actually used for more  
17 than one purpose (e.g. for more than one diagnosis). The analysis in this domain can help both HTA

1 experts and decision makers better understand all relevant implications of applying or implementing  
2 a health technology.

3 National decision-makers are interested in the extent of utilization of technology in their own  
4 country, and in knowing about regional variation. On the other hand, international benchmarking  
5 may have a great impact on decision-making process {4,5}. Particularly important it may be when  
6 the estimation of the harm-benefit-costs equation is inconclusive. It might be important to be aware  
7 of the variation in the management patterns and current use of the technology in Europe; this may  
8 reflect country-specific epidemiology and priorities, but can also be an indication of regional or  
9 national under- or overuse of the technology. In Europe, great variation in approval status of  
10 technologies is seldom expected; therefore it may be of interest to compare the status with non-  
11 European countries.

12 Finally, answers provided to questions defined within this domain give important input to questions  
13 in other domains (see below).

## 14 **Relations to other domains**

15 The issues in this domain should be considered at an early stage of a core HTA information project,  
16 because they may help in refining the research questions and formulating the methodological  
17 approach in e.g. effectiveness, costs and organisational aspects domains. The life cycle of the  
18 technology, its regulatory (approval and coverage) status and manufacturer information are of joint  
19 interest with other domains (description and technical characteristics, organisational, social, ethical,  
20 and legal aspects domains).

21 The answers to questions of this domain together with the TEC and ORG domains may render the  
22 original scope of a HTA project partially outdated or targeting matters of secondary importance.  
23 Consequently it is recommended that project groups reconsider the scope of their project after  
24 preliminary results of these three domains become available.

25 Some issues in this domain will necessarily overlap with issues in the effectiveness and costs  
26 domains (e.g. issues of consequences and alternative interventions), organizational domain (e.g.  
27 utilisation issues), description and the technical characteristics domain (e.g. life-cycle), social  
28 domain (coverage and access issues), legal and ethical domains as well as safety domain (e.g. over-  
29 diagnosis, false positive and false negative test results). It is important to coordinate the work with  
30 these issues, and determine who answers them within a particular core HTA information project. .

## 31 **Diagnostics-specific content**

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

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

38 Effect of available treatments on the course and prognosis of the health condition should be  
39 included. Background information for estimating benefits and harms, e.g. the consequences of a  
40 correct or wrong diagnosis should be described.

## 1 Screening-specific content

2 Usually a technology is proposed for screening after a long experience in clinical diagnostic use.  
3 This means that assessing a screening technology is usually assessing the features of the technology  
4 in a new application context. Screening as context means that the assessment should include the  
5 whole management chain, from the screening test, through the subsequent diagnostic tests to  
6 treatments. It is therefore important to distinguish if the proposed assessment topic includes a new  
7 screening technology, that only slightly modifies the existing screening pathway, or whether it is an  
8 assessment of a completely new screening pathway. Regulatory processes hardly ever distinguish  
9 between these two uses of a technology: clinical or screening setting.

10 Knowledge on the following aspects is essential for the construction of decision analytic models for  
11 screening technologies:

- 12 1. Natural course of the health problem,
- 13 2. Diagnosis of the health problem,
- 14 3. Effect of available treatments on the course and prognosis,
- 15 4. Burden of disease, incidence, mortality, survival,
- 16 5. Current guidelines and existing screening flow charts
- 17 6. Effects of the screening technology on the epidemiology (incidence, prevalence, over-diagnosis) of  
18 the health problem

## 19 Methodology

### 20 Process for answering research questions

21 Although the HTA Core Model calls all questions that derive from the generic issues as "research  
22 questions", it is important to keep in mind that the questions and answering methodologies of this  
23 domain are in many senses different from several other domains. Instead of trying to find out about  
24 the "value" of the technology - as is the case e.g. in the effectiveness and cost-effectiveness domains  
25 - the analysis in this domain aims at providing many of the other domains and the whole collection  
26 of HTA information a pragmatic and practical set of background information. The information  
27 should be gathered and compiled in an adequately reliable manner that matches the intended extent  
28 of analysis within the other domains and the collection type. Extensive collections, such as core  
29 HTAs most likely benefit from a robust set of information in this domain, whereas a rapid  
30 assessment may need less information.

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

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

1 An example of such a survey is available in a core HTA on abdominal aortic aneurysm screening at  
2 <https://www.corehta.info/DownloadAttachment.aspx?id=106.COL%20Appendix%201>.

### 3 **Gathering information**

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

5 The source of information will depend on the location of a technology within its product life cycle.  
6 Review articles and textbooks can be helpful when searching for information about the history and  
7 characteristics of established technology. The information concerning the technology may be  
8 obtained from manufacturers of the technology, clinical experts and other health professionals using  
9 of the technology but also from the literature (i.e. descriptive publications) and patients or patient  
10 organisations. For prototypes and innovative technologies published peer reviewed literature may  
11 be limited. It may need to be supplemented by grey literature (includes non-peer reviewed and non-  
12 published literature, as well as confidential commercial information) as well as anecdotal  
13 information from general web-searches.

14 There are some issues, e.g. the coverage status of a technology (inclusion in the benefit catalogue,  
15 levels of co-payment, etc.), where information is not easy to retrieve. It requires local knowledge of  
16 the health-care system to identify adequate and usable information sources. {6} These data can be  
17 obtained through a survey early within the project.

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

20

## 1 Databases and search strategies

2 Some important databases and other sources of information possibly useful for the analysis in this  
3 domain are listed below. We recommend also using the Summarized Research in Information  
4 Retrieval for HTA (SuRe Info, available at <http://vortal.htai.org/?q=sure-info>) which provides  
5 research-based information relating to the information retrieval aspects of producing health  
6 technology assessment.

## 7 Bibliographic databases on published literature:

### 8 • Health sciences:

- 9 ○ MEDLINE (published by the United States National Library of Medicine) / Pubmed  
10 (<http://www.ncbi.nlm.nih.gov/pubmed/>),
- 11 ○ EMBASE (Excerpta Medica published by Elsevier) (<https://www.embase.com/>),
- 12 ○ Cochrane Library (<http://www.thecochranelibrary.com/view/0/index.html>)
- 13 ○ CRD Databases
  - 14 ▪ DARE (Centre for Reviews and Dissemination / Database of Abstracts of Reviews of
  - 15 Effects)
  - 16 ▪ HTA (Health Technology Assessment)
  - 17 ▪ NHS EED (National Institute for Health Research / Economic Evaluation Database)
- 18 ○ Cinahl (Cumulative Index to Nursing and Allied Health Literature)
- 19 ○ PsycInfo (literature in behavioral sciences and mental health)

### 20 • Social Science databases:

- 21 ○ Sociological Abstracts, Social Services Abstracts,
- 22 ○ Social Care on line / Caredata and SocINDEX,
- 23 ○ ASSIA (Applied Social Sciences Index and Abstracts)

### 24 • Administrative studies:

- 25 ○ General science publishers' databases such as Emerald Library,
- 26 ○ Science Direct and Ebsco Academic Search Elite,
- 27 ○ Pub Med Central (PMC) and Bio Med Central (BMC),
- 28 ○ ProQuest Health Management

### 29 • Educational database:

- 30 ○ ERIC (Education Recourses Information Center)

## 31 Other databases:

- 32 • GIN (Guideline International Network) at <http://www.g-i-n.net/>
- 33 • Experience of organisations e.g. NHS Technology Adoption Centre  
34 <http://www.technologyadoptionhub.nhs.uk/>
- 35 • The EUnetHTA pool of structured HTA information will be a pertinent source of information on e.g.  
36 disease incidence
- 37 • HTAi Vortal includes information for conducting HTA (<http://www.htai.org>)
- 38 • The Joanna Briggs Institute Library at <http://www.joannabriggslibrary.org/jbilibrary/>
- 39 • Ongoing research databases, e.g.
  - 40 ○ EUnetHTA POP database at <http://eunethta.dimdi.de/PopDB/>
  - 41 ○ ClinicalTrials.gov at <http://www.clinicaltrials.gov/>
  - 42 ○ Prospero (International prospective register of systematic reviews) at  
43 [http://www.crd.york.ac.uk/NIHR\\_PROSPERO/](http://www.crd.york.ac.uk/NIHR_PROSPERO/)
- 44 • Horizon scanning databases and web sites, e.g. EuroScan at [www.euroscan.org.uk](http://www.euroscan.org.uk) BIOSIS (life  
45 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);
  - Scirus (Reports of Hospital Studies and Doctoral Thesis),
  - OAlster (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
- 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  
[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

## 1 **Own primary research**

2 There could be different reasons why own research is needed, for example if no studies were found  
3 in the literature search, and if there is a specific need for information of your own country not  
4 available in the literature.

5 Some aspects to consider when considering own research:

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

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

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

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

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

20



1 **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

2 **Screening-specific content**

3 It is difficult to obtain information on misuse or overuse of a screening technology, or the  
4 spontaneous diffusion of using a test in the healthy population before the implementation of a  
5 screening programme. Consequently, this information needs to be collected from indirect sources.

A case report that describes routine use of a screening test in all cases admitted for a certain disease or health problem in a certain hospital gives 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 the information retrieved may be difficult, as there is often no standard way of doing it and due to the fact that many aspects and facets must be taken into account when information is evaluated in quality terms.

The validity of the information may differ considerably depending on the source (see Table 1) 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 (i.e. policy studies) they are likely to be rapidly outdated. Information obtained from the web site or telephone query of the relevant authorization and reimbursement agencies or from the local HTA agencies will be more reliable and practical.

The Canadian CADTH has recently reviewed quality assessment tools and provides useful insights into the topic and details beyond what is included in this chapter {9}.

Appropriate methods for appraising the available evidence should be selected considering also the level of detail and precision one aims at in providing information on the CUR domain. 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>.

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 randomized 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 (Randomized Controlled Trials) and quasi-RCT represents one 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. See Critical Appraisal Checklists for RCT in Joanna Briggs Institute Reviewer's Manual, 2011 {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}.

*\*Newcastle Ottawa scale (see Appendix 3) 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 (see Appendix 3).*

### **Cohort/Case-controlled 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. See Critical Appraisal Checklists for Cohort or Case-controlled studies in {10}.

**Descriptive/Case series:** See Critical Appraisal Checklists for Case series in {10}.

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

2    The information provided by manufacturers might be limited by issues of confidentiality and  
3    marketing. This source can be useful in order to answer questions concerning the requirements for  
4    use of the technology, development status or forthcoming innovations of the technology.  
5    Manufacturers may also provide information on on-going research and on scientific literature which  
6    has not been published yet. Scientific information provided by manufacturers needs to be evaluated  
7    for validity and applicability. Own analysis of administrative data often requires authorization from  
8    the data owner, which in some countries might be difficult to obtain due to issues of privacy  
9    protection and confidentiality.

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

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

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

19   The focus on limiting bias to establish validity in the appraisal of quantitative studies is not  
20   possible when dealing with text and opinion. In appraisal of text, the opinions being raised are  
21   vetted, the credibility of the source investigated, the motives for the opinion examined, and the  
22   global context in terms of alternate or complementary views are considered. Validity in this context  
23   therefore relates to what is being said, the source and its credibility and logic; and consideration of  
24   the overt and covert motives at play.

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

### **26   *Registers***

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

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

- 31        • How representative is the register? (European, national, regional, local?)
- 32        • What kind of information is coded?
- 33        • What are the inclusion/exclusion criteria for data entered?
- 34        • What is the quality of information?
- 35        • 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 utilisation of technology. By definition, these data have been collected for other purposes than research and they cannot be used to answer scientific questions without previous processing. Analysis of this kind of data might be very time consuming, since data need to be “prepared” before analysis, and hence the data may not be feasible to use within an HTA project. The use of routinely collected statistics has several limitations. The reliability of the diagnosis varies and usually it is not possible to differentiate between different stages of the disease. Even the validity of the coding of causes of death may be variable, and in some countries it is known to be very limited. Several national and international sources of statistics exist which can be used to assess the incidence, prevalence, mortality, or burden of disease. These statistics are usually available in aggregated form and increasingly through the internet.

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* (available at [www.corehta.info](http://www.corehta.info)) that defines specific rules for using non-public data.

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

There are a variety of checklists and tools available to assess the 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 meeting a pre-determined proportion of all criteria, or on certain criteria being met. Some tools use weighted scores to evaluate different criteria.

Appraisal should consider appropriateness of research method(s), sampling, data collection and analysis. Although several quality assessment instruments are available, there is disagreement about the appropriate criteria for critical appraisal of qualitative research or, should quality assessment be done at all (appendix 3).

For example, within a Cochrane Intervention review critical appraisal of qualitative studies is an essential step. According to Cochrane guidance (put here the link), critical appraisal involves (i) filtering against minimum criteria, involving adequacy of reporting detail on the data sampling, - collection and-analysis, (ii) technical rigour of the study elements indicating methodological soundness and (iii) paradigmatic sufficiency, referring to researchers’ responsiveness to data and theoretical consistency. In choosing an assessment instrument Cochrane review teams need to consider the appropriateness of their choice in the context of their review and be aware of the fact that whether or not a study meets the standard might depend on the instrument used. {14}

#### ***Analyzing and synthesizing evidence***

There are several issues defined in the HTA Core Model, particularly in this domain, where systematic data retrieval is not necessary (see Table 1). Unsystematic gathering of information from

books, surveys, introduction sections of reviews and articles, registers and internet until saturation is reached, may be enough. However, one should consider the risk of selection bias due to insufficient or selective inclusion of information sources and data and reflect the possible limitations in the domain discussion chapter.

When using systematic data retrieval, data extraction approach must be appropriate to the review question, the type of review and the available evidence. It needs to be systematic and transparent. Data extraction can be a subjective process and therefore the design of these forms should be undertaken carefully {15}. The amount of information to be extracted should be directly related to the questions posed and must be balanced 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) are 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.

Different form may be necessary if there are findings from qualitative studies. The Cochrane handbook has aggregated different kind of extraction forms of qualitative studies {16}. One example of data extraction form for qualitative studies is SUMARI (System for the Unified Management, Assessment and Review of Information, available at <http://joannabriggs.org/sumari.html>) made by Joanna Briggs Institute. SUMARI is designed to assist health and other researchers and practitioners to conduct systematic reviews with evidence of Feasibility, Appropriateness, Meaningfulness and Effectiveness and to conduct economic evaluations of activities and interventions. It is composed by 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 done when assessing organisational issues. Triangulation compares the results from either 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 to ensuring comprehensiveness and encouraging a more reflexive analysis of data than as a pure test of validity. {17}



## 1 **Evidence tables**

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

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

- 6 • The Cochrane Handbook for Systematic Reviews of Interventions,  
7 <http://www.cochrane.org/training/cochrane-handbook> and <http://handbook.cochrane.org/>,  
8 particularly chapter 11.5 “Summary of findings tables”
- 9 • Guidelines International Network: Evidence Tables Working Group, [http://www.g-i-](http://www.g-i-n.net/activities/etwg)  
10 [n.net/activities/etwg](http://www.g-i-n.net/activities/etwg)
- 11 • Sign 50: A Guideline Developer’s Handbook,  
12 <http://www.sign.ac.uk/guidelines/fulltext/50/index.html>, example at  
13 <http://www.sign.ac.uk/guidelines/fulltext/50/compevidence.html>
- 14 • NICE: The Guidelines Manual 2012, appendices J-K, [http://publications.nice.org.uk/the-guidelines-](http://publications.nice.org.uk/the-guidelines-manual-appendices-jk-pmg6c)  
15 [manual-appendices-jk-pmg6c](http://publications.nice.org.uk/the-guidelines-manual-appendices-jk-pmg6c)
- 16 • HTA 101: V. Appraising the evidence, <http://www.nlm.nih.gov/nichsr/hta101/ta10107.html>

## 17 **Meta-analysis**

18 Meta-analysis is rarely used in CUR, TEC, ORG domains because most studies are qualitative or  
19 otherwise not suitable for meta-analysis.

## 20 **Qualitative synthesis**

21 Qualitative evidence synthesis is a process of combining evidence from individual qualitative  
22 studies to create new understanding by comparing and analyzing concepts and findings from  
23 different sources of evidence with a focus on the same topic of interest. It can be an aggregative or  
24 interpretive process which requires authors to identify and extract evidence: categorizing the  
25 evidence, and combine categories to develop synthesized findings. Important is to understand why  
26 people feel or behave certain way and not just make a description of it. {18}

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

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

35 Qualitative and quantitative findings could be synthesized in two ways: multilevel synthesis  
36 (separate and combined synthesis) and parallel (separate and juxtaposed synthesis) {18}.

37 Quantitative and qualitative studies can be synthesized together; one example is systematic review  
38 on teenage pregnancy and social disadvantage {22}.

## Reporting and interpreting

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

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

Overview of guidelines synthesizing the main recommendations on management practises would be illustrative.



## 1 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 (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	1
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	1
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
	Screening Technologies (2.1) - PUBLIC DRAFT	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 for all patients with the condition, or only those in the early stages, or at a specific severity level, or for those at moderate risk of having the condition.</p> <p>Personalised medicine divides the target population into even smaller units when targeting the intervention to specific subgroups based on e.g. genetic profile. Use the target population defined in the scope of the project, and consider adding further details and description of who defined the selected subgroups and why.</p> <p>Point out e.g. if certain populations should be excluded from the analysis.</p>					
Methodology and sources	<p><b>Common to all used applications</b></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 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24}</p>					
Content relations						

<b>Sequential relations</b>	
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1

<p style="text-align: center;"><b>A0023 Assessment element card</b></p> <p style="text-align: center;"><b>Issue: How many people belong to the target population?</b></p> <p style="text-align: center;"><b>Topic: Target Population</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 (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	2
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	2
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	2
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	2
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>This information can be used to give an idea of the resource requirements in general 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>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Sources: text books, HTAs, national registries, statistics, systematic reviews. Method: A descriptive summary.</p>					
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Burls 2000 {1}, Velasco 2002 {25}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24}</p>					
<b>Content relations</b>						
<b>Sequential relations</b>						

2

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 (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	3
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	3
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	3
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	3
Clarification	<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 adding details such as: description of anatomical site, disease aetiology and pathophysiology, types of disease or classification according to origin, severity, stages, or risk level, and different manifestations of the condition. The following properties of the target condition are defined in separate assessment elements: risk factors (A0003), natural course (A0004), symptoms (A0005), and burden of disease for the society (A0006).</p>					
Methodology and sources	<p><b>Common to all used applications</b></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 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	4
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	4
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	4
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
Clarification	<p><b>Common to all used applications</b></p> <p>Describing risk factors is especially important when they suggest possibilities for primary and secondary prevention. This information may affect the choice of comparator or the appraisal of the overall value of the technology under assessment. The risk factors for acquiring the condition, and the risk factors for relapses or worsening of the condition should be reported here, separately. The prevalence of the various risk factors might differ in different geographic areas and among different sub-populations.</p>					
Methodology and sources	<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>					
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>					
Content relations						
Sequential relations						

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 (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	5
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	5
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	5
	Screening Technologies (2.1) - PUBLIC DRAFT	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 untreated. This information is relevant for appraising the overall value of the technology. A technology targeted to cure a life-threatening condition has a different significance from a technology intended to alleviate the symptoms of self-limiting conditions. It may also guide the assessment of the predicted value or effectiveness of the technology, as technologies may work differently at different stages or severity grades of the disease, and there may be a relationship between earlier intervention and better prognosis. This element should also provide information on the time lag between the onset of disease and the symptoms or other findings that eventually trigger the need of diagnostics and care.</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 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 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 (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	6
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	6
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	6
	Screening Technologies (2.1) - PUBLIC DRAFT	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 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.</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>					
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}</p>					
Content relations						
Sequential relations						

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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	7
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	7
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	7
	Screening Technologies (2.1) - PUBLIC DRAFT	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 that is prevented or treated by using the technology; disease-specific mortality and disability, life years lost and/or disability-adjusted life years, quality of life, QALYs.</p>					
Methodology and sources	<p><b>Common to all used applications</b></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 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 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 (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	8
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	8
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	8
	Screening Technologies (2.1) - PUBLIC DRAFT	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) untouched.</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>The application of the diagnostic technology may target only one aspect of the burden of disease, eg. disability but not mortality. Or mortality but not symptomatology</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Screening may increase disease incidence due to early diagnosis and over diagnosis.</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

1

## A0017 Assessment element card

Issue: What are the differences in the management for different stages of the disease or health condition?

Topic: Current Management of the Condition

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	9
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	9
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	9
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	9
Clarification	<p><b>Common to all used applications</b></p> <p>Identification of practice variations due to the differences in the forms, stages or severity of the disease. May be useful to understand the proper place of technology in the health care delivery process.</p> <p>Different stages of disease may call for different therapeutic procedures (for example aortic insufficiency is first treated with medication and at a certain point of cardiac structural changes an operation is preferred).</p> <p>Provide an overview of other treatment alternatives. Likewise diagnostic or monitoring methods used for various diseases may vary depending on the stage of disease..</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Surveys, utilisation reviews, clinical guidelines, recommendations. If such information is lacking: expert surveys / expert interviews</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>					
Content						

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

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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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	10
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	10
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	10
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	10
Clarification	<b>Common to all used applications</b>  Provide an overview of other treatment alternatives. Focus primarily on those used within professional health care delivery. Consider including technologies that people may commonly seek or use even if these wouldn't be commonly provided in professional health care (e.g. technologies for self-testing or self-treatment, or alternative medicine).					
Methodology and sources	<b>Common to all used applications</b>  Clinical guidelines, recommendations, systematic reviews					
References	<b>Common to all used applications</b>  Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24}					
Content relations	<b>Common to all used applications</b>					

	B0001
<b>Sequential relations</b>	

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<p style="text-align: center;"><b>A0024 Assessment element card</b></p> <p style="text-align: center;">Issue: How is the disease or health condition currently diagnosed according to published guidelines and in practice?</p> <p style="text-align: center;">Topic: Current Management of the Condition</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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	11
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	11
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	11
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	11
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>The effectiveness of an intervention may vary in differently diagnosed populations. A sensitive test tends to have low specificity such that there are several people who do not have the condition among the test-positive population. The effectiveness of an intervention in that population may be lower than in a population examined with a less sensitive test (but with more true positive cases). It is important to point out possible discrepancies between guidelines and actual practice.</p>					
<b>Methodology and sources</b>	<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>					
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Burls 2000 {1}, Velasco 2002 {25}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007</p>					

	{24}
<b>Content relations</b>	
<b>Sequential relations</b>	

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<p style="text-align: center;"><b>A0025 Assessment element card</b></p> <p style="text-align: center;"><b>Issue: How is the disease or health condition currently managed according to published guidelines and in practice?</b></p> <p style="text-align: center;"><b>Topic: Current Management of the Condition</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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	12
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	12
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	12
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	12
<b>Clarification</b>	<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. Are there differences in the treatment of diseases at their different stages? Identification of practice variations may imply differences in the quality of health care. Deviation from evidence-based guidelines may suggest over/under use of the technology.</p>					
<b>Methodology and sources</b>	<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 management pathways.</p>					
<b>References</b>						

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

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<p align="center"><b>A0001 Assessment element card</b></p> <p align="center"><b>Issue: For which health conditions and populations, and for what purposes is the technology used?</b></p> <p align="center"><b>Topic: 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 (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	13
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	13
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	13
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	13
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>All relevant conditions and populations should be included. This question is especially relevant when there are multiple potential target conditions and populations for which the technology is used, and multiple intended uses, both indicated and other. There may also be differing views about the appropriate use of the technology that it is essential to highlight. Describe the differences in the use of the technology for the various indications and how it might act differently in different patient groups. Point out e.g. if certain populations should be excluded from using the technology, or if they require e.g. a different dosage. Certain technologies may be primarily indicated for second-line use but also used for first-line treatment.</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Sources: HTAs, guidelines, reviews, clinician consultation, developers/manufacturers.</p> <p>Method: A descriptive summary.</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>
<b>Content relations</b>	
<b>Sequential relations</b>	

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<p><b>A0011 Assessment element card</b></p> <p><b>Issue: How much are the technologies utilised?</b></p> <p><b>Topic: 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 (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	14
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	None	No	14
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	14
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	14
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Provide national estimates for current and future utilisation rates, for the indication under assessment, for both the technology under assessment and its comparators. Variations in utilisation reflect market access, sales figures, actual usage in hospital level and adherence to the use of the technology by both professionals and patients. Data on current and previous utilisation reflect the phase of the technology (experimental, emerging, established or obsolete). This also has implications for the availability of evidence and the level of uncertainties.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>What is the current rate of screening adherence?</p>					
<b>Methodology and sources</b>	<b>Common to all used applications</b>					

	National statistics, surveys, technology and procedure registers, disease management studies, utilisation studies, manufacturer sales data
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Burlis 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24}</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>G0009</p> <p>G0010</p>
<b>Sequential relations</b>	

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<p><b>A0012 Assessment element card</b></p> <p><b>Issue: What kind of variations in use are there across countries/regions/settings?</b></p> <p><b>Topic: 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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	15
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	15
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	15
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	15
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>This information can be useful for decision-makers to understand regional variations in their own country and also understand the situation in comparison with other countries.</p>					
<b>Methodology and sources</b>	<b>Common to all used applications</b>					

	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).
<b>References</b>	<b>Common to all used applications</b>  Burlis 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24}
<b>Content relations</b>	<b>Common to all used applications</b>  G0009  G0010
<b>Sequential relations</b>	

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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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	16
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	16
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	16
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	16
<b>Clarification</b>	<b>Common to all used applications</b>  Provide information on who are the key actors in deciding on the use of the technology. Do most important decisions take place on the national level (e.g. population screening) or for example by individual professionals (e.g. surgical method for a specific disease)? How is the decision made; are there some documented criteria?					



	<p>Information about the possible variations in the decision level and criteria has ethical implications.</p> <p>This issue is related to the issue of work processes (G0001)</p> <p><b>Specific to Pharmaceuticals (2.1) - PUBLIC DRAFT</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 class of pharmaceuticals for a targeted patient group or sub-groups. How companion diagnostic should be used to identify eligible patient should be specified and explained.</p> <p>Criteria must be specified for higher risk groups of patients such as elderly and children.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Decisions about the people eligible for screening is done in the beginning of the screening. Usually, it has 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 result 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 study: 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>Kristensen 2007 {24}</p> <p>{14}</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>A0011</p> <p>A0012</p> <p>:B0016, D0021, F0012, I0012, H0012</p>
<b>Sequential relations</b>	
<b>Other domains</b>	<p>Also in: Organisational aspects</p>

## B0003 Assessment element card

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

Topic: Utilisation

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	17
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	17
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	17
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	17
Clarification	<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 while the evidence base may change rapidly for technologies that are at an earlier stage in their development. It is also important to establish whether new versions of the technology with substantial improvements are expected in the near future. For end users it is useful to know 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 effectiveness, safety, organisational, social and ethical domains.</li> </ul>					

<b>Methodology and sources</b>	<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 (2.1) - PUBLIC DRAFT</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</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</p> <p>A0021</p> <p>A0011</p> <p>A0019</p> <p>A0020</p> <p>F0001</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Effectiveness</p>
<b>Sequential relations</b>	
<b>Other domains</b>	Also in: Description and technical characteristics of technology

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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	18
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	18
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	18
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	18
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 to 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 {26}</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 (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	19
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	19
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	19
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	19
Clarification	<p><b>Common to all used applications</b></p> <p>There are both international and national market authorisation systems. For pharmaceuticals the systems are established but for devices and procedures less so. An overview of the status with regard to key processes, e.g. CE marking, EMA/FDA approval is recommended. Also information on national data and an analysis of possible discrepancies can be highly useful.</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Imaging devices may require approval. Substances needed for obtaining images may require additional approval (e.g. radiotracers). In some cases the approval for primary screening is different to that for clinical use (FDA recently licensed tests explicitly for screening), but in most cases approval is obtained for diagnostic use and the test is proposed for screening without any other formal approval.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Imaging devices may require approval. Substances needed for obtaining images may require additional approval (e.g. radiotracers). In some cases the approval for primary screening is different to that for clinical use (FDA recently licensed tests explicitly for screening), but in most cases approval is obtained for diagnostic use and the test is proposed for screening without any other formal approval.</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</p>					

	approval
<b>References</b>	<b>Common to all used applications</b> Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24}
<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

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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 (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	20
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	20
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	20
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	20
<b>Clarification</b>	<b>Common to all used applications</b> Information on national reimbursement status from different countries for the technology as well as the comparators, including key dates and anticipated licensing timeframe should be listed here. Notice that reimbursement status may differ for different purposes: e.g. treatment vs. prevention. Information on full coverage, co-payments, coverage under special circumstances/conditional coverage is useful.					

<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Appendix 1 of REA model = List of websites of national agencies with information on reimbursement,</p> <p>EVIDENT database.</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>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>I0012</p> <p>B0002</p>
<b>Sequential relations</b>	
<b>Other domains</b>	Also in: Description and technical characteristics of technology

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# ***Description and technical characteristics of technology***

## **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 was it 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. The material requirements for premises, equipment and staff are described, as well as 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 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 main three topics: 1) training and information needed to use the technology, 2) features of the technology, 3) investments and tools required to use the technology. Table 1 below shows the topics and issues specific to this domain.

20

**Table [1]: Topics and issues in the TEC domain**

Topic	Issue	Assessment element ID
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 comparators?	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 comparators and in what context and level of care are they provided?	B0004
Features of the technology	Are the 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?	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?	B0010
Training and information needed to use the technology	What kind 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 kind of training and information is needed for the personnel/carer using this technology?	B0013
Training and information needed to use the technology	What kind of training and information should be provided for the patient who uses the technology, or for his family?	B0014
Training and information needed to use the technology	What information of the technology should be provided for patients outside the target group and the general public?	B0015
Other	Who manufactures the technology?	A0022

## 1 **Why is this domain important?**

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

## 8 **Relations to other domains**

9 Taking into account that the health technology is the topic of this evaluation, it can be said that the  
10 TEC domain is related with all other domains: health problem and current use, safety, effectiveness,  
11 cost and economic evaluation, organisational aspects, ethical aspects, social aspects, and legal  
12 domains. In practice there is a considerable overlap with the current use, organizational and legal  
13 Domains. The authors of TEC domain should co-operate with the authors of those domains to avoid  
14 duplication of work.

## 15 **Methodology**

### 16 **Process for answering research questions**

17 Although the HTA Core Model calls all questions that derive from the generic issues as "research  
18 questions", it is important to keep in mind that the questions and answering methodologies of this  
19 domain are in many senses different from several other domains. Instead of trying to find out about  
20 the "value" of the technology - as is the case e.g. in the effectiveness and cost-effectiveness domains  
21 - the analysis in this domain aims at providing many of the other domains and the whole collection  
22 of HTA information a pragmatic and practical set of background information. The information  
23 should be gathered and compiled in an adequately reliable manner

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

30 The researchers working on this domain should consider their basic approach very early in the  
31 project as several other domains depend on the answers of this domain. The same applies to the  
32 current use and organisational issues domains. A joint survey early in the project should be  
33 considered as a pragmatic approach to finding answer to key questions of these three domains and  
34 other domains should contribute to the survey questions so that they provide useful information for  
35 all domains.

36

## 1 **Gathering information**

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

3 The source of information will depend on the location of a technology within its product life cycle.  
4 Review articles and textbooks can be helpful when searching for information about the history and  
5 characteristics of established technology. The information concerning the technology may be  
6 obtained from its manufacturers, clinical experts using the technology but also from the literature  
7 (i.e. descriptive publications). For prototypes and innovative technologies published peer reviewed  
8 literature may be limited. It may need to be supplemented by grey literature (includes non-peer  
9 reviewed and non-published literature, as well as confidential commercial information) as well as  
10 anecdotal information from general web-searches. There are some issues, e.g. the coverage status of  
11 a technology (inclusion in the benefit catalogue, levels of co-payment, etc.), where information is  
12 not easy to retrieve. It requires local knowledge of the health-care system to identify adequate and  
13 usable information sources {1}. These data can be obtained through a survey early within the  
14 project. Whenever the research group considers using confidential information e.g. from  
15 manufacturers, they should take into account the relevant principles defined in the *Policy for HTA*  
16 *Core Model and core HTA information*.

### 17 **Databases and search strategies**

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

### 28 **Useful other sources and links**

29 Grey literature (e.g. working papers from research groups or committees, white papers, or preprints),  
30 hand-searching of reference lists, as well as conference proceedings may be identified by searching  
31 the websites of HTA and related agencies, professional associations.

32 Contacting manufacturers, clinicians, nurses, paramedics and patients and reading Internet  
33 discussion forums may be valuable

34 Key information may also be extracted from the life sciences database BIOSIS  
35 (<http://science.thomsonreuters.com/training/biosis>), which includes patents, journals, conferences,  
36 books, review articles etc. While selection of the most relevant of these sources to search will  
37 largely depend on the technology in question, compilations of potentially relevant sources of  
38 information, such as the HTAi IRG Vortal (<http://www.htai.org>) and Institute of Health Economics  
39 (IHE) 'Health technology assessment on the net' report (<http://www.ahfmr.ab.ca>) can provide a  
40 useful starting point [see also other sources in [111] in Appendix 1].

If the technology has obtained regulatory approval then 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 the major EU or US regulatory bodies as well as 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 direct request to the manufacturer.

There may be also relevant user information on clinicians', nurses', paramedics' and patients' web sites. Published information may be supplemented through 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 sources of information possibly useful for the analysis in this domain are listed below. 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 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://eunethhta.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 (life sciences database) <http://science.thomsonreuters.com/training/biosis>
  - 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),

- OALster (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 associations' web sites
- Clinicians' web sites
- Patient associations' web sites
- Manufacturer's 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  
[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



## 1 Own primary research

2 There could be different reasons why own research is needed, for example if no studies were found  
3 in the literature search, and if there is a specific need for information of your own country not  
4 available in the literature.

5 Some aspects to consider when considering own research:

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

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

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

## 17 Tools for critical appraisals

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

22 Quality assessment of the information retrieved may be difficult, as there is often no standard way  
23 of doing it and due to the fact that many aspects and facets must be taken into account when  
24 information is evaluated in terms of its quality.

25 The validity of the information may differ considerably depending on the source and type of  
26 information requested (quantitative or qualitative; registers, administrative data etc).

27 The specificity and uniqueness of certain health technology could generate little information, and  
28 when the novelty is added, the researchers are faced usually with a lack of evidence. For example, it  
29 might be difficult to find up-to-date information on the approval status of a technology by  
30 reviewing published literature. Even if there are scientific publications on the issue (i.e. policy  
31 studies) they are likely to be rapidly outdated. Information obtained from the web site or telephone  
32 query of the relevant authorization and reimbursement agencies or from the local HTA agencies is  
33 likely to be more reliable and practical.

34



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

2 The information provided by manufacturers might be limited by issues of confidentiality and  
3 marketing. This source can be useful in order to answer questions concerning the requirements for  
4 use of the technology, development status or forthcoming innovations of the technology.  
5 Manufacturers may also provide information on on-going research and on scientific literature which  
6 has not been published yet. Scientific information provided by manufacturers needs to be evaluated  
7 for validity and applicability. Own analysis of administrative data often requires authorization from  
8 the data owner, which in some countries might be difficult to obtain due to issues of privacy  
9 protection and confidentiality.

## 10 ***Quality assessment of Expert opinion***

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

18 The focus on limiting bias to establish validity in the appraisal of quantitative studies is not  
19 possible when dealing with text and opinion. In appraisal of text, the opinions being raised are  
20 vetted, the credibility of the source investigated, the motives for the opinion examined, and the  
21 global context in terms of alternate or complementary views are considered. Validity in this context  
22 therefore relates to what is being said, the source and its credibility and logic; and consideration of  
23 the overt and covert motives at play.

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

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

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

- 29 • How representative is the register? (European, national, regional, local?)
- 30 • What kind of information is coded?
- 31 • What are the inclusion/exclusion criteria for data entered?
- 32 • What is the quality of information?
- 33 • How complete is the coverage?

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

37

## 1 **Statistics and routinely collected data:**

2 Routinely collected administrative data (e.g. DRGs, discharge databases, reimbursement claims  
3 databases) can be useful, when available. For example sickness funds collect large amounts of  
4 information which could be used to analyse utilisation of technology. By definition, these data have  
5 been collected for other purposes than research and they cannot be used to answer scientific  
6 questions without previous processing. Analysis of this kind of data might be very time consuming,  
7 since data need to be “prepared” before analysis, and hence the data may not be feasible to use  
8 within an HTA project. The use of routinely collected statistics has several limitations. The  
9 reliability of the diagnosis varies and usually it is not possible to differentiate between different  
10 stages of the disease. Even the validity of the coding of causes of death may be variable, and in  
11 some countries it is known to be very limited. Several national and international sources of statistics  
12 exist which can be used to assess the incidence, prevalence, mortality, or burden of disease. These  
13 statistics are usually available in aggregated form and increasingly through the internet.

14 Own analysis of administrative data often requires authorization from the data owner, which in  
15 some countries might be difficult to obtain due to issues of privacy protection and confidentiality.  
16 Researchers of this domain should be aware of the *Policy for HTA Core Model and core HTA*  
17 *information* that defines specific rules for using non-public data.

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

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

23 Appraisal should consider appropriateness of research method(s), sampling, data collection and  
24 analysis. Although several quality assessment instruments are available, there is disagreement about  
25 the appropriate criteria for critical appraisal of qualitative research or whether quality assessment  
26 should be done at all (see appendix 3).

27 For example, within a Cochrane Intervention review a critical appraisal of qualitative studies is an  
28 essential step. According to Cochrane guidance, critical appraisal involves (i) filtering against  
29 minimum criteria, involving adequacy of reporting detail on the data sampling, - collection and -  
30 analysis, (ii) technical rigour of the study elements indicating methodological soundness and (iii)  
31 paradigmatic sufficiency, referring to researchers’ responsiveness to data and theoretical  
32 consistency. In choosing an assessment instrument Cochrane review teams needs to consider the  
33 appropriateness of their choice in the context of their review and be aware that whether or not a  
34 study meets the standard might depend on the instrument used {3}.

## 35 **Analysing and synthesizing evidence**

### 36 **Data extraction**

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

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

## 5 ***Qualitative synthesis***

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

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

13 The qualitative synthesis is a process of combining evidence from individual qualitative studies to  
14 create new understanding by comparing and analyzing concepts and findings from different sources  
15 of evidence with a focus on the same topic of interest. It can be an aggregative or interpretive  
16 process which requires authors to identify and extract evidence, categorizing the evidence, and  
17 combining categories to develop synthesized findings. Important is to understand why people feel  
18 or behave certain way and not just make a description of it {4}.

19 There is range of methods available for synthesizing diverse forms of evidence, for example meta-  
20 ethnography, grounded theory, thematic synthesis, narrative synthesis, realist synthesis, content  
21 analysis. Some of the methods maintain the qualitative form of the evidence such as meta-  
22 ethnography and some involve converting qualitative findings into a quantitative form such as  
23 content analysis {6}.

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

## 27 **Reporting and interpreting**

28 Transparency in information retrieval is crucial when reporting core HTA information; the sources  
29 and methods of retrieval, systematic or not, and quality assessment criteria (also when missing)  
30 should be explicitly stated for each issue.

31 The issues in this domain need to be described in sufficient detail to differentiate the technology  
32 from its comparators. Terms and concepts should be used in a manner that allows those unfamiliar  
33 with the technology to get an overall understanding of how it functions and can be used. It is  
34 important to distinguish between scientifically proven versus suspected mechanisms of action.  
35 Important terms should be defined, and a glossary or a list of product names provided. The section  
36 may include pictures, diagrams, videos, or other visual material, in order to facilitate understanding,  
37 for persons who are not experts in the field.

38 The users of HTA require sufficient information on the design and function of the technology to  
39 understand the technology's mode of action, its technical requirements and possible problems and

- 1 alternatives, its staffing requirements, its applicability range, its variants, and its possible direct  
2 risks. For medical devices it may be helpful to include drawings or schematics for the technology  
3 that illustrate the components, dimensions and materials of construction of the device.
- 4 For diagnostic and monitoring technologies (laboratory tests, imaging, questionnaires etc.), it is  
5 important to include sufficient information about the technical precision of the technology. This  
6 information, which is different from the accuracy data presented in the clinical effectiveness  
7 domain, should be reported in this domain.
- 8 For management processes (such as screening programs) the position and interaction of the  
9 technology within the broader healthcare sequence should be described. This also may require  
10 listing alternative technologies.

11

## 1 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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	1
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	1
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
Clarification	<p><b>Common to all used applications</b></p> <p>This is relevant in all assessments. Use the descriptions of the technology and comparator(s) defined in that scope and elaborate them here in more detail. Technology may include a single device, a questionnaire, imaging or sequence of technologies. The HTA may address one or several similar technologies.</p> <p>Describe separately for the technology and the comparator: the type of device, technique, procedure or therapy; its biological rationale and mechanism of action, and also, describe how the technology differs from its predecessors, and the various current modifications or different manufacturers' products, especially if the 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 (2.1) - PUBLIC DRAFT</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p>					

	<b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b>  Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005
<b>Content relations</b>	<b>Common to all used applications</b>  A0022  A0018  F0001
<b>Sequential relations</b>	

1

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 (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	2
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	2
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	2
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	2
Clarification	<b>Common to all used applications</b>  This issue is especially relevant in new technologies with uncertain expectations and claims of benefit.  Describe the following aspects:  -How is it expected to be an improvement over previous /existing technologies used for the same health problem?					

	<p>-The expressed objectives for the implementation of the technology in health care; what are the claimed objectives e.g. increased safety, health benefit, accuracy or patient compliance, and whether it is intended to replace or to supplement existing technologies. Is the technology licensed as a mono-intervention, or in addition to current interventions (which should be specified) Are there stopping rules for use of the technology? Is there evidence that the technology works (or is used) outside its current indication area, or produces incidental findings that can have consequences relevant to effectiveness, safety, organisational, social and ethical domains? This information may explain the choice of comparator(s) and outcomes for the assessment and helps in appraising the overall results.</p>
<b>Methodology and sources</b>	<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 (2.1) - PUBLIC DRAFT</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</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</p> <p>A0009</p> <p>C0008</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	3
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	3
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	3
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	3
Clarification	<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 while the evidence base may change rapidly for technologies that are at an earlier stage in their development. It is also important to establish whether new versions of the technology with substantial improvements are expected in the near future. For end users it is useful to know 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 effectiveness, safety, organisational, social and ethical domains.</li> </ul>					



<b>Methodology and sources</b>	<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 (2.1) - PUBLIC DRAFT</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</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</p> <p>A0021</p> <p>A0011</p> <p>A0019</p> <p>A0020</p> <p>F0001</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Effectiveness</p>
<b>Sequential relations</b>	
<b>Other domains</b>	Also in: Health Problem and Current Use of the Technology

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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
Clarification	<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 carers, 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 tertiary care. If secondary or tertiary care, describe whether it is intended to be used in the outpatient or inpatient setting.</p> <p>Its role in the management pathway can be as a replacement, an add-on or for triage</p>					
Methodology and sources	<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 (2.1) - PUBLIC DRAFT</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</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>Current use, organizational A0012 A0025 G001 G0005</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Current Use</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Current use, Organisational</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Current use D1007</p>
<b>Sequential relations</b>	

1

2

B0018 Assessment element card						
Issue: Are the reference values or cut-off points clearly established?						
Topic: Features of the technology						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	5
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	5
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	5
Clarification	<b>Common to all used applications</b>  Are conflicting /varying definitions of an abnormal finding likely to affect the interpretation of the results? (please describe them)					
Methodology and sources	<b>Common to all used applications</b>  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.					
References	<b>Common to all used applications</b>  Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005  <b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b>  Liberati A. et al. 1997; Busse R. et al. 2002  <b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b>  Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005					
Content						

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

1

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 (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	6
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	6
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	5
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	6
Clarification	<p><b>Common to all used applications</b></p> <p>There are both international and national market authorisation systems. For pharmaceuticals the systems are established but for devices and procedures less so. An overview of the status with regard to key processes, e.g. CE marking, EMA/FDA approval is recommended. Also information on national data and an analysis of possible discrepancies can be highly useful.</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Imaging devices may require approval. Substances needed for obtaining images may require additional approval (e.g. radiotracers). In some cases the approval for primary screening is different to that for clinical use (FDA recently licensed tests explicitly for screening), but in most cases approval is obtained for diagnostic use and the test is proposed for screening without any other formal approval.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Imaging devices may require approval. Substances needed for obtaining images may require additional approval (e.g. radiotracers). In some cases the approval for primary screening is different to that for clinical use (FDA recently licensed tests explicitly for screening), but in most cases approval is obtained for diagnostic use and the test is</p>					

	proposed for screening without any other formal approval.
<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>	<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>	<p><b>Common to all used applications</b></p> <p>I0015</p> <p>B0002</p>
<b>Sequential relations</b>	
<b>Other domains</b>	Also in: Health Problem and Current Use of the Technology

1

2

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 (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	7
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	7
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	6
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	7

<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Information on national reimbursement status from different countries for the technology as well as the comparators, including key dates and anticipated licensing timeframe should be listed here. Notice that reimbursement status may differ for different purposes: e.g. treatment vs. prevention. Information on full coverage, co-payments, coverage under special circumstances/conditional coverage is useful.</p>
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Appendix 1 of REA model = List of websites of national agencies with information on reimbursement,</p> <p>EVIDENT database.</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>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>I0012</p> <p>B0002</p>
<b>Sequential relations</b>	
<b>Other domains</b>	Also in: Health Problem and Current Use of the Technology

1

2

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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	8
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	8
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	7
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	8
Clarification	<p><b>Common to all used applications</b></p> <p>Devices, machinery, computer programs, etc. Those parts of the technology that need to be purchased (and often installed) by an organisation in order to use the technology. Includes need for back-up investment to cover for breakdowns 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 (2.1) - PUBLIC DRAFT</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</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>E0001</p> <p>E0002</p> <p>G0006</p> <p>G0003?</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Current use, Organisational</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>E0001, E0002, G0006</p>
<b>Sequential relations</b>	

1

<p><b>B0008 Assessment element card</b></p> <p><b>Issue: What kind of special premises are needed to use the technology and the comparator(s)?</b></p> <p><b>Topic: Investments and tools required to use the technology</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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	9
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	9
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	8
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	9
<b>Clarification</b>	<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</p>					

	<p>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>A clear description of necessary facilities is needed instead of general statement (e.g. to be used in hospitals only)</p>
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Sources: User information from manufacturer, and market approval authority. HTAs, applicability studies, interviews with clinical experts and hospital managers.</p> <p>Manufacturer, applicability studies, clinical experts, user information. National or local judgement 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 (2.1) - PUBLIC DRAFT</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</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>None</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Safety domain, Organisational domain</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Current use Organisational, Legal</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Organisational domain</p>
<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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	10
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	10
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	9
	Screening Technologies (2.1) - PUBLIC DRAFT	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 to identify patients eligible for treatment.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Sources: Information from manufacturer, HTAs, applicability studies, interviews with clinical professionals and hospital managers.</p> <p>Manufacturer, applicability studies, clinical experts, user information. National or local judgement can be also used.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>.</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 (2.1) - PUBLIC DRAFT</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p>					

	<b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b>  Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005
<b>Content relations</b>	<b>Common to all used applications</b>  E0001  E0002  G0006  <b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b>  Current use
<b>Sequential relations</b>	

1

<p align="center"><b>B0010 Assessment element card</b></p> <p align="center"><b>Issue: What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?</b></p> <p align="center"><b>Topic: Investments and tools required to use the technology</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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	11
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	11
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	10
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	11
<b>Clarification</b>	<b>Common to all used applications</b>  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,					

	<p>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 to monitor the use of this particular technology and the comparator. Are there existing registries that should be used, or should a registry be established, to collect the necessary data to monitor safety or true life effectiveness? Provide national examples.</p> <p><b>Specific to Pharmaceuticals (2.1) - PUBLIC DRAFT</b></p> <p>Refer to SPC and EPAR.</p> <p>Sometimes registries are connected with the risk sharing scheme that innovative pharmaceuticals require in some countries. Notice also the requirements of pharmacovigilance monitoring.</p>
<b>Methodology and sources</b>	<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>
<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 (2.1) - PUBLIC DRAFT</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</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>G0008</p> <p>G0003</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Current use, Legal</p>
<b>Sequential relations</b>	
<b>Other</b>	Also in: Safety

domains

1

## B0012 Assessment element card

**Issue:** What kind 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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	12
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	12
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	11
	Screening Technologies (2.1) - PUBLIC DRAFT	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 make clinical decisions. 3. taking care of service and maintenance.</p> <p>Describe what 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) and if regular or frequent standardisation or quality checks are required (E.g. CME points). Provide an estimate to what extent 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 judgement 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 (2.1) - PUBLIC DRAFT</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</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</p> <p>C0020</p> <p>C0062</p> <p>C0063</p> <p>E0001</p> <p>E0002</p> <p>G0006</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Current use, , Legal</p>
<b>Sequential relations</b>	

1

2

B0013 Assessment element card						
Issue: What kind of training and information is needed for the personnel/carer using this technology?						
Topic: Training and information needed to use the technology						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	13
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	None	No	13
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	None	No	12
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	None	No	13
Clarification	<p><b>Common to all used applications</b></p> <p>Describe what 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); if the technology requires a specific skill that is developed over a period of time using the technology (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 to what extent the training and quality assurance measures may affect the efficacy and safety of the technology.</p>					
Methodology and sources	<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>					
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 (2.1) - PUBLIC DRAFT</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC</b></p>					



	<p><b>DRAFT</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</p> <p>C0020</p> <p>C0062</p> <p>C0063</p> <p>I0008</p> <p>F0006</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Current use, , Legal</p>
<b>Sequential relations</b>	

1

2

B0014 Assessment element card						
Issue: What kind of training and information should be provided for 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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	14
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	14
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Optional	None	No	13
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	14
Clarification	<p><b>Common to all used applications</b></p> <p>Describe what type of training materials should be provided (writing and/or translation, other adaptation) by whom, and the characteristics of the personal training (individual and/or group sessions, number and length of sessions, number and qualifications of trainers) and if the informed consent regarding the risk/benefits of 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 (2.1) - PUBLIC DRAFT</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al.</p>					

	2005
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>C0008</p> <p>C0003</p> <p>C0005</p> <p>C0007</p> <p>C0062</p> <p>F0004</p> <p>F0006</p> <p>G0004</p> <p>H0003</p> <p>H0007</p> <p>H0008</p> <p>I0002</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Current use, ,</p>
<b>Sequential relations</b>	

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2

B0015 Assessment element card						
Issue: What information of the technology should be provided for patients outside the target group and the general public?						
Topic: Training and information needed to use the technology						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	15
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	15
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	14
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	15
Clarification	<p><b>Common to all used applications</b></p> <p>Describe what type of information materials should be provided (writing and/or translation, other adaptation) and if the informed consent for participating 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 (2.1) - PUBLIC DRAFT</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al.</p>					

	2005
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>F0005</p> <p>F0011</p> <p>G0004</p> <p>H0002</p> <p>H0007</p> <p>H0008</p> <p>I0002</p> <p>I0008</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Current use,</p>
<b>Sequential relations</b>	

1

2

A0022 Assessment element card						
Issue: Who manufactures the technology?						
Topic: Other						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	16
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	16
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	15
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	16
Clarification						
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Manufacturers' information, clinical guidelines, legislation, HTAs, approving authority, 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 (2.1) - PUBLIC DRAFT</b></p> <p>Liberati A. et al. 1997; Busse R. et al. 2002</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</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>Related to Organisational domain</p>					

<b>Sequential relations</b>	<b>Common to all used applications</b>  I0037
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26



# 1 **Safety**

## 2 **Description**

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

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

8 The diversity of types of health technology means that there are many different types of safety  
9 issues and legitimate differences can occur in the way an assessment of safety may be undertaken.  
10 The authors of a core HTA should cover safety issues that are important to patients or otherwise  
11 likely to be important in guiding the decision of health care providers and policy makers.

### 12 **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 public and environment may occur when using the technology?	C0040

Safety risk management	How does the safety profile of the technology vary between different generations, approved versions or products?	C0060
Safety risk management	Can different organizational settings increase or decrease harms?	C0061
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 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?	B0010

1

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

- 4
- 5 • 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  
6 e.g. insufficient training or experience, lack of equipment maintenance, or inappropriate patient  
7 selection.
  - 8 • Indirect harms can further be grouped into **operator or setting dependent** and **patient dependent**  
9 harms. The former can be modified by changing practices or improving user knowledge, skills and  
10 behaviour. The latter may indicate vulnerable patient groups that require special protection.
  - 11 • Harms are often classified according to their **fatality** or **intensity** into mild, moderate, and serious  
12 or severe {2}. '**Serious**' refers to adverse effects that have significant medical consequences: they  
13 can for example lead to death, permanent disability, or prolonged hospitalisation. In contrast,  
14 '**severe**' refers to the intensity of a particular adverse effect. A non-serious adverse effect, such as  
15 headache, may be severe in intensity (as opposed to mild or moderate).
  - 16 • Harms can occur not only in **patients** or individuals using the technology. Their **family** and close  
17 ones, **foetus**, other patients, health care **professionals**, **public**, and the **environment** can also be  
18 affected.
  - 19 • **Risk** is an estimate of the probability of the harm.
  - 20 • Harms can be classified according to their **dose-relatedness** or **time-relatedness**. Increasing  
21 amount of exposure to technology (larger dose or longer time) can increase the risk of an adverse  
22 effect.
  - 23 • Harms can be previously **known** or **unexpected**. Control of known harms can be attempted by e.g.  
24 using specific monitoring tests to identify vulnerable patients or limiting the dose or time of  
25 exposure. Unexpected harm should especially be considered when expanding the use of a  
26 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.

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[1]. This includes the NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4 and the WHO system-organ class categories[2]. 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 {3}.

The HTA Core Model suggests following definitions for safety related terms. All sources have been accessed in June 2013. The terms “medicine”, “pharmaceutical” “medicinal product” and the like are retained to reflect correctly the original reference; for other types of technologies, these can be changed to “technology”, “intervention” or similar relevant terms.

**Adverse effects and adverse reaction:** The two terms refer to the same phenomenon, but an adverse effect is seen from the point of view of the pharmaceutical, whereas an adverse reaction is seen from the point of view of the patient. The pharmaceutical causes an effect, whereas the patient has a reaction. {4}

**Adverse event:** Any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (for example, including an abnormal laboratory finding,), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. {5}

**Adverse reaction/adverse drug reaction:** Noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product. The suspicion of an adverse drug reaction, meaning that there is at least a reasonable possibility of there being a causal relationship between a medicinal product and an adverse event should, be sufficient reason for reporting. {6}

**Adverse reaction (Serious):** An adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect, and is a medically important event or reaction. For the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided: The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.{5, 7}

## Severity Grades for Adverse events

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- 1 Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate  
2 instrumental Activities of Daily Living (ADL)\*.
- 3 Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or  
4 prolongation of hospitalization indicated; disabling; limiting self-care ADL\*\*.
- 5 Grade 4: Life-threatening consequences; urgent intervention indicated.
- 6 Grade 5: Death related to AE.
- 7 Activities of Daily Living (ADL):
- 8 \* Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the  
9 telephone, managing money, etc.
- 10 \*\* Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking  
11 medications, and not being bedridden. {8}
- 12 **Adverse reaction (Unexpected):** An adverse reaction, the nature or severity of which is not  
13 consistent with the applicable product information. {7}
- 14 An adverse reaction whose nature, severity, specificity, or outcome is not consistent with the term  
15 or description used in the local/regional product labelling (e.g. Package Insert or Summary of  
16 Product Characteristics) should be considered unexpected. When a Marketing Authorisation Holder  
17 is uncertain whether an adverse reaction is expected or unexpected, the adverse reaction should be  
18 treated as unexpected. {7}
- 19 **Benefit-Risk-Balance (Benefit-harm-balance):** In the regulatory context: an evaluation of the  
20 positive therapeutic effects of the medicinal product in relation to its risks (any risk relating to the  
21 quality, safety or efficacy of the medicinal product as regards patients' health or public health and  
22 any risk of undesirable effects on the environment). {9} (NOTE: "Risk" is the concept of benefit-  
23 risk-balance is used in the meaning for which "Harm" is otherwise used in this document.)
- 24 **Case by Case Causality assessment:** The evaluation of the likelihood that a medicine was the  
25 causative agent of an observed adverse reaction. Causality assessment is usually made according  
26 established algorithms. {10}
- 27 **Classification of causality {11}:**
- 28 • **Certain:** A Clinical event, including a laboratory test abnormality, that occurs in a plausible time  
29 relation to drug administration and which cannot be explained by concurrent disease or other  
30 drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically  
31 plausible. The event must be definitive pharmacologically or phenomenologically, using a  
32 satisfactory rechallenge procedure if necessary.
  - 33 • **Probable/likely:** A clinical event, including a laboratory test abnormality, with a reasonable time  
34 relation to administration of the drug, unlikely to be attributed to concurrent disease or other  
35 drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge).  
36 Rechallenge information is not required to fulfil this definition

- **Possible:** A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear
- **Unlikely:** A clinical event, including a laboratory test abnormality, with a temporal relation to administration of the drug, which makes a causal relation improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations
- **Conditional/unclassified:** A clinical event, including a laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are being examined
- **Unassessable/unclassifiable:** A report suggesting an adverse reaction that cannot be judged, because information is insufficient or contradictory and cannot be supplemented or verified

**Causal relationship:** A relationship between one phenomenon or event (A) and another (B) in which A precedes and causes B. {10}

**Harms:** The totality of possible adverse consequences of an intervention or therapy; they are the direct opposite of benefits, against which they must be compared. {12}

**Pharmacovigilance:** The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem. {10}

**Risk:** The probability that an event will occur, e.g., that an individual will become ill or die within a stated period of time or by a certain age. Also a nontechnical term encompassing a variety of measures of the probability of a (generally) unfavourable outcome. {13}

**Safety:** Substantive evidence of an absence of harm. The term is often misused when there is simply absence of evidence of harm. {12}

**Side effect:** Unintended drug effects. The term, however, does not necessarily imply harm, as some side effects may be beneficial. Furthermore, it tends to understate the importance of harms because “side” may be perceived as denoting secondary importance. {12}

It is recommended that this term no longer be used and particularly should not be regarded as synonymous with adverse event or adverse reaction.

**Tolerability:** A term that usually refers to medically less important (i.e. without serious or permanent sequelae) but unpleasant adverse effects of drugs. These include symptoms such as dry mouth, tiredness, etc, that can affect a person’s quality of life and willingness to continue the treatment. As these adverse effects usually develop early and are relatively frequent, RCTs may yield reliable data on their incidence. {14}

**Toxicity:** Describes drug-related harms. The term may be most appropriate for laboratory-determined measurements, although it is also used in relation to clinical events. Abnormal laboratory values may be described as laboratory-determined toxicity. The disadvantage of the term “toxicity” is that it implies causality. If authors cannot prove causality, the terms “abnormal laboratory measurements” or “laboratory abnormalities” are more appropriate to use. {12}

## 1 Why is this domain important?

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

5 Assessment of safety issues should be considered always, but it is especially needed when { 14 }:

- 6 • The technology presents any risk of serious harm or a high risk of milder harms.
- 7 • The technology is used in large populations {2}
- 8 • The benefit-harm-balance is close to even
- 9 • Several technologies with similar effectiveness can be used for the condition, and they have  
10 different safety profiles
- 11 • The false positive rate of a diagnostic or screening test is high and patients may be subjected to  
12 unnecessary, potentially harmful investigations or treatments, or
- 13 • Adverse effects or poor tolerability threaten the acceptability and use of the technology.

## 14 Relations to other domains

15 Work in the safety domain should be carefully coordinated with the clinical effectiveness domain.  
16 Benefit-harm-balance is an essential issue in the effectiveness domain. It is worthwhile to discuss  
17 how to avoid duplicate work in finding information for that. Safety domain may require information  
18 from health problem and current use, description and technical characteristics, and ethical analysis  
19 domains. Information provided by safety domain is of relevance to at least organizational, costs and  
20 economic evaluation, ethical and possibly also legal domains.

## 21 Screening-specific content

22 Since screening technologies are used for large numbers of healthy persons, the tolerance threshold  
23 for harms should be very low { 15 }. Indirect harms specific to screening technologies are:

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

33 [1] <http://cbit.nci.nih.gov/ncip>

34 [2] <http://www.unc-products.com/graphics/3149.pdf>

## 35 Pharmaceutical-specific content

36 The safety issues specific to pharmaceutical technologies (drug safety, patient safety, adverse drug  
37 reactions, patient susceptibility, pharmaceutical safety) should be considered while working on the safety



1 domain {16}. For further details see the guideline “Endpoints used in REA of pharmaceuticals – Safety”,  
2 available at <http://www.eunethta.eu/outputs/methodological-guideline-rea-pharmaceuticals-safety>.

## 3 **Methodology**

### 4 **Gathering information**

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

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

- 12 • National or international safety monitoring systems of adverse events which may be managed by a  
13 national statutory body or by a supra-national body; Risk Management Programs and systematic  
14 safety research; particular attention to label warnings and open questions in pharmacovigilance is  
15 needed
- 16 • Disease or technology monitoring registries of patients receiving treatment, which may be  
17 organised at an international, national or regional level and managed by a government agency,  
18 professional body or the manufacturer.
- 19 • Pharmacovigilance data analysis and pharmacovigilance systems or spontaneous adverse event  
20 databases, such as:
  - 21 ○ The Uppsala Monitoring Centre spontaneous reporting database ([http://www.who-](http://www.who-umc.org)  
22 [umc.org](http://www.who-umc.org)) and the Vigibase Services, maintained by Uppsala Monitoring Centre, responsible  
23 for the management of the WHO Programme for International Drug Monitoring
  - 24 ○ The EMA collects adverse reactions reports on medicines licensed across the EU through  
25 the EudraVigilance database. Reports are received from EU regulatory agencies and  
26 pharmaceuticals companies.
  - 27 ○ Adverse Event Reporting System (AERS), the database supported by the FDA’s post  
28 marketing safety surveillance program for approved drugs. The MedWatch website, on  
29 which the FDA collects information about adverse reactions.
- 30 • Manufacturers’ product data sheets or applications for a product license if available. European  
31 Public Assessment Reports of pharmaceuticals. Risk Management Plans for pharmaceuticals.
- 32 • Manufacturers’ periodic safety update reports (PSUR), a pharmacovigilance tool; collecting  
33 information from a variety of different sources (spontaneous reports from different countries,  
34 clinical trials, registries).
- 35 • Specific enquiries to manufacturers (e.g. industry submissions, product information), regulators,  
36 professional bodies or patient group perspectives may help identify additional sources of  
37 information.

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

41 When information is scarce, it may be necessary to look for grey literature (drug monographs,  
42 bulletins, or conference proceedings); to do reference checking of retrieved literature or hand  
43 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 {17}. In some cases routine statistics from hospital, primary care or health system funders may be available and provide suitable information. Information from patient associations may provide valuable patient experiences especially in emerging technologies {18}.

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 specified adverse effects have to be defined for search strategies in each database separately{19}. New, previously unrecognised adverse effects remain therefore easily undetected {20}. Several study types should be considered for inclusion in the search. Systematic reviews of adverse effects have often used inadequate searches to identify studies {21}.

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 for 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 lack of consistency of reporting harms. A predefined classification of adverse effects could help the authors to approach the data {14}.

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 in their assessment {2}. The demographic characteristics



of the population in which the technology is to be used should be defined for later comparison against the populations in which safety data has been identified.

Core HTA authors may choose to narrow 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 to identify harms relevant for the assessment, as they bring different and complementary information. Randomised controlled trials, observational studies and case reports provide evidence on the types and frequencies of harms. Randomised trials are methodologically most solid, and may alone be an appropriate source of evidence for some review questions about harm. However, safety reporting in randomized trials is heterogeneous and often inadequate {16, 22}.

Rare adverse effects are not usually detected in randomised trials, and even relatively frequent harms with a longer latency period cannot be quantified easily. Information about new, serious, rare or long-term adverse effects are thus typically found in observational studies (cohort, case-control, and cross-sectional studies). Risk of late onset harms (e.g number of radiation induced cancers) can be estimated based on analogies and assumptions from epidemiological studies.

Besides published research, routinely collected data or register data can be used. Often these databases are generic and may not contain enough information. However, their advantages are 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 to identify safety signals for marketed drugs. Its primary purpose is to provide early warnings of adverse drug reactions not recognized 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). QALY is a non-disease specific measurement of outcomes incorporating both quality and duration of life, defined as years of healthy life lived {23}. 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 {24, 25}. 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) {26}. For meta-analyses, risk ratio (RR) is the most common summary statistic, followed by Peto odds ratio. Risk difference (RD) is rarely used in meta-analyses although it is the most interpretable statistics and is particularly appropriate when examining rare event data {27}.

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

Suggested index terms:

- Primary Prevention [Mesh] or Mass Screening [Mesh] or Public Health Practice [Mesh]. Medicalisation, false positive, false negative, over-diagnosis, 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 {18}.
  - Internet discussion forums may provide valuable, but probably unreliable, additional information.

### **Useful other sources of information**

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 {17}.

## 1 Tools for critical appraisal

2 There is often a trade-off between the comprehensiveness and quality of the harms data to be  
3 included in an assessment. Including evidence that is likely to be biased, even if no better evidence  
4 exists, may lead to biased conclusion. All included data should be critically appraised. There is a  
5 lack of a relevant quality assessment tool to risk analysis {14}. Any available tool should be used  
6 cautiously. Comparing evidence from randomised trials and observational studies is useful.

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

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

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

20 Different methods of monitoring harms yield different results which make comparisons between  
21 studies meaningless. Active surveillance and use of checklists yield higher harm frequencies than  
22 passive or less focused methods {14}. Case reports of suspected adverse events are widely  
23 published in scientific journals and few of these reports have been subsequently investigated or  
24 confirmed to be valid {28}. Some spontaneous reporting systems are inevitably erroneous {14}.

25 Original studies may report only some outcome categories although several were measured; the  
26 intervention groups may be combined (e.g. X participants withdrew from the study); or statements  
27 are unclear or too generic (e.g. no unexpected adverse effects were seen). Be aware of poor  
28 reporting styles for harms-related data {12} such as:

- 29 • Vague statements, such as “the drug was generally well tolerated”.
- 30 • No separate safety data for each study arm are given, or only summed numbers of all adverse  
31 events are presented.
- 32 • Severity or seriousness of adverse events is not given.
- 33 • Vague frequency rate of harm presented: e.g. > 3 % of patients.
- 34 • Reporting adverse events only by means or medians instead of extreme values.
- 35 • Improper handling of the relative timing of the adverse events.
- 36 • Not distinguishing between patients with one adverse event and those with multiple adverse  
37 events.
- 38 • Providing statements on harm with p values without giving exact count of events.
- 39 • Not providing data on harms of all study participants but only for “completers”.

40 Two persons should assess all included studies. Their background and the way they resolved  
41 disagreements should be reported. Results of the quality assessment of original studies should be

presented in a table or graphically. Individual quality items should be investigated as a potential source of heterogeneity.

Methods used to assess bias should be clearly described and the risk of bias reported regarding both the information sources and how the data were collected. The way risk of bias information is used in the report should be clearly explained. Detailed recommendations on how to assess the risk of bias and the quality of data on harms are included in section 2.4 of the guideline Endpoints used in REA of pharmaceuticals – Safety (<http://www.eunethta.eu/outputs/methodological-guideline-rea-pharmaceuticals-safety>).

## **Trials**

Adverse events are variably and sometimes poorly reported in randomised trials {22} and in systematic reviews of trials {19}. The definition of a particular harm may vary between studies, as can definitions of severity. Harms can be measured in different ways and different thresholds can be used. An extension of the CONSORT Statement (Consolidated Standards for reporting Trials) supports better reporting of harms in randomised trials {12}.

Basic requirements for the data are: it should be presented in numbers (at least the frequency of serious events should be provided per study arm); the severity of adverse effects should be stated; and data should be given separately for each type of adverse effect {29}. 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 {14}.

Even in cases where adverse events are examined and reported adequately, there is often insufficient evidence for conclusion since most trials are tailored towards optimizing efficacy estimates {26}. Note 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 {14}.

Caution is needed when interpreting withdrawal or drop-out data as surrogate measures for safety or tolerability. Reasons for withdrawal can be anything from mild side effects to serious toxicity, lack of efficacy or non-medical issues {12}. Patients or investigators in a trial may be more (or less) willing than usual to continue when side effects occur {14}.

## **Observational studies**

Trials may report small, fragmented pieces of evidence of harms that are not primary outcomes, whereas observational studies may be primarily devoted to assessing specific harms. Nested case control studies, full cohort analyses, and survival analysis methodologies are study designs used for harms assessment. Major sources of bias in observational studies include confounding by factors associated with both treatment and outcome, differential recall of exposure, and differential detection of outcomes {29}. The STROBE checklist of items to be addressed in reports of observational studies {30} 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), are tools to assess observational studies. The strengths and weaknesses of different study designs that may be included in a systematic review of harms are discussed by Jefferson and Demicheli {31}.

## **Diagnostics-specific content**

1 Aspects of study quality of diagnostic accuracy studies include the selection of a clinically relevant cohort,  
2 the consistent use of a single good reference standard, and mutual blinding of results from experimental  
3 and reference tests {32}.

4 There are different tools to assess the quality of diagnostic accuracy studies. The Cochrane handbook for  
5 Systematic Reviews of Diagnostic Test Accuracy {33} recommends the QUADAS tool.

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

7 Quality assessment of diagnostic accuracy studies is subjective and hampered by poor reporting.  
8 Incorporation of quality in overall assessment is difficult due to limited studies. Relation between  
9 quality items and bias are not as straightforward as it is for interventions. Screening studies may in  
10 addition be confounded by lead time bias, length time bias, and overdiagnosis.

## 11 **Analysing and synthesising evidence**

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

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

18 Harms are frequently insufficiently reported {22}. Poor safety reporting of the original research can  
19 lead to misinterpretation and inadequate conclusion of the technology assessed.

20 Reported harm frequencies may differ greatly by study type. A study comparing harms reported in  
21 randomised and observational studies found that observational studies yield lower estimates of  
22 absolute risk of harm {34}.

23 Randomized trials have frequently restrictive inclusion and exclusion criteria which can result in  
24 underestimating harm. Trials may exclude harm-sensitive subgroups because of ethical concerns, or  
25 include them in insufficient numbers. Measurements of late onset harms (e.g number of radiation  
26 induced cancers) are seldom seen in publications. Frequency of rare harms is always an estimate,  
27 based on analogies and presumptions from epidemiological research. Adverse effects data are  
28 usually equally well reported in studies funded by industry or from other sources. However,  
29 interpretations and conclusions by industry funded authors may be biased {21}.

## 30 ***Evidence tables***

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

- 32 • Description of harm
- 33 • Frequency or probability of harm in intervention and control groups
- 34 • Fatality (mild, moderate, severe, life-threatening, death)
- 35 • Intensity (mild, moderate, severe)
- 36 • 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 (how the data were collected etc.)
- Comments on generalizability of the evidence
- Reference or other source

## ***Meta-analysis***

Safety events are usually rare (incidence <5%). Thus safety estimates would require large sample sizes in trials to detect differences between patient groups. For rare event data, exact methods in meta-analyses seem to be superior to the asymptotic Mantel-Haenzel method and to the Peto method when trials are balanced {35}.

Because asymptotic approximations in dichotomous data require a non-zero event rate, most reviewers add 0.5 to each cell instead of zero. 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. Although asymptotic approximations are known to be imprecise with rare events, the majority of systematic reviews use them.

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

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

In many circumstances it is not possible to calculate frequencies, and information about harms is best presented in a qualitative or descriptive manner. Data derived from different study designs, different populations or different data collection methods cannot be combined. Anticipated adverse effects can be reported congruently, whereas unanticipated harms detected during a trial might be reported in markedly different ways by different investigators {34}

## **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. Presentation in tables is transparent and may be helpful in summarising data {1}. Information sources should be clearly stated.

When discussing the safety of a technology, the way harms were caused should be described. 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 be considered {14}.

The safety of a technology should always be assessed in balance with its benefits, even if the patient populations used in the benefit analysis and the harm analysis differ {14}. Once a possible relationship between technology and a harm is suspected, causality assessment can be made using established algorithms {2}; e.g. for pharmaceuticals those 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 RCT's cannot be



1 performed. In RCTs presenting adverse event rates, non-statistically significant differences are  
2 associated with low statistical power. A high probability of type II error may lead to erroneous  
3 inferences {12}.

4 Whenever possible, the overall effect of harms needs to be quantified, and information on the  
5 frequency of occurrence, relative risk or number needed to harm (NNH or NNTH) provided. A  
6 small absolute risk is still clinically important if an adverse effect is serious or severe, or if the  
7 absolute benefit from the intervention is small {34}. Finally, a comment is needed about the  
8 generalizability of the findings to the population in which HTA results will be applied {2}.

9 Estimates of risk from case-control studies are presented as the exposure odds ratio of cases  
10 compared to controls. The unintuitive odds ratios can be used to calculate the number needed to  
11 harm (number of patients needed to be treated for one additional patient to experience an adverse  
12 event) {36}. In case adverse events are incorporated in utility values or quality of life measures, the  
13 source of quantification should be accessible.

14

## 1 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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
Clarification	<p><b>Common to all used applications</b></p> <p>Here one should identify and describe the direct harms of the use and the administration of the technology and the comparator(s). Highlight the differences in the most important risks (i.e. the most severe and frequent harms) of the technology and its comparator(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 separately harms identified in spontaneous reporting databases. Harms should be reported per indication or target population. The identified harms should be categorised 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 the occurrence of each harm is usually presented in comparison with placebo or no treatment, as percentages or risk ratios. Finally, the harms should be grouped by their severity and frequency and ordered so that the severe and/or frequent harms are presented first. If there are many different harms reported in the literature, concentrate on reporting the most serious and the most frequent harms</p> <p><b>Specific to Pharmaceuticals (2.1) - PUBLIC DRAFT</b></p> <p>The important identified and potential adverse events/reactions presented in Risk Management Plan of the pharmaceutical (RMP) should be considered, 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>Special attention should be given to drug interactions. Information in the label warnings and</p>					



	<p>PSUR should be evaluated using literature and registration data.</p> <p>Distinction should be made 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>Attention should be paid to the possibility of medication errors. Errors may be classified 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, or replacement of two pharmaceuticals which look alike or difficulties of handwriting readings that lead to mistakes by patient or professional.</p> <p>For further information see Endpoints used in REA of pharmaceuticals – Safety <a href="http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Safety.pdf">http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Safety.pdf</a></p>
<b>Methodology and sources</b>	<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>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>{ 1, 12, 14, 16, 28, 29, 34, 37 }</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>B0001</p> <p>A0018</p> <p>D0009; D0003 A0001 A0007</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Current use</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Current use/ organisational aspects/ costs, economic evaluation</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Current use, Clinical Effectiveness and Ethical domains</p>

<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>B0001</p> <p>A0018</p> <p>A0001</p> <p>A0007</p>
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1

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 (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	2
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	2
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	2
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	2
Clarification	<p><b>Common to all used applications</b></p> <p>Information should be included if safe use of the technology is sensitive to even small changes of the dose because this may have implications for the training and organisation of care. The potential for accumulated harm due to repeated dosage or testing should also be considered.</p> <p><b>Specific to Pharmaceuticals (2.1) - PUBLIC DRAFT</b></p> <p>For further information see Endpoints used in REA of pharmaceuticals – Safety</p> <p><a href="http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Safety.pdf">http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Safety.pdf</a></p>					
Methodology and sources	<b>Common to all used applications</b>					

	Phase 1 studies for pharmaceuticals, other research articles, HTAs, manufacturers' product data sheets, safety monitoring databases. Method: Systematic review.
<b>References</b>	<b>Common to all used applications</b>  { 2, 11 }
<b>Content relations</b>	<b>Common to all used applications</b>  A0017  B0001
<b>Sequential relations</b>	<b>Common to all used applications</b>  A0017  B0001

1

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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	3
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	3
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	3
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	3
<b>Clarification</b>	<b>Common to all used applications</b>  This issue is especially relevant for new or evolving technologies where there are considerable uncertainties in the safety evidence, and in technologies with steep learning curves. How does the safety profile of the technology vary between different generations,					

	approved versions or products? Is there evidence that harms increase or decrease in different organisational settings?
<b>Methodology and sources</b>	<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>
<b>References</b>	
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>Current use, effectiveness (D0001; D0008; D0009) , costs domains</p> <p>B0004</p> <p>B0001</p>
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>B0004</p> <p>B0001</p>

1

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 (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	4
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	4
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	4
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	4

<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Typically, people with comorbidities and co-medication, pregnancy, intolerances, or specific genetic profiles, elderly people, children and immunosuppressed patients. Are there any relevant contra-indications or interactions with other technologies?</p>
<b>Methodology and sources</b>	<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>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>{ 2, 11 }</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>Ethical, Effectiveness domain (D0008;D0009)</p> <p>B0016</p> <p>B0001</p>
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>B0016</p> <p>B0001</p>

1

2

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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	5
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	5
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	5
Clarification	<p><b>Common to all used applications</b></p> <p>What are the consequences of false positive, false negative and incidental findings generated by using the technology?</p> <p>False negative test results (Type II error) identify sick people incorrectly as healthy with the possible consequence of incorrectly rejected or delayed treatment. 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) identify healthy people incorrectly as sick with the possible consequence of overtreatment. 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 (2.1) - PUBLIC DRAFT</b></p> <p>In screening programmes one should consider separately the false negative screening test results and the subsequent false negative diagnostic test results.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Research articles, manufacturers' product data sheets, safety monitoring databases</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, Schwartz L, Woloshin S. Overdiagnosed: Making people sick in pursuit of health, Beacon Press, Boston, 2011</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>Effectiveness domain D0028, D0027</p> <p>D0009</p> <p>D0003</p> <p>B0001</p> <p>D0003</p> <p>E0001</p> <p>F0001</p> <p>G0001, G0100</p>
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>B0001</p>
<b>Other domains</b>	Also in: Clinical Effectiveness

1

2

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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	6
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	6
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	5
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	6
Clarification	<p><b>Common to all used applications</b></p> <p>Describe here what is known of the harms caused by the properties or behaviour of professionals, patients or other individuals who apply or maintain the technology. Is there e.g. a noteworthy risk of malfunction of a device, due to deficient user training or personal attitude; or a risk of errors related to reconstitution, dosage, administration, or storage of medicines, that may have serious consequences; or, is there a risk of addiction? Describe what is known of the learning curve, intra- or inter-observer variation in interpretation of outcomes, errors or other user-dependent concerns in the quality of care.</p> <p>For further information see Endpoint used in REA of pharmaceuticals – Safety. <a href="http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Safety.pdf">http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Safety.pdf</a></p>					
Methodology and sources	<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>					
References	<p><b>Common to all used applications</b></p> <p>{ 2, 11 }</p>					
Content relations	<p><b>Common to all used applications</b></p>					



	<p>Description and technical characteristics and Organisational domains B0006</p> <p>B0001</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Description</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Description</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Description and technical characteristics and Organisational domains</p>
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>B0006</p> <p>B0001</p>

1

2

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 (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	7
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	7
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	6
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	7
Clarification	<b>Common to all used applications</b>  Consider if there are possible harms to professional applying the technology: working positions, radiation or infection risks, etc.					
Methodology and sources	<b>Common to all used applications</b>  Research articles, manufacturers' product data sheets, safety monitoring databases					
References						
Content relations	<b>Common to all used applications</b>  Ethical and Social domains  B0012  B0013					
Sequential relations	<b>Common to all used applications</b>  B0012  B0013					

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 (2.1) - PUBLIC DRAFT	Yes	Optional	Partial	No	8
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Optional	Partial	No	8
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Optional	Partial	No	7
	Screening Technologies (2.1) - PUBLIC DRAFT	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 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>Research articles, manufacturers' product data sheets, safety monitoring databases</p> <p>Method: Systematic review.</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>Ethical and Social domains</p>					
Sequential relations						

C0060 Assessment element card						
Issue: How does the safety profile of the technology vary between different generations, approved versions or products?						
Topic: Safety risk management						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	9
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	9
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	8
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	9
Clarification						
Methodology and sources	<b>Common to all used applications</b> Research articles, manufacturers' product data sheets, safety monitoring databases					
References						
Content relations	<b>Common to all used applications</b> Description and Technical Characteristics					
Sequential relations						

C0061 Assessment element card						
Issue: Can different organizational settings increase or decrease harms?						
Topic: Safety risk management						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	10
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	10
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	9
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	10
Clarification						
Methodology and sources	<b>Common to all used applications</b>  Research articles, manufacturers' product data sheets, safety monitoring databases. Descriptive review on accuracy and effectiveness research, epidemiological risk research					
References						
Content relations	<b>Common to all used applications</b>  Current use, Effectiveness (D0009; Organisational B0020 A0012					
Sequential relations	<b>Common to all used applications</b>  B0020 A0012					

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 (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	11
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	11
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	10
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	11
Clarification	<p><b>Common to all used applications</b></p> <p>Is there 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 may 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>Ethical F0006, Description and technical characteristics B0012, B0014, B0015</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Organisational aspects</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Ethical F0006, Description and technical characteristics B0012, B0014, B0015</p>					

<b>Sequential relations</b>	
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1

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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	12
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	12
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	11
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	12
Clarification	<p><b>Common to all used applications</b></p> <p>Is there 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 may 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	<p><b>Common to all used applications</b></p> <p>Organisational and Social Domains</p>					
Sequential relations						

1

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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	13
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	13
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	12
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	13
Clarification	<p><b>Common to all used applications</b></p> <p>Is there 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 may 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	<p><b>Common to all used applications</b></p> <p>Social Domain</p>					
Sequential relations						

2



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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	14
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	14
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	13
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	14
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 to monitor the use of this particular technology and the comparator. Are there existing registries that should be used, or should a registry be established, to collect the necessary data to monitor safety or true life effectiveness? Provide national examples.</p> <p><b>Specific to Pharmaceuticals (2.1) - PUBLIC DRAFT</b></p> <p>Refer to SPC and EPAR.</p> <p>Sometimes registries are 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>					

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<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>G0008</p> <p>G0003</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Current use, Legal</p>
<b>Sequential relations</b>	
<b>Other domains</b>	Also in: Description and technical characteristics of technology

1

2

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22

## 1 ***Clinical Effectiveness***

### 2 **Description**

3 The effectiveness domain in a health technology assessment considers two questions: Can this  
4 technology work, and does this technology work in practice? Two definitions are commonly used in  
5 this assessment {1, 2}

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

13 Commonly, the focus of the evaluation of clinical effectiveness is to determine the magnitude of  
14 health benefits and harms or in other words of the net benefit (benefits minus harms) that is caused  
15 by a technology and the certainty of the evidence ({3}). As the harms are addressed in the core  
16 model in a separate domain ('safety') this domain focuses on the assessment of the health benefits  
17 and the benefit-harm-balance. The generally accepted standard for proving the evidence of a causal  
18 relationship between intervention and health outcomes is an appropriately designed and conducted  
19 randomised controlled trial (RCT), even without a need for a deeper biological theory as to why the  
20 intervention works or not {4} .

21 Two or more alternative methods to prevent, diagnose, treat and monitor a clinical condition or to  
22 improve the delivery of care are compared in comparative clinical effectiveness research. The two  
23 key elements are that effective interventions should be directly compared and studied in patients  
24 who are typical of day-to-day health care settings{5}.

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

27  
28  
29

**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
Mortality	What is the effect of the technology on the mortality due to causes other than the target disease?	D0003
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 test-treatment intervention modify the magnitude and frequency of morbidity?	D0032
Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	D0006
Test-treatment chain	Is there an effective treatment for the condition the test is detecting?	D0024
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 hospitalization?	D0010
Change-in management	How does the technology modify the need for other technologies and use of resources?	D0023

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	Was the use of the technology worthwhile?	D0017
Patient satisfaction	Is the patient willing to use the technology again?	D0018
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
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 does it classify the target condition correctly?	D1003
Test accuracy	What are the requirements for accuracy in the context 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
Benefit-harm balance	What are the overall benefits and harms of the technology in health outcomes?	D0029

## 1 Why is this domain important?

2 In health policy, the insurer, agency or government providing care as well as users, citizens and  
3 consumers require primarily information on the effectiveness and safety of a technology. It is of no  
4 interest to examine the other aspects such as the costs of a technology if the technology is not  
5 effective.

## 6 Relations to other domains

- 7 • Effectiveness domain requires information from **health problem and current use** domain, as well as
- 8 **safety** domain in order to specify the appropriate populations, interventions, comparisons and
- 9 outcomes for the research questions.
- 10 • There is a possibility of overlapping with **safety** domain, so co-operation is needed in the protocol
- 11 phase.
- 12 • The **costs and economic evaluation** domain requires information from the effectiveness domain in
- 13 order to determine the incremental health benefit part of the incremental cost-effectiveness ratio
- 14 • Depending on the technology the **ethical** domain may be important for the setting of the
- 15 framework of the effectiveness analysis. For example how patient relevant outcomes are defined
- 16 for which value judgments may be important. {6}
- 17 • Effectiveness may sometimes strongly depend on **organisational** aspects.
- 18 • Effectiveness may also be related to the **legal** domain, e. g. when there is legal support to a public
- 19 health programme (mandatory vaccination or mass screening)

## 20 Pharmaceutical-specific content

21 From a legal viewpoint, following the European transparency guideline (Transparency Directive  
22 89/105/EEC<sup>1</sup>), countries have the legal obligation to do an assessment within a certain time period

<sup>1</sup> 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).

(90/180 days). In these cases a ‘rapid’ assessment is preferred in order to meet these strict timelines. Assessments of pharmaceutical should take the pharmaceuticals’ marketing authorisation status (e.g. <http://www.ema.europa.eu/> ) into account, 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.

## 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

The specification of the research question using the PICO scheme (Appendix 3) is the first step in performing the evaluation of the clinical effectiveness of a technology. 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 (Appendix 3 REA/Full Pharma Model, {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 were developed stating under which conditions 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 stress the linkage between them. Therefore diagnostic-specific content of the HTA core model is relevant for evaluation of screening programmes, too.

As for all health technologies 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. But screening is a complex intervention with several intermediate steps to patient relevant endpoints.

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

- the prevalence and incidence of a disease
- the natural history of disease and the proportion of subclinical or reversible cases that would not become clinically relevant (potential for overdiagnosis and overtreatment)
- the participation rate as the number of participants divided by the number of eligible individuals in the target screening population
- the screening interval
- the accuracy of the screening test
- the proportion of subjects with positive screening test results which have a diagnostic follow-up
- the test accuracy of the tests used in the diagnostic follow-up
- the impact of the test results on treatment decisions and quality of life
- the 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 with true and false test results, the possibility of adverse effects from the test, the accuracy and potential for adverse effects of the subsequent confirmatory diagnostics, the losses to follow up before the therapeutic intervention is provided, and the effectiveness and adverse events of the therapeutic intervention. {3}

Large randomised controlled trials in a representative asymptomatic population comparing a group invited to screening with a group not invited to screening with a follow-up until all patient relevant outcomes can be analysed are rarely available, especially when the development of the disease takes a long time as, for example, in the case of cancer. Therefore, often indirect evidence from different study types has to be linked.

Additionally, it is probable that the effectiveness will fall during the early stages of a new screening programme. This occurs as a larger number of cases (both early stage and late stage disease) are likely to be picked up 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?**

Many different sources of information should be searched, including published and grey literature, searching of 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

1 Specialised databases for specific questions such as

- 2 • CINAHL,
- 3 • PSYCINFO,
- 4 • ASSIA, (Applied Social Sciences Index and Abstracts)
- 5 • SOCIOLOGICAL ABSTRACTS
- 6 • Social Services Abstracts,
- 7 • Social Care on line/Caredata and SocINDEX,
- 8 • ERIC

9 Administrative studies: General science publishers' databases such as

- 10 • Emerald Library,
- 11 • Science Direct and Ebsco Academic Search Elite,
- 12 • Pub Med Central (PMC),
- 13 • Bio Med Central (BMC),
- 14 • ProQuest Health Management

15 Trial registers such as

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

19 Databases on specific study designs / publication types:

- 20 • DARE,
- 21 • NHS EED,
- 22 • CDSR,
- 23 • Cochrane CENTRAL.
- 24 • GIN guidelines

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

- 26 • Hand searching of journals and abstract books, and the so-called “grey literature” can be
- 27 performed if information is scarce (Dissertational Abstracts, Scirus - Reports of hospital studies and
- 28 doctoral thesis, OAlster).
- 29 • Additional information can be collected also from contacts with manufacturers and consultation
- 30 with domestic and foreign experts and agencies (Handbooks).
- 31 • Performing an additional SCI-search of the included articles is a valuable complementary approach.
- 32 Add information about other sources and links specific to clinical effectiveness.
- 33 • Other sources: Conference proceedings (Web of Science Database), national and regional
- 34 guidelines, expert opinions, International, national and regional routinely collected statistics
- 35 (Health Information Database DRG)

## 36 **Diagnostics-specific content**

37 *Sources and search strategies for testing accuracy information*

38 Inadequate and inconsistent reporting of diagnostic accuracy studies and their indexing in medical  
39 reference databases make their identification particularly challenging. Unpublished and ongoing studies of

diagnostic accuracy would be valuable but not as easily detected as trials. Reviewers are likely to retrieve thousands of records 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 needed to read {10, 11}. Over 20% of studies included in diagnostic accuracy reviews were not found in MEDLINE and 6 % were not found by the electronic searches {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**

1. Source data / data base for assessment: it should include normally 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 data base 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***

With a bit of luck one may 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 judged to be transferable to one's own health care system and the local setting, or for the overall goals of a core HTA information collection, then the work might end right here. Following the hierarchy of study designs {13}, reviews on efficacy / effectiveness are generally limited to randomised designs. To assess the 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 them {14}. In addition, registry data reflecting clinical routine care help judging whether study populations, interventions and outcomes in RCT are comparable to clinical practice. It may be necessary to broaden the inclusion to 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* (see Appendix 3).

Key elements of a benefit assessed under routine conditions are that (a) effective interventions should be directly compared and (b) studies should include patients who are typical of day-to-day health care settings {5}. Benefit compared to placebo should have been proven before or parallel to

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, the use of indirect methods may be helpful (See *guideline Comparator and comparisons - Direct and indirect comparisons* ).

The assessment of health benefits should primarily consider clinically meaningful endpoints such as mortality, morbidity, and quality of life (See guideline *Endpoints used in REA of pharmaceuticals- clinical endpoints*). 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 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 uncertainties associated and the limits of their use should be explicitly explained (See guideline *Endpoints used in REA of pharmaceuticals- surrogate endpoints*).

A number of effect measures are in use for describing the treatment effect. For binary data, common measures are 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), often converted into number needed to treat (NNT) or events per thousand patients to allow for a comparison across studies. 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 are often more difficult to summarize. 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. This measure allows a meaningful interpretation to clinicians {15} For more details about effect measures and their calculations, we 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 QALY or 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 for 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** (see Applicability of evidence in the context of a relative effectiveness assessment) of the trial results to the intended population for treatment;
- **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. life-time 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 Domain Costs and Economic Evaluation”

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}

## ***Diagnostics-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 on accuracy information only 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 to provide **direct evidence** of effectiveness of a diagnostic technology. However these studies are rarely available. Furthermore, they are not always feasible or even necessary to determine the effectiveness of the technology. When direct trial evidence is not available other study types, that provide evidence about test safety, accuracy, impact on management and the effectiveness of the treatment, are relevant to the assessment of effectiveness. Evidence from these studies can be linked to yield an estimate of effectiveness of the diagnostic technology (**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 in the test-treatment chain at which patients are randomized can vary depending on the study question or other constraints, the most simple design randomizing subjects to receive 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 is due to the selection of the diagnostic



1 pathway and in subsequent treatment decisions. Other comparative study designs like cohort and case-  
2 control studies have greater potential for bias.

### 3 **Linked evidence**

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

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

6

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

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

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

22 Change-in-management studies are required if other factors than the test result, like individual patient  
23 characteristics or patient preference, influence treatment decision. They are also valuable when the impact  
24 of test information is uncertain, as it is when the test is used to distinguish between multiple differential  
25 diagnoses, or when accuracy studies are conducted in patients with different prevalence or severity of  
26 disease than the intended patient population or usual practice.

27 When there is a trade-off between benefits and harms, e.g. when better safety of a less invasive but less  
28 specific new test needs to be assessed against the harms arising from additional false-positive results,



1 decision analytic modelling can be used. Decision analysis allows also the comparison of the test  
2 effectiveness in those with a different prevalence of the disease and of multiple test-and-treat strategies of  
3 existing tests in clinical practice where it is unfeasible to directly compare all strategies in clinical trials. In  
4 fast developing fields completed clinical trials may not be applicable to current practice standards.  
5 Modelling can help to assess the trade-offs of a newer test and could also consider potential shifts in the  
6 disease spectrum. Modelling can explicitly account for uncertainty in key parameters and assumptions  
7 {29}. Decision analysis is an appropriate method to link the evidence on test accuracy with the evidence on  
8 treatment effect, if patient-relevant long-term outcomes cannot be extracted from trials. The uncertainty  
9 of model results due to parameter uncertainty and model assumptions can be transparently evaluated and  
10 reported in sensitivity analyses. However, high-quality evidence on patient-relevant long term benefits and  
11 harms should be assessed in randomised trials. In these situations, trials investigating the effect of  
12 treatment in patients who have positive results on the new test and negative results on the old test may be  
13 more efficient and more clinically relevant than trials conducted in all patients who are new-test-positive  
14 {30}.

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

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

20 The design of a basic diagnostic accuracy study is that of a group of patients with the suspected target  
21 disease undergoes the test (strategy) under consideration (index test) and the best possible test (strategy)  
22 to verify the diagnosis (reference standard, gold standard). Positive and negative results from both tests are  
23 shown in a 2x2 table or a variation thereof, depending on the number of cut-off points chosen.

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

32 If a new technology can **replace** an existing one, the accuracy of the new test (index test) and the routine  
33 test (comparator test) has to be compared in comparable groups or preferably in the same patients {33}.  
34 This can be done indirectly by looking at studies where test A has been compared with a reference  
35 standard, and other studies where test B has been compared with the same reference standard. Studies  
36 that do the index test, the comparator test and the reference test to all patients are preferred (paired  
37 study). If not all patients had verification with the reference standard test, then the sensitivity and  
38 specificity of the two technologies cannot be calculated, but relative true and false positive rates can still be  
39 estimated, which allows the accuracy of the two tests to be compared against a common reference  
40 standard.

1 Another option is a randomised controlled trial where patients are randomly allocated to receive either  
2 new or existing test, after which all patients undergo the reference standard testing. Randomised trials are  
3 preferred if the new test is too invasive to be done to all patients or if the tests interfere with each other  
4 {34}. For further options see {26}.

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

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

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

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

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

27

## 1 Outcome measures for test accuracy studies

2 Diagnostic test results are often reported as a numeric quantity on a continuous scale which is then divided  
3 by a threshold value above which the test is positive and below which it is negative. Results may then be  
4 summarized in a 2x2 table to reflect the agreement between the "true" disease state and the test result.  
5 Sensitivity, specificity and positive and negative predictive values are derived from these 2x2 tables for  
6 further details see Appendix 3 and Centre for Reviews and Dissemination, Chapter 2 Systematic Reviews on  
7 Clinical Tests

8

9 Figure 2x2 table

	Diseased	No disease
Test positive	TP	FP
Test negative	FN	TN

10

11

12 The numbers in the table state the number of true-positive, false-positive, true-negative and false-negative  
13 results. Changing the threshold, changes these figures and thus the sensitivities and specificities and other  
14 summary measures calculated out of the numbers in the 2x2 table.

## 15 *Screening-specific content*

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

21 Additionally, it is probable that the effectiveness will fall during the early stages of a new screening  
22 programme. This occurs as a larger number of cases (both early stage and late stage disease) are  
23 likely to be picked up in the first screening round when compared to later rounds. Thus it is  
24 desirable to analyse the results of several screening intervals in order to estimate the effectiveness  
25 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. But 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 a comparison of different screening policies but cannot give a reliable estimate of the difference between screening and no screening because their confounding factors can not be controlled{35}.

Often HTA does need to evaluate the evidence regarding the test characteristics like the 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 in comparing many different screening options varying in test combinations, screening intervals and treatment options incorporating alternative eligible populations, whereas 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 synthesize 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 from overdiagnosis and overtreatment caused by 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 RCTs should be considered for the assessment of health benefits of pharmaceuticals. Non-randomised intervention studies or observational studies can be considered where an RCT is not feasible or complementary data is presented to RCTs. If all of the studies concerning a technology have been performed under strict clinical trial conditions, no information on the benefit of the technology under routine conditions is available. This is often the case just after marketing authorisation. Generally, information on benefit under routine conditions may be collected in trials with a pragmatic approach (a trial setting that corresponds to usual circumstances of healthcare instead of a strict protocol-driven setting that is used in trials of an explanatory nature) or by observational studies. The results of pragmatic trials and country-specific observational studies are usually affected by local clinical practices. Consequently, the transferability and generalisability of the results may suffer and should be considered carefully. For more details see section 2.1 of the 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

## 1 Tools for critical appraisals

2 The effect of a technology in studies on clinical effectiveness should be estimated with little error.  
3 Errors are classified traditionally in either random or systematic. Systematic errors or biases  
4 describe the opposite of validity, while the opposite of random error is precision. Unbiased  
5 estimates are considered valid. The validity of a study is composed by the internal validity, which  
6 concerns inferences related to the study population, and the external validity or generalizability,  
7 which concerns inferences related to the target population outside the study.{38}

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

- 9 • the whole base of evidence by publication and reporting bias (see below Analyzing and synthesizing  
10 evidence. Biases, confounding factors, level of evidence)
- 11 • on individual study level
- 12 • for individual endpoints in a study

13 Sources of bias in studies designed to evaluate the effectiveness of a technology can relate to  
14 differences in patients assigned to intervention and control group, including differences in the  
15 selection process (selection bias); the unbalanced provision of care (performance bias); the methods  
16 of measuring or interpreting the outcomes (detection bias); or imbalances in patient drop-out  
17 (attrition bias {39, 40}). Bias may result from manufacturer involvement in a study. It is important to  
18 determine if any trials were funded through industry sponsorship. It is advisable to compare the  
19 results with and without sponsored trials included in the analysis.

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

28 Two assessors are recommended. Background of assessors should be reported, and the way they  
29 resolved disagreements. Results of the quality assessment of the original studies should be  
30 presented in a table or graphically. Individual quality items should be investigated as a potential  
31 source of heterogeneity.

## 32 ***Trials***

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

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

### 3 ***Observational studies***

4 Agreement on the methodological criteria for non-randomised trials and observational studies are  
5 considerably less well developed. However, a methodological HTA-report by John Deeks provides  
6 a good overview of available instruments to assess non-randomised intervention studies {47}{48-  
7 50} (Equator web site). More recently, ISPOR Task Forces are also creating checklists on relevance  
8 and credibility of observational studies which can be found at the ISPOR homepage  
9 ([www.ispor.org](http://www.ispor.org))

### 10 ***Modelling studies***

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

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

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

##### 19 **Direct trial evidence**

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

##### 24 **Linked evidence**

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

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

#### 34 **Quality assessment of test accuracy studies**

35 Quality assessment of diagnostic accuracy studies is not as straightforward as it is for interventions. It is  
36 hampered by poor reporting and the fact that so far there is less methodological and empirical evidence on

the importance of the different potential sources of bias. There are many different tools to assess the quality of diagnostic accuracy studies. The Cochrane handbook recommends QUADAS-2 tool..

### **Screening-specific content**

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

- People taking part in screening are usually healthier than those who do not (healthy screenee 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 by screening not because the patients actually live longer but because the diagnosis is known earlier and therefore for a longer period of time (lead-time bias) {35, 54}. The bias occurs e. g. when two tests are compared, and one test diagnoses the disease earlier, but there is no effect on the outcome of the disease. Then, it may 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 never progress to cause 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 are found to have had prostate cancer). Aside from issues with unnecessary treatment and risk of harms, overdiagnosis, by contributing disproportionately to early diagnosis of lethal conditions, has the effect of inflating survival statistics. {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.

See also shared methodologies in Appendix 3.

### **Analyzing and synthesizing evidence**

Ideally systematic reviews on randomized controlled trials (RCTs) are the basis of knowledge of effectiveness of an intervention. The principles on how to conduct a systematic review are nowadays widely agreed upon and most of the methodologies published by different organisations vary only in details (See Appendix 3).

### **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 unpublished studies and elective outcome reporting. A systematic review showed that reporting bias is 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 the individual studies, researchers attempt to capture the overall quality of the body of evidence. The concept of the GRADE Working Group captures the currently most comprehensive approach {13, 77}. Besides looking at the quality of the individual studies, they also include the consistency or heterogeneity of the results of all included studies and the directness of the comparisons (i.e. how directly does the identified literature address



the questions of our HTA-report regarding the population, the intervention and comparators and the selected endpoints, they comment on imprecision of the available data (number of total events and width of the confidence interval) and provide an estimate about the likelihood of the presence of reporting bias. Deficiencies in any of those considerations can lower the methodological quality of the entire body of evidence. On the other hand, the overall judgement about the methodological quality of the evidence can be raised in the presence of strong and plausible associations between intervention and outcome or an obvious dose-response gradient.

### ***Qualitative Syntheses and evidence tables***

A meaningful presentation of the study results is essential for an informative and transparent HTA report. A high degree of reliability and transparency are required for the transfer of HTA reports from one setting to another. Comprehensive and informative evidence tables about the methodology and content of the individual studies are the best guarantor for transparency and reliability. They should allow a judgement of the similarities and differences of the included studies and should provide the basis for the conclusions of 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 that could have an impact on the results). Although the items reported in each cell will always be driven by the questions of the review, 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 allow 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 researchers can provide only a descriptive summary of the data, it can nevertheless be very helpful to display the results in a forest plot, but omitting the summary.

Presenting a measure of precision for the estimate of the treatment effect (confidence interval) is needed for the interpretation of the 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 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 their results. While homo-/ heterogeneity in the clinical data is often a matter of judgement, there are statistical tests available to help assessing the presence of statistical heterogeneity {79} which should then be further explored and considered in the discussion. Pre-specified sensitivity



analyses based on clinical or methodological issues allow further exploration of the stability of the data. 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 judgement 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 to 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-analyzing test accuracy studies**

##### **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, and possible trade-off between sensitivity and specificity, and may show the 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, simple summary measures for sensitivity, specificity, or likelihood are adequate.

When pooling pairs of sensitivity and specificity, the statistical model used depends on the studies selected. A fixed effect model 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 weights individual studies based on the inverse variance of the accuracy or the number of participants. Random effects model 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.

##### **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 heterogeneity detected is needed, and it starts with examining of threshold effect. Threshold effect can be seen in 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 to examine the data further.

##### **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 allows assessment of their interdependence. Summary DOR (SDOR) of the test and a comparator test can be presented with 95 % CIs to compare differences in diagnostic performance. The area under SROC curve and its 95% confidence interval provides a global summary of overall test accuracy. The point on the curve where sensitivity equals specificity, the  $Q^*$  statistics, can also be used as a summary measure of the accuracy of the test. These summary measures can also be used to compare the accuracy of two test strategies. Software for diagnostic meta-analysis include Meta-Test, Meta-Disc, Stata and SAS.

#### **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 changes along the threshold. In such cases advanced methods for fitting the SROC is used. Advanced methods to pool are indicated if heterogeneity in the results can be attributed to known sources of variation (see above Chapter 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. Poor reporting of primary studies may though lead to biased estimates. The two main advanced 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}. Model is infrequently used, probably due to the 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 researches either impute or adjust for the missing data {31}. If 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 design, the authors of a Core HTA should be careful with the results.

Sometimes the reference standard is known to be imperfect: i.e. it does not distinguish the diseased from healthy quite 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 of 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 imperfect reference standard is a sensitivity analysis to demonstrate the effect of imperfect reference test to the accuracy of the index test.

#### **Assessing heterogeneity across test accuracy studies**

Heterogeneity in test accuracy across studies is very common. Any differences in the results of 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 are

1. Chance
2. Different test threshold

3. Different study designs, methods, biases: 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 can not 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}.

Methods to test for heterogeneity {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 are available, plot the paired sensitivity and 1-specificity results for each study on the ROC plane to detect heterogeneity and identify outliers. A small number of studies will limit the power of regression to detect 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. Regression model is 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 in the model the slope  $b$  (estimated regression coefficient) is not statistically significant and approaches zero, 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 using the device and analysing the test results

### **Screening-specific content**

For diagnostic and treatment interventions in patients already showing symptoms or being ill there is a trade-off between benefits and harms of diagnostics and treatment on the individual level. Because screening is usually done in asymptomatic people there is an additional trade-off on the population level between healthy people who will not benefit from screening but can be harmed by a loss in quality of life by false positive screening results, potential over-diagnosis and over-treatment and 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, adverse effects from a treatment, unnecessary treatment due to overdiagnosis and overtreatment caused by screening programs etc.). Therefore, systematic evidence assessments in the effectiveness domain should include both the evidence assessment of patient-relevant outcomes regarding benefits and harms and a judgement on the benefit-harm balance. Currently, different approaches

are used to inform about the benefit-harm balance. In the GRADE methodology the evidence on benefits and harms of those outcomes identified as critical are used to judge in an expert consensus on the benefit-harm balance. {17}

Balancing benefit and harms contains explicit or implicit value judgements. 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) clarifying (e.g. in footnotes) the reasons for up-/down-rating.
  - Another option is a clear distinction between the risk of bias (internal validity) and aspects of generalizability (i.e. directness, external validity). If all trials concerning a technology have been performed under ideal conditions one 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 wouldn't work in specific circumstances.
  - For the assessment of the risk of bias, usually 2 categories (low and high) are used (according to the Cochrane methodology).
- Step 2: Interpreting the clinical relevance of the findings:
  - Statistical significance is an important criterion quantifying random error, but – numerically small differences can be statistically significant, but clinically meaningless;. 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'. But 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 other threshold values (alpha-levels) than 0.05 might be chosen.
  - Considering the relevance of the outcomes for clinical decision making (distinguishing between a critical and an important outcome as done when formulating the question)
  - Identify knowledge gaps by comparing the research questions (including the predefined outcome) with the available evidence.

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 randomized 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.

The issues described in the assessment elements may be answered through primary research if so needed. Describing the design of clinical trials in detail is beyond the scope of this document; whenever possible, however, clinical trials must be randomized, head to head comparisons against the gold standard therapy. The primary endpoint should be a clinically relevant variable or if this is not possible, a validated surrogate variable for a clinically relevant variable.

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

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

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

### 11 ***Analyzing applicability of evidence***

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

19 To allow transfer of data across countries, HTAs have to be sufficiently transparent and distinguish  
20 between evidence ("facts") and judgements (including values and preferences). Value judgements  
21 and preferences (of individuals or of health care systems) have to be labelled as such as well as the  
22 anticipated influence in transferring the result from one health care system to another. There will be  
23 situations where only the body of evidence ["evidence summary"] of an HTA can be used, but the  
24 data need to be interpreted in the context of the health care system and the prevailing values. For  
25 this reason, reviewers have flagged context-sensitive outcomes (=issues) when formulating the  
26 questions and have documented the underlying values that were driving certain decisions.

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

28 Pair of sensitivity and specificity is a general measure of test performance. The numbers (0.0–1.0) per se  
29 are not very informative in determining whether the test performs well. The intended use of the  
30 technology determines the requirements for the test accuracy. If sensitivity is sufficiently high, a negative  
31 test result rules out the disease. High sensitivity is particularly important if the penalty for missing a disease  
32 is high. Sufficiently high specificity rules in the disease. High specificity is particularly important if a false  
33 positive result can harm the patient. Positive and negative predictive values are clinically informative  
34 measures of the accuracy of a diagnostic test, but must be considered in relation to the prevalence of the  
35 disease.

36 Summary likelihood ratios can be estimated from the pooled estimates of sensitivity and specificity.  
37 Likelihood ratio tells how many times more likely the disease is in patients with that test result compared to  
38 those without the disease. A likelihood ratio 1 indicates that the test does not provide any useful diagnostic  
39 information. Positive likelihood ratios more than 10 and negative likelihood ratios less than 0.1 can provide  
40 convincing diagnostic information. Some guidelines suggest that positive likelihood ratios more than 5, and  
41 negative likelihood ratios less than 0.2 can provide strong diagnostic evidence. However, the interpretation

- 1 depends on the context and prevalence of the condition. Likelihood ratios usually have to be more than 10  
2 for a test to be useful {28}, although this is very seldom the case.
- 3 Diagnostic odds ratio shows the association between a dichotomous test result and the diagnosis. If the  
4 diagnostic odds ratio (DOR) is 1 then the test does not provide any useful information. The size of the DOR  
5 greater than 1 reflects the strength of the test to discriminate between the presence and absence of  
6 disease. A DOR of 100 provides convincing evidence of the presence or absence of disease and correspond  
7 to a positive likelihood ratio of 10 and a negative LR of 0.1. It is often 50-90 but can be even thousand, and  
8 it should be over 80 in a good test. A DOR less than 1 indicates that the test identifies more positives  
9 among the non diseased than the diseased. Diagnostic odds ratio is useful summary measure for meta-  
10 analysis but it does not provide information that can be directly applied to clinical decisions. {28}
- 11 Variation in results by cut-off points, prevalence or any other covariate and characteristics of the SROC  
12 curve should be explained. Area under SROC curve can be used to compare accuracy of two test strategies.  
13 The test whose SROC curve encloses the largest area is the most accurate.
- 14 Additional methods of expressing test accuracy beyond sensitivity and specificity, e.g. likelihood ratios or  
15 diagnostic odds ratios, are preferred. Explaining how many patients will be missed (false negative rate) and  
16 how many treated unnecessarily (false positive rate) using certain cut-off point in a population with certain  
17 disease prevalence, may be illustrative.
- 18

## 1 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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	1
	Screening Technologies (2.1) - PUBLIC DRAFT	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. Overall mortality and disease-specific mortality are distinguished. Overall mortality refers to all-cause mortality. It is expressed either as mortality rates (incidence in given population, at given time point and usually risk standardised), or survival (number of people alive for a given period after an intervention). Disease-specific mortality is a proportion of the all-cause mortality. It should be noted that even if a given treatment reduces one type of death, it could increase the risk of dying from another cause, to an equal or greater extent. Disease-specific mortality is typically presented as rates and as age- and risk- adjusted measures such as hazard ratio. It is a frequently used endpoint in screening trials, where it is considered to be subject to bias.</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>Consider separately absolute mortality (compared to placebo or waiting list) and mortality relative to the comparator. See also Methodological guideline for REA of pharmaceuticals: Endpoints used for relative effectiveness assessment of pharmaceuticals, clinical endpoints <a href="http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf">http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf</a></p> <p>Supplement with relevant data if differences can be expected for specific subgroups.</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</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 (2.1) - PUBLIC DRAFT</b></p> <p>See also Methodological guideline for REA of pharmaceuticals: Endpoints used for relative effectiveness assessment of pharmaceuticals, clinical endpoints  <a href="http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf">http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf</a></p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</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>
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Systematic reviews of trials, trials, both placebo- controlled and with active control. In the absence of head to head trials, studies with indirect comparison (see Methodological guideline for REA of pharmaceuticals: Direct and indirect comparison, <a href="http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Direct%20and%20indirect%20comparisons.pdf">http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Direct%20and%20indirect%20comparisons.pdf</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 (2.1) - PUBLIC DRAFT</b></p> <p>Submission file, SPC, EPARs,</p>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Hochman 2011, Black 2002</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>E0005</p> <p>F0001</p>
<b>Sequential relations</b>	



D0003 Assessment element card						
Issue: What is the effect of the technology on the mortality due to causes other than the target disease?						
Topic: Mortality						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	2
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	2
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	2
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	2
Clarification	<p><b>Common to all used applications</b></p> <p>This issue includes all unintended, either positive or negative effects of the technology on mortality. There may be e.g. decrease of mortality of another disease observed or suspected; or increased mortality due to accidents or hazardous medical interventions after false positive or incidental test results.</p> <p>Supplement with relevant data if differences can be expected for specific subgroups.</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>In diagnostic and screening technologies this issue refers to the effect of the test-treatment-chain,</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>In diagnostic and screening technologies this issue refers to the effect of the test-treatment-chain,</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Systematic reviews of trials, trials, both placebo- controlled and with active control. In the absence of head to head trials, studies with indirect comparison (see Methodological guideline for REA of pharmaceuticals: Direct and indirect comparison, <a href="http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Direct%20and%20indirect%20comparisons.pdf">http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Direct%20and%20indirect%20comparisons.pdf</a>). If these are not available, non-controlled studies and respective systematic reviews. Health care register data. Modelling studies.</p>					

	<p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>.</p> <p><b>Specific to Pharmaceuticals (2.1) - PUBLIC DRAFT</b></p> <p>Submission file, SPC, EPARs,</p>
<b>References</b>	
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>C0008</p> <p>E0005</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>C0006</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>C0005</p> <p><b>Specific to Pharmaceuticals (2.1) - PUBLIC DRAFT</b></p> <p>C0005</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>C0006</p>
<b>Sequential relations</b>	

1

2

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 (2.1) - PUBLIC DRAFT	No				
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	3
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	3
	Screening Technologies (2.1) - PUBLIC DRAFT	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: Endpoints used for relative effectiveness assessment of pharmaceuticals, clinical endpoints  <a href="http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf">http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf</a></p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Trials, observational studies</p> <p><b>Specific to Pharmaceuticals (2.1) - PUBLIC DRAFT</b></p> <p>„SPC and EPAR.</p>					
References						
Content relations	<b>Common to all used applications</b>					

	H0005 E0005
<b>Sequential relations</b>	

1

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 (2.1) - PUBLIC DRAFT	No				
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Report here outcomes such as complete cure, progression-free survival, time-to-event (next stage of disease, relapse). Describe here the duration of treatment effect on symptoms and findings: permanent, short term, long term, intermittent, undulating. Report the results both in absolute terms and relative to the comparator. See also Methodological guideline for REA of pharmaceuticals: Endpoints used for relative effectiveness assessment of pharmaceuticals, clinical endpoints  <a href="http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf">http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf</a></p> <p>Supplement with relevant data if differences can be expected for specific subgroups.</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Trials, prognostic studies</p> <p><b>Specific to Pharmaceuticals (2.1) - PUBLIC DRAFT</b></p>					

	, SPC and EPAR.
<b>References</b>	
<b>Content relations</b>	<b>Common to all used applications</b>  E0005
<b>Sequential relations</b>	

1

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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	3
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	No				
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	5
<b>Clarification</b>	<b>Common to all used applications</b>  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. E.g. treatment may work differently in screening-identified cases than in cases that are diagnosed at regular physician's appointment					
<b>Methodology and sources</b>	<b>Common to all used applications</b>  Trials, observational studies, accuracy studies					

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

1

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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	No				
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
	Screening Technologies (2.1) - PUBLIC DRAFT	No				
<b>Clarification</b>	<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 thus improved outcomes.</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Accuracy and other observational studies, trials, qualitative research</p>					
<b>References</b>						
<b>Content relations</b>	<b>Common to all used applications</b>					

	H0005
<b>Sequential relations</b>	

1

<p><b>D0024 Assessment element card</b></p> <p><b>Issue: Is there an effective treatment for the condition the test is detecting?</b></p> <p><b>Topic: Test-treatment chain</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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	5
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	No				
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	6
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>The effectiveness or clinical utility of a test usually requires that an effective treatment for the target condition exists and is available to the patients.</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>F0001</p>					
<b>Sequential relations</b>						

2

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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	6
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	No				
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	7
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 change sufficiently the pre-test probability 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, users' ability to make a correct diagnosis may depend on their knowledge and 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, Tugwell PX, Feeny DH, Haynes RB, Drummond M. A framework for clinical evaluation of diagnostic technologies. CMAJ 1986 Mar 15;134(6):587-594.</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>G0001</p>					
Sequential relations						



D0010 Assessment element card						
Issue: How does the technology modify the need for hospitalization?						
Topic: Change-in management						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	9
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	5
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	5
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	10
Clarification	<b>Common to all used applications</b>  Consider also changes at different levels of care e.g. ward instead of intensive care.					
Methodology and sources	<b>Common to all used applications</b>  Trials, observational studies					
References						
Content relations	<b>Common to all used applications</b>  E0001  G0001					
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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	7
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	No				
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	8
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, ability and attitude to decision making. Management decisions mean 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, Tugwell PX, Feeny DH, Haynes RB, Drummond M. A framework for clinical evaluation of diagnostic technologies. CMAJ 1986 Mar 15;134(6):587-594.</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>G0001, G0008, G0009</p>					
Sequential relations						

D0023 Assessment element card						
Issue: How does the technology modify the need for other technologies and use of resources?						
Topic: Change-in management						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	10
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	6
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	6
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	11
Clarification	<p><b>Common to all used applications</b></p> <p>New (less invasive) interventions can reduce the need for surgical interventions. Some treatments require ongoing monitoring and healthcare visits including hospitalisation.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Screening tests may cause further diagnostic testing and different treatment due to detection of 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 utilization of resources. Observational studies, statistics</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>B0013</p> <p>E0001</p> <p>F0003</p> <p>G0001, G0003, G0004, G0007</p>					

<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>G0001,G0003,G0007</p>
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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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	8
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	No				
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	9
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Management decisions mean both testing and treatment decisions. Notice issue C0006 which deals also with incidental findings.</p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Trials, accuracy studies</p>					
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Guyatt GH, Tugwell PX, Feeny DH, Haynes RB, Drummond M. A framework for clinical evaluation of diagnostic technologies. CMAJ 1986 Mar 15;134(6):587-594.</p>					
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>F0003</p>					

<b>Sequential relations</b>	
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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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	11
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	7
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	7
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	12
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, 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 (2.1) - PUBLIC DRAFT</b></p> <p>See also Methodological guideline for REA of pharmaceuticals: Endpoints used for relative effectiveness assessment of pharmaceuticals, clinical endpoints  <a href="http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf">http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf</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 (2.1) - PUBLIC DRAFT</b></p> <p>SPC and EPAR..</p>					

<b>References</b>	<b>Common to all used applications</b>  ICF <a href="http://apps.who.int/classifications/icfbrowser">http://apps.who.int/classifications/icfbrowser</a>
<b>Content relations</b>	<b>Common to all used applications</b>  H0005  E0005  F0101
<b>Sequential relations</b>	

1

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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	12
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	8
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	8
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	13
<b>Clarification</b>	<b>Common to all used applications</b>  Describe the effects of the intervention on sick leave, absenteeism, presenteeism, return-to-work, retirement and other relevant outcomes describing working ability					
<b>Methodology and sources</b>	<b>Common to all used applications</b>  Trials and other studies with return-to-work or work ability outcomes reported.					

<b>References</b>	<p><b>Common to all used applications</b></p> <p>Fit for Work Europe website. Available at: <a href="http://www.fitforworkeurope.eu">www.fitforworkeurope.eu</a></p> <p>European Commission (2007). Together for Health: A Strategic Approach for the EU 2008-2013. 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>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>H0005</p> <p>E0001</p>
<b>Sequential relations</b>	

1

<p><b>D0015 Assessment element card</b></p> <p><b>Issue: What is the effect of the technology on return to previous living conditions?</b></p> <p><b>Topic: Function</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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	13
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	9
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	9
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	14
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Discharge to the living conditions in which patients lived before admission is one of the most important treatment goals particularly for elderly patients. Implications for family members and carers should be considered too.</p>					
<b>Methodology and sources</b>	<b>Common to all used applications</b>					

	<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-centered models, such as the Program of All-Inclusive Care for the Elderly (PACE).</p>
<b>References</b>	
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>H0005</p>
<b>Sequential relations</b>	

1

<p><b>D0016 Assessment element card</b></p> <p><b>Issue: How does the use of the technology affect activities of daily living?</b></p> <p><b>Topic: Function</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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	14
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	10
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	10
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	15
<b>Clarification</b>	<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, comprising those activities or tasks that people undertake routinely in their every day life. The activities can be subdivided into personal care and domestic and community activities. Report the results both in absolute terms and relative to the comparator. For further information see guideline Health-related quality of life and utility measures <a href="http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Health-related%20quality%20of%20life.pdf">http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Health-related%20quality%20of%20life.pdf</a>, and guideline: Endpoints used for relative effectiveness assessment of pharmaceuticals, clinical endpoints</p>					



	<a href="http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf">http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf</a> Supplement with relevant data if differences can be expected for specific subgroups.
<b>Methodology and sources</b>	<b>Common to all used applications</b> Trials and observational studies reporting ADL outcomes <b>Specific to Pharmaceuticals (2.1) - PUBLIC DRAFT</b> , SPC and EPAR
<b>References</b>	
<b>Content relations</b>	<b>Common to all used applications</b> H0005
<b>Sequential relations</b>	

1

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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	15
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	11
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	11
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	16
<b>Clarification</b>	<b>Common to all used applications</b> Health related quality of life (HRQL) is typically measured with self- or interviewer-					

	<p>administered questionnaires to measure 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). Two basic approaches to quality-of-life measurement are available: generic instruments that provide a summary of HRQL; and specific instruments that focus on problems associated with single disease states, patient groups, or areas of function. Generic instruments include health profiles and instruments that generate health utilities. Each approach has its strengths and weaknesses and may be suitable for different circumstances. See also •Methodological guideline for REA of pharmaceuticals: Health-related quality of life and utility measures. <a href="http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Health-related%20quality%20of%20life.pdf">http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Health-related%20quality%20of%20life.pdf</a></p> <p>Supplement with relevant data if differences can be expected for specific subgroups.</p>
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Trials, observational and qualitative studies</p> <p><b>Specific to Pharmaceuticals (2.1) - PUBLIC DRAFT</b></p> <p>, SPC and EPAR.</p>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>EMA 2005, FDA 2009, Chassany 2002, Terwee 2007, Revicki 2008, Puhon 2006</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>H0005</p> <p>E0005</p>
<b>Sequential relations</b>	

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2

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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	16
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	12
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	12
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	17
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 to measure 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). Two basic approaches to quality-of-life measurement are available: generic instruments that provide a summary of HRQL; and 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 •Methodological guideline for REA of pharmaceuticals: Health-related quality of life. <a href="http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Health-related%20quality%20of%20life.pdf">http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Health-related%20quality%20of%20life.pdf</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 (2.1) - PUBLIC DRAFT</b></p> <p>SPC and EPAR.</p>					
References	<p><b>Common to all used applications</b></p>					

	EMA 2005, FDA 2009, Chassany 2002, Terwee 2007, Revicki 2008, Puhon 2006
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>H0005</p> <p>E0005</p>
<b>Sequential relations</b>	

1

<p><b>D0017 Assessment element card</b></p> <p><b>Issue: Was the use of the technology worthwhile?</b></p> <p><b>Topic: Patient satisfaction</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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	18
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	13
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Optional	None	No	13
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	19
<b>Clarification</b>	<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. See also Methodological guideline for REA of pharmaceuticals: Endpoints used for relative effectiveness assessment of pharmaceuticals, clinical endpoints <a href="http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf">http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf</a></p>					
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Surveys, qualitative research, observational studies, trials</p>					
<b>References</b>						

<b>Content relations</b>	<b>Common to all used applications</b>  H0006  F0001, F0011
<b>Sequential relations</b>	<b>Common to all used applications</b>  H0006

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<p style="text-align: center;"><b>D0030 Assessment element card</b></p> <p style="text-align: center;">Issue: Does the knowledge of the test result affect the patient's non-health-related quality of life?</p> <p style="text-align: center;">Topic: Quality of life</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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	17
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	No				
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	18
<b>Clarification</b>	<b>Common to all used applications</b>  Test result may alleviate or trigger or worsen symptoms as well as improve or worsen the quality of life, although there is no effectiveness to the primary outcome.					
<b>Methodology and sources</b>	<b>Common to all used applications</b>  Qualitative research, observational studies, trials					
<b>References</b>						

<b>Content relations</b>	<b>Common to all used applications</b>  H0005, H0006  F0001, F0003
<b>Sequential relations</b>	<b>Common to all used applications</b>  H0006

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D0018 Assessment element card  Issue: Is the patient willing to use the technology again?  Topic: Patient satisfaction						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	19
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	14
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	20
<b>Clarification</b>	<b>Common to all used applications</b>  Differences in acceptability may predict the overall uptake of the technology and would impact on the overall effectiveness.					
<b>Methodology and sources</b>	<b>Common to all used applications</b>  Qualitative research, observational studies, trials					
<b>References</b>						
<b>Content relations</b>	<b>Common to all used applications</b>					

	H0006
<b>Sequential relations</b>	<b>Common to all used applications</b>  H0006

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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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	20
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	15
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	21
Clarification	<b>Common to all used applications</b>  What are the consequences of false positive, false negative and incidental findings generated by using the technology?  False negative test results (Type II error) identify sick people incorrectly as healthy with the possible consequence of incorrectly rejected or delayed treatment. Volume of false negative test results can be estimated to be 1 - sensitivity of the test.  False positive test results (Type I error) identify healthy people incorrectly as sick with the possible consequence of overtreatment. 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.  <b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b>  In screening programmes one should consider separately the false negative screening test results and the subsequent false negative diagnostic test results.					

<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> <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, Schwartz L, Woloshin S. Overdiagnosed: Making people sick in pursuit of health, Beacon Press, Boston, 2011</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>Effectiveness domain D0028, D0027</p> <p>D0009</p> <p>D0003</p> <p>B0001</p> <p>D0003</p> <p>E0001</p> <p>F0001</p> <p>G0001, G0100</p>
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>B0001</p>
<b>Other domains</b>	Also in: Safety

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2



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 (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	21
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	No				
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	22
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 (2.1) - PUBLIC DRAFT</b></p> <p>In screening programmes one should consider separately 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 (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	22
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	No				
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	23
Clarification	<b>Common to all used applications</b>  Consider also how does the technology compare to other development stages of the same technology?					
Methodology and sources	<b>Common to all used applications</b>  Accuracy studies					
References						
Content relations						
Sequential relations						

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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	30
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	16
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	14
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	31
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 even qualitatively a balanced and meaningful presentation is difficult to reach.</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) 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 (2.1) - PUBLIC DRAFT</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 true positive test result in a prior diagnostic or screening test.</p> <p><b>Specific to Pharmaceuticals (2.1) - PUBLIC DRAFT</b></p> <p>See Template 7 in the the HTA Core Model for Rapid Relative Effectiveness Assessment of pharmaceuticals <a href="http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Model%20for%20Rapid%20REA%20of%20pharmaceuticals_final_20130311_reduced.pdf">http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Model%20for%20Rapid%20REA%20of%20pharmaceuticals_final_20130311_reduced.pdf</a></p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</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 true positive test result in a prior diagnostic or screening test.</p>					

<b>Methodology and sources</b>	<b>Common to all used applications</b>  Trials, observational studies, modelling studies
<b>References</b>	
<b>Content relations</b>	<b>Common to all used applications</b>  A0007, A0011, C0008, C0003, C0004, C0005, C0006, C0007, C0061, E0005, F0001, F0011
<b>Sequential relations</b>	<b>Common to all used applications</b>  A0007, A0011, C0008, C0003, C0004, C0005, C0006, C0007, C0061,

1

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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	23
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	No				
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
Clarification	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	24
	<b>Common to all used applications</b>  Consider also the situation when there is no proper reference standard.					
<b>Methodology and sources</b>	<b>Common to all used applications</b>					

	Accuracy studies
<b>References</b>	<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>
<b>Content relations</b>	
<b>Sequential relations</b>	

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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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	24
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	No				
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	25
Clarification	<p><b>Common to all used applications</b></p> <p>Discuss what could be an estimate for 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 (2.1) - PUBLIC DRAFT</b></p> <p>In screening programs one should consider separately the screening test and the subsequent diagnostic tests.</p>					

<b>Methodology and sources</b>	<b>Common to all used applications</b>  Descriptive ethical literature, expert advice, prevalence data, modelling studies, calculations
<b>References</b>	
<b>Content relations</b>	<b>Common to all used applications</b>  F0017
<b>Sequential relations</b>	

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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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	25
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	No				
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	26
<b>Clarification</b>	<b>Common to all used applications</b>  Sensitivity and specificity vary according to the threshold value. 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.  <b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b>  S In screening programs one should consider separately the screening test and the subsequent diagnostic tests.					

<b>Methodology and sources</b>	<b>Common to all used applications</b>  Screening studies with varying thresholds, accuracy studies with varying thresholds, modelling studies
<b>References</b>	
<b>Content relations</b>	<b>Common to all used applications</b>  F0017
<b>Sequential relations</b>	

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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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	26
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	No				
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	27
<b>Clarification</b>	<b>Common to all used applications</b>  This question is relevant in e.g triage situation where the aim of the test is to rule out a severe condition in patients to avoid further testing which may be more harmful and expensive.  <b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b>  When assessing screening programs one should consider here the combination of the screening test and the subsequent diagnostic tests.					

<b>Methodology and sources</b>	<b>Common to all used applications</b>  Accuracy studies, modelling studies
<b>References</b>	
<b>Content relations</b>	<b>Common to all used applications</b>  C0008  F0017
<b>Sequential relations</b>	

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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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	27
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	No				
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	28
Clarification	<p><b>Common to all used applications</b></p> <p>How do 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, optimal age range for a screening programme and 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>					

D1008 Assessment element card						
Issue: What is known about the intra- and inter-observer variation in test interpretation?						
Topic: Test accuracy						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	28
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	No				
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	29
Clarification	<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>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Accuracy studies, trials, observational studies</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Accuracy studies, trials, observational studies</p>					
References						
Content relations						
Sequential relations						

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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	29
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	No				
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	30
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 (2.1) - PUBLIC DRAFT</b></p> <p>In screening programs one should consider separately 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, Irwig L, Simes RJ. When is measuring sensitivity and specificity sufficient to evaluate a diagnostic test, and when do we need randomized trials? Ann.Intern.Med. 2006 Jun 6;144(11):850-855.</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>C0008</p> <p>F0001</p>					

<b>Sequential relations</b>	<b>Common to all used applications</b>  C0008
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7

## 1 Appendices

2 **NOTE:** In the first published version of HTA Core Model 2.0 this chapter contained a second time  
3 appendices 1 and 3 that are actually appendices to the whole Model. This was a technical error and these  
4 redundant copies have been removed in this document. See end of document for the correct appendices.

5

6

## 1 ***Costs and economic evaluation***

### 2 **Description**

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

4 The main aim of the costs and economic evaluation domain within HTA is to provide information  
5 about the relative costs and ‘cost effectiveness’ of health-care technologies under assessment.  
6 Economic evaluation has been defined as a comparative analysis of alternative courses of action in  
7 terms of both their costs and consequences {1}. The aim of this domain is to inform value-for-  
8 money judgements about health technologies {2} and is intended to summarise the economic  
9 evidence available when allocating resources to emerging, new and existing health technologies  
10 {3}.

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

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

31 Methodological guidelines for producing the information will be developed in another work  
32 package of EUnetHTA Joint Action 2, further acknowledging the possibility of variations in  
33 requirements for economic evaluations across countries or jurisdictions.

34 Table 1 lists the topics and issues included in this domain. The topics and issues are limited to items  
35 that are important for all health-care settings and that are required to allow other jurisdictions to  
36 assess the transferability of the information provided in the costs and economic evaluation domain  
37 to their own setting. This is in line with one of the main objectives of the HTA Core Model, being  
38 to allow agencies to use core HTA information produced by other agencies.

39

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

Topic	Issue	Assessment element ID
Resource utilization	What types of resources are used when delivering the assessed technology and its comparators (resource-use identification)?	E0001
Resource utilization	What amounts of resources are used when delivering the assessed technology and its comparators (resource-use measurement)?	E0002
Resource utilization	What were the measured and/or estimated costs of the assessed technology and its comparator(s) (resource-use valuation)?	E0009
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)?	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)	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 health-care 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

1 time-consuming and demanding, for instance, in terms of the need for multidisciplinary input in the  
2 form of statistical, modelling and clinical expertise. For this reason, it would be advantageous to  
3 spread the workload between organisations and jurisdictions. On the other hand, the  
4 recommendations, methods and data requirements for estimating, for example: baseline risk;  
5 treatment effect; resource utilisation; health-state measures; and costs differ across populations or  
6 health-care systems (see, e.g., {7} and {8}). Such differences lead to different evidence being used  
7 as inputs to decisions made about reimbursement and access for new health technologies. Indeed,  
8 having the same clinical and economic evidence will not necessarily result in the same decision  
9 across, e.g., jurisdictions, because of national and regional differences in decision-making processes  
10 and value judgements (see, e.g., {9}).

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

## 21 Relations to other domains

22 The **Costs and economic evaluation domain** should collaborate with the **Clinical effectiveness**  
23 and **Safety** domains in order to receive timely and appropriate information on efficacy or  
24 effectiveness and to ensure that the outcome measures considered appropriate for the economic  
25 evaluation are also included in these domains. However, **Costs and economic evaluation** may also  
26 benefit from information gathered by the **Health problem and current use**, and **Social** domains in  
27 order to specify appropriate populations, interventions, comparisons and outcomes for the “Costs  
28 and economic evaluation” -research questions. In addition, the work undertaken in the **Costs and**  
29 **economic evaluation** domain is likely to be of importance for organisational considerations, too.  
30 The production of information on the impact of health technologies on the budgets of different  
31 stakeholders should be shared with the **Organisational aspects** domain. A dialogue between  
32 research on the **Costs and Economic Evaluation** and **Organisational aspects** domains should be  
33 initiated at an early stage, so that Costs and Economic Evaluation domain -researchers understand  
34 the organisational context and can help to provide the Organisational aspects domain researchers  
35 with any relevant information. There is also a possibility of overlapping work, especially with the  
36 **Clinical effectiveness** and **Safety** domains, and co-operation is likely to be needed even when  
37 drawing up the domain-specific protocol.

38 Depending on the technology, the **Ethical** and **Social** domains may provide important information  
39 in helping to decide the appropriateness of the type or perspective of study undertaken within the  
40 **Costs and economic evaluation** domain. For instance, the research in the **Ethical** domain on the  
41 benefits and harms of the technology for patients or any other stakeholders (relatives, other patients,  
42 organisations, commercial entities, society, etc.) should be reflected upon, including any other  
43 hidden or unintended consequences of the technology and its applications for the whole range of  
44 stakeholders. In a similar manner, the **Social** domain may investigate the value of the technology in  
45 terms of return to employment, e.g., seen from the view of the patient; a wage rather than pension,



for instance, may have a substantial impact on an individual or family. **Social** domain considerations increasingly fall within the scope of some cost estimates and economic evaluations, if they attempt to encompass wider outcomes.

The **Costs and economic evaluation** may also be related to the **Legal** 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 we make 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, we set out some commonly-used approaches when conducting research on costs and economic evaluation.

## **Process for answering research questions**

Analysis of costs and economic evaluation normally starts by an initial scoping and structuring of 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 **Analyzing 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 searching for information 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, health-care systems, clinical guidelines, resource use, and time horizon, differ significantly {12}



1 (See section **Transferability of evidence concerning costs and economic evaluation** for more  
2 details).

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

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

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

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

17 It is theoretically and practically possible to conduct meta-analyses of economic evaluations.  
18 However, their use is not widespread, as the heterogeneity which exists between studies would  
19 often demand major adjustment. Indeed, such adjustments are often not either possible or practical  
20 {14}.

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

22 Various data sources are usually used in order to populate an economic model with appropriate  
23 structures and parameters. These include, for example, RCTs; observational studies; administrative-  
24 record databases; disease registers; and expert opinion. Typically, at least the evidence concerning  
25 the health effects and transition probabilities of the technologies under assessment can be identified  
26 through systematic literature review. The methods used in systematic reviews of health effects have  
27 been described in the **Safety** and **Clinical effectiveness** domains.

#### 28 **Databases and search strategies**

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

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

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

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

1 Five main types of economic evaluation can contribute to HTA: cost-effectiveness analysis (CEA),  
2 cost-utility analysis (CUA), cost-consequences analysis (CCA), cost-benefit analysis (CBA), and  
3 cost-minimisation analysis (CMA). However, it is known that these terms are used in various ways  
4 by different authors and do not always accurately describe the nature of published studies {1}.

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

11 **Cost-effectiveness analysis** (CEA) is traditionally associated with the economic concept of  
12 technical efficiency, CEA compares the costs and effects of at least two alternative technologies.  
13 The effects of the different technologies are usually measured using unidimensional final (e.g., life-  
14 years gained) or surrogate outcomes (e.g., progression-free survival), providing information on the  
15 ‘greatest effect for a given cost’, or alternatively, one that achieves a ‘given effect at minimum cost’  
16 {15}. One potential disadvantage of CEA is that, because the different disease areas use different  
17 natural units (or metrics) to measure outcomes, the results are not comparable between disease areas  
18 in the same way as they are in cost-utility analysis (CUA). The results of such analysis are generally  
19 expressed in the form of an incremental cost-effectiveness ratio (ICER). An ICER represents the  
20 estimated difference in costs between the comparators divided by the estimated difference in effect  
21 between the comparators. In an example where the effects of the comparators are measured in life  
22 years, the estimated ICER could be reported as the cost per life-year gained. One difficulty is that  
23 the measure of effectiveness used must be appropriate and common to the treatments being  
24 compared {1}. In addition, CEA, in the form of CUA, is also widely associated with the economic  
25 concept of allocative efficiency, through the production of information which directly relates to the  
26 economic opportunity costs of technologies.

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

37 **Cost-consequences analysis** (CCA) examines costs and consequences, without the necessity of  
38 focussing on a single consequence and without combining disparate consequences into a single,  
39 commensurable measure (see, e.g., {15}, {16} and {17}). It has been classed both as a variant of  
40 CEA {1} and as a balance sheet approach to CBA {4}. It can be usefully used to enhance reporting  
41 transparency {18} and it can be especially useful when the outcomes are not adequately measured  
42 using, say, generic HRQoL measures {19}, despite its known limitations {20}. This approach may  
43 be preferred to CEA or CUA by policy makers when multiple consequences are to be weighed  
44 together simultaneously. In this situation CUA and CEA can be considered to be inappropriate, as  
45 they may conceal important information through the calculation of a single ratio and, therefore, may

not allow to 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 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, one main reason for this being 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 health-care resources. BIA, on the other hand, estimates the financial and organisational consequences of adopting a new technology in health care without directly taking health consequences into account. In the HTA Core Model, BIA is to be shared between the Organisational aspects domain and the Costs and economic evaluation 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 health-care systems, resource utilisation and costs will generally limit the transferability of BIA.

#### **Model-based economic evaluation**

As 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, considering 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}.

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 simulation, 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 area of health-care decision making. 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}.

The requirements for modelling are different in different jurisdictions or health-care 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 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. Often model parameters would need to be changed in order to better represent the population, jurisdiction, or health-care 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’. 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 providing 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 will generally 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, 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 outcome(s) of an economic evaluation 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 that 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 an 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, or a so-called ‘ICER threshold’. If one main aim of a health system is to maximize 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 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 recognized that a single ICER threshold value that fits all decisions for any decision-maker, does not exist. For some decision-making authorities, the ICER threshold may vary between technologies or diseases, depending on 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 of the decision maker, an ICER threshold value approach may offer little relevant information. Even if this is the case, the impact of an technology on the separate components of the ICER, such as life expectancy, health-related quality of life and health-care expenditures (e.g., through Budget Impact Analysis), may be of prime importance. The outcomes from the **Costs and economic evaluation** domain will therefore reflect the context in which the evaluation is undertaken.

## Tools for critical appraisals

Several published guidelines and check-lists for critical appraisal of economic evaluations are available {50}. These guidelines and check-lists 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 check-lists 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 check-list developed to assess the quality of decision-analytic models used in economic evaluation is available {53}.

These guidelines and check-lists are typically used for obtaining an overview of completeness of reporting and methodological quality. However, when undertaking a critical appraisal of economic evaluations, a more detailed descriptive assessment is often required. Compared to the use of check-list a more detailed descriptive approach enables assessment of the implications of the strengths and weaknesses of the analyses 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.

## Analyzing and synthesizing evidence

In this section, **Analyzing and synthesizing evidence**, we describe 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, we will provide links to (or indicate) other useful material under the subheading of **Tools**. In the section that follows this one, **Reporting and interpreting**, we then provide a common reporting structure for analyses of costs and economic evaluation.

### ***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 its associated recommended methodology. 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 a reference case is often defined in local guidelines, their content may vary substantially between settings, jurisdictions or health-care systems. Therefore, in the study frame presented below, we list the elements that are usually included in a reference case. For any particular economic evaluation, a ‘base case’ would be 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 that are 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	Preferred measure(s) of health effects that are to be used in the analysis or analyses (e.g., QALY, LYG).  Preferred source of data for measurement of health-related quality of life, if applicable.  Source of preference data for valuation of health-related quality of life, if applicable.
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.

## 1 Target population

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

8 The target population should be chosen to represent the characteristics of the patient population or  
9 populations in the jurisdiction(s) or the health-care setting the economic evaluation is intended for.  
10 For that reason, the target population in the economic evaluation can be more restrictive than that  
11 described in the scope of the rest of the Core HTA. In addition, there is often a need to specify the  
12 target population in greater detail in this domain. If a more restricted target population or subgroup  
13 is to be used in this domain, it should also be included in the scope of the other domains in order to  
14 avoid it being isolated from the rest of the domains, especially the **Clinical effectiveness** domain.

15 *[Transferability considerations:]* Because the characteristics of target populations can vary both  
16 across jurisdictions and within national borders, the characteristics of target populations are one of  
17 the key features that can limit the transferability of economic evaluation. Typically, for example,  
18 parameters related to baseline risk need to be specific to a population, jurisdiction or health-care  
19 setting.

20 *[Tools:]* National guidelines.

### 21 *Pharmaceutical specific content*

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

## 24 Subgroup

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

29 In general, any subgroup analyses should be pre-specified in order to avoid unwarranted post-hoc-  
30 analysis driven conclusions (see, e.g., {54}, {55} and the **Clinical effectiveness** domain). However,  
31 it might not always be possible to identify all important subgroups in the scoping stage of a HTA  
32 {56}. It should also be noted that it is possible to specify more subgroups for the cost and economic  
33 evaluation domain than for the domains **Clinical effectiveness** and **Safety**.

1 *[Transferability considerations:]* There might be differences between jurisdiction or health-care  
2 system in how subgroups are operationalised in routine clinical practice and in informed decision  
3 making.

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

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

## 10 **Technology under assessment and its comparators**

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

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

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

## 25 *Screening-specific content*

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

## 29 **Resource use and costs**

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



1 Direct costs can include all costs directly related to a disease or technology. They may include costs  
2 borne inside the health-care sector (e.g., materials, equipment, personnel and tests – often referred  
3 to as direct health-care costs) as well as outside the health-care sector (e.g., patients' travel time –  
4 often referred to as direct non-health-care costs). A broad agreement exists, on a theoretical level,  
5 that all costs related to the disease or technology in question should be included in the analysis.  
6 However, the way in which this is applied may vary between jurisdictions or health-care systems. A  
7 particularly debated issue is whether to include the unrelated future health-care costs or not, such as  
8 health-care costs of other diseases which people experience when they live longer due to treatment.  
9 The answer to the question of whether any such related, or unrelated, future costs should be  
10 discounted is associated with the chosen perspective of the analysis and may depend on national  
11 guidelines, if such guidelines exist and are considered to be applicable to the Core HTA in question.

12 Indirect costs can include any patient's temporary absence from work due to illness, reduced  
13 working capacity due to illness and disability, or lost productivity due to early death. Lost  
14 production can be estimated either by, e.g., means of the human capital method or the friction cost  
15 method. Lost production is often reported separately and not integrated in the cost estimate used for  
16 the calculation of the incremental cost-effectiveness ratio or 'cost-utility ratio'. Valuation and  
17 inclusion of productivity costs should be made in situations where it is judged to be relevant. The  
18 concept of lost production should not be confused with a 'transfer payment'-like sickness benefit.  
19 Inclusion of transfer payments depends on the perspective of the analysis; they are a cost to the  
20 paying organisation (e.g., government), a gain to the recipient, but from a societal point of view, not  
21 either a cost or a gain, in static economic evaluation.

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

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

37

1 **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.

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

4 *Screening-specific content*

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

14 When identifying the costs of screening, all the costs associated to the screening programme should  
15 be included. This means, that in addition to the costs of screening test itself, also costs of the  
16 screening organisation, invitations to screening, further examinations as well as possible treatment  
17 costs need to be included. In the HTA Core Model, BIA is to be shared between the Organisational  
18 aspects -domain and the Costs and economic evaluation domain. In addition, travel costs to and  
19 from the screening location, depending on the chosen perspective, may also be taken into account.

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

24 **Health-related outcomes**

1 *[General:]* There are a wide range of health-related outcomes which can usefully be incorporated  
2 into an economic evaluation. The choice of health-related outcomes in an economic evaluation  
3 depends, to a large extent, on the purpose or purposes of the information being produced, with  
4 different recommendations existing in different jurisdictions or health-care systems. For instance,  
5 the use of disease-specific measures is often recommended for comparison between technologies  
6 addressing similar health problems. In addition, the use of generic health-state-value or composite  
7 measures is also often recommended for comparison of technologies addressing diverse health  
8 problems, as they form a more comparable core set of health indicators. The use of a combination  
9 of both these types of measures and other measures of health outcome has been widely advocated  
10 (see, e.g., {18}, {60} and {61}). The suitability of using one or more health-outcome measures  
11 depends on the type of technology that is being analysed, as well as on the plausibility that it  
12 appropriately describes relevant aspects of health (see, e.g., {61} and {60}).

13 Although many health-related outcomes are dealt with in the “**Clinical Effectiveness**” domain,  
14 there are health outcomes which are more specific to the “**Costs and economic evaluation**”  
15 domain. Within the **Costs and economic evaluation** domain some of the terminology used for  
16 health outcomes frequently differs somewhat from that used in the **Clinical effectiveness** and  
17 **Safety** domains. In the health-outcomes literature, the terms 'endpoint' and 'outcome' are often used  
18 interchangeably. However, in this domain the term 'outcome' will be used as it is more frequently  
19 used and encountered in the health-economic evaluation literature. Further, we will use the term  
20 “**surrogate outcome**” instead of the closely-related term, “intermediate endpoint” and the term  
21 “**final outcome**” instead of terms such as “true health outcome” or “actual endpoint”. We will also  
22 use the term “**wider outcome**” to express the renewed interest in taking into account of some of  
23 broader effects of technologies, such as the impact of technologies on other stakeholders and  
24 impact(s) on innovation (see, e.g., {62}, {63} and {64}). Health outcomes may be measured,  
25 estimated or valued as changes in clinical indicators, number of health-related events (e.g., cases of  
26 diseases or deaths), QALYs or any other effects which could be deemed important to, or by,  
27 decision makers, such as:

- 28 • surrogate outcomes (e.g., mmHg or maximal isometric handgrip strength)
- 29 • final outcomes (e.g., deaths prevented or QALYs ‘gained’)
- 30 • wider outcomes (e.g., broader effects on families or effects on communities at large)

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

- 32 • measures related to mortality (e.g., ‘life-years gained’ (LYG))
- 33 • measures of self-rated health (e.g., individuals evaluate their own health status)
- 34 • generic health-status measures (e.g., RAND-36)
- 35 • disease-specific measures (e.g., EORTC QLQ C-30 and UCLA Prostate Cancer Index)
- 36 • health-state-value measures (e.g., EQ-5D, SF-6D, 15D)
- 37 • direct ‘utility’ measures (e.g., Standard Gamble or Time Trade-Off -approaches)
- 38 • composite measures (e.g., using QALY, DALY, or HYE -approaches)

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

## 1 **Composite measures**

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

13 *[Transferability considerations:]* The QALY-approach and similar approaches can be seen as  
14 useful in policy analysis and decision-making processes because they are generic and consequently  
15 can facilitate broad comparisons between technologies and across diseases. In order to usefully  
16 facilitate comparisons across diverse technologies, care should be taken that the same methodology  
17 is being used, and applied, consistently.

18 *[Tools:]* Further details related to health outcomes can be found from the **Clinical effectiveness**  
19 domain. Many relevant issues related to HRQoL have also been dealt with in the guideline which  
20 gives general recommendations related to HRQoL that are applicable to Relative Effectiveness  
21 Assessment (REA) of pharmaceuticals ([Endpoints used for relative effectiveness assessment of pharmaceuticals: HEALTH-RELATED QUALITY OF LIFE and UTILITY MEASURES](#)).  
22

## 23 **Health-state-value measures**

24 Health-related quality of life (HRQoL) refers to aspects of quality of life that are related to health.  
25 Different health-state-value measures can be used to estimate HRQoL and there is no single  
26 measure which has been accepted as a gold standard. Health-state-value measures, also referred to  
27 as indirect ‘utility’ measures, are generic instruments capable of providing single-index scores  
28 suitable for the calculation of QALYs. These generic instruments include the AQoL (Assessment of  
29 Quality of Life), EQ-5D (EuroQol), 15D, HUI (Health Utilities Index Mark II/Mark III), QWB  
30 (Quality-of-Well Being Scale), and SF-6D (based on a selection of questions from the RAND-36 or  
31 SF-36 survey instruments). Single-index HRQoL scoring systems combine the answers from  
32 individual questions into a single index number (usually ranging between 0 and 1, although  
33 negative scores for states do occur, e.g., when using the UK-TTO scoring system of the EQ-5D-3L)  
34 {66}.

## 35 **Direct ‘utility’ measures**

36 A direct ‘utility’ measure, or direct preference elicitation technique, is one which values health  
37 states without using the intermediary of a descriptive system. The main methods include standard  
38 gamble (SG), time trade-off (TTO) and visual analogue scale (VAS), but related methods include,  
39 e.g., person trade-off (PTO) and discrete choice experiments (DCE). These techniques generally ask  
40 respondents to make choices between two hypothetical situations, or indicate relative value, and  
41 then derive ‘utility’ values for health states based on the responses. The choice between these  
42 preference elicitation techniques, the way they are administered, and the context in which they are

1 used all have important implications for the validity and reliability of the estimates of ‘preference’  
2 or ‘utility’ elicited {66}.

### 3 *Screening-specific content*

4 An economic evaluation of a screening programme may usefully take the following into account:  
5 the sensitivity and specificity of the screening technology; the number of positive and negative  
6 results (true and false, i.e., positive predictive value PPV and negative predictive value NPV); and  
7 the implications of false-positive and false-negative results. The potential benefits of screening  
8 include a more timely diagnosis, allowing more timely treatment with associated reductions in  
9 morbidity or mortality. Some of the potential harms of screening include the false-positive results  
10 which are commonly associated with screening modalities; anxiety associated with the screening  
11 process; the possibility of overdiagnosis (detection of cases that would not have caused a problem  
12 during the remaining lifetime of a screenee) and the associated possibility of overtreatment; in  
13 addition to the cost.

14 Screening programmes differ fundamentally from the situation where a patient seeks care due to  
15 symptoms, as screening is usually targeted to populations who are mostly healthy. This implies that  
16 these ostensibly ‘healthy’ people may become patients due to the screening results and thus the  
17 effect of screening on their utility may be significant, although data on such effects is fairly limited  
18 {67}. Screening may cause anxiety and concern, especially in the case of false-positive test results.  
19 Hence, another issue to be considered is the incorporation of ‘utilities’ in the analyses. Screening  
20 programmes profoundly differ from the situation where a patient seeks care due to symptoms, as  
21 screening targets populations who are asymptomatic with respect to the target condition. Otherwise  
22 healthy people may receive a feared or stigmatising diagnosis due to their screening result and thus  
23 the effect of screening on their utility may be significant. Economic evaluations of screening  
24 programmes should attempt to investigate the reduction in utility associated with a positive  
25 screening result as well as the change in utility associated with a negative result, e.g., increase in  
26 utility due to justified relief (or decrease in utility due to unjustified relief in case of a false-negative  
27 screening result). The effects on patients’ utility or HRQoL of screening results are still not well  
28 known, yet some qualitative evidence exists from cancer screening studies that false-positive  
29 screening results, including abnormal findings, have a negative impact on certain psychosocial  
30 domains (see, e.g., {67} and {68}).

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

38 Screening models are often more complex than models dealing with only diagnostic or curative  
39 technologies, because screening targets the early stages of a disease. This often leads to the need to  
40 model the natural history or pathogenesis of the whole disease and, often, with very limited  
41 empirical data. Evidence is often not available directly from RCTs of screening programmes but has  
42 to be evaluated from ‘linked’ or ‘chained’ evidence. The generalisability of clinical trial data may  
43 be limited due to the range of choices concerning the preferred screening test, screening interval,  
44 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, where all relevant costs and outcomes of the technologies have to be identified, measured and valued, no matter on whom these costs and consequences fall. However, the way in which ‘the societal perspective’ is defined varies, e.g., between health-care 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 hospital perspective may be more appropriate. If information from the **Costs and economic evaluation** domain is intended to improve decision-making within the health-care sector, an appropriate viewpoint may be, e.g., a ‘health-care payer’ (both public or private), a ‘third-party payer’, or a ‘health-care sector’ perspective (see, e.g., {1} and {69}).

*[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 analyze 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., health-care 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 in 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 parameterize 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*. Particularly informative may be univariate sensitivity analyses conducted 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 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 health-care 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 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 health-care 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 generalisable, transferable or not transferable. Studies are considered generalisable if their results and conclusions can be applied to a range of jurisdictions or health-care 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)
- health-care 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 **Analyzing 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 of costs and economic evaluation is critical to allow the transferability of economic evaluations performed as part of an HTA 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.

## 1 **Assumptions**

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

10 In order to increase transferability, all assumptions can be systematically presented, e.g., in a tabular  
11 form, and include appropriate reasoning and all references to support the assumptions made. If  
12 statements are made concerning the ‘conservative’ nature of assumptions, these too should include  
13 appropriate reasoning and all references to support such claims. For example, an important  
14 assumption concerns the modelling of current practice, does the model under consideration assume  
15 perfect adherence to existing medical guidelines, or is the potential impact of non-adherence to such  
16 guidelines also taken into account? – appropriate assumptions may vary greatly between settings or  
17 depending on the research question.

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

## 21 **Model validity**

22 To be able to evaluate how the results of a model should be used, a model user benefits from  
23 knowing how well the model predicts the outcome(s) of interest. To be able to do this, the model  
24 needs to be transparently reported and validated.

25 In this context, transparency means that model users can see how the model was built and validation  
26 relates to methods to evaluate the extent of a model’s accuracy in making relevant predictions or in  
27 abstracting from a complex reality. Five main types of validation have recently been described: face  
28 validity, verification (or internal validity), cross validity, external validity and predictive validity  
29 {38}. In comparative analysis of alternative technologies, one of the key questions is how well the  
30 model predicts health outcomes (external and predictive validity). Therefore, in cases where  
31 validation is possible, e.g., using a relevant data set, it is recommended.

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

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

40 The health effects predicted by the model are often at least partly transferable between populations,  
41 due in many instances 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 transferability point of view, 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 best practices for making models transparent and for validating them {38}.

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

The parameters related to **Clinical effectiveness** and **Safety** 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 **Clinical effectiveness** and **Safety** 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 analysis 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).

## 1 Reporting and interpreting

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

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

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

## 22 Literature review

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

- 28 • Eligibility criteria
- 29 • Literature search
  - 30 ○ including the search strategies for individual databases
- 31 • Study selection and data collection
  - 32 ○ a copy of the data extraction can be included
- 33 • Additional analyses

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

- 38 • Study selection
  - 39 ○ including a flow chart of included and excluded studies
- 40 • 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 check-list is also recommended {88}. In the domain **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 subheading 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 to ‘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 check-lists for critical appraisal of economic evaluations were used, these can be included in the appendices.

## 1 Comparison of costs and outcomes

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

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

## 15 Characterising uncertainty

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

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

24 When reporting the results of uncertainty analyses it may be useful to follow the recommendations  
25 of the ISPOR-SMDM Modelling Good Research Practice Task Force {37}. This document also  
26 includes more about the ability for the different approaches to gauge aspects of the uncertainty  
27 surrounding economic evaluation.

28

1    **Characterising heterogeneity**

2    The results should be given for all subgroups analysed. For ICER estimates the components of  
3    numerator (cost of each alternative) and denominator (outcomes of each alternative) should be  
4    shown.

5    **Model validation**

6    The report should describe the process of validation and the types of validation addressed in the  
7    model, in order to help assessment of validity.

8    It would be valuable if the results of validation included, at least, the following:

- 9        • How well the model predicts health effects
- 10       • Whether model includes all important aspects of resource use and costs considered important (by,  
11       e.g., clinical or organisational experts )
- 12       • Estimates of the potential direction or potential magnitude of bias induced (e.g., has sensitivity  
13       analysis been conducted concerning validity-related assumptions)
- 14       • An attempt to identify key factors that could compromise the validity of the model (e.g., the  
15       extrapolation technique used, structural assumptions in the model, base-case parameters)

16



## 1 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 utilization						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
Clarification	<b>Common to all used applications</b>  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.					
Methodology and sources	<b>Common to all used applications</b>  Health-care registers and databases, RCT's with resource utilization 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.					
References	<b>Common to all used applications</b>  Gold et al. {59}; Drummond et al. {1}; CADTH {18}; Kristensen and Sigmund {3}; Cleemput et al. {57}; Husereau et al. {51}.					
Content relations	<b>Common to all used applications</b>  A0011, A0017, A0024, A0025  B0007, B0008, B0009					



	D0010, D0014, D0023  F0012  G0001, G0003, G0004, G0005, G0006, G0007  H0003, H0010  <b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b>  G0010
<b>Sequential relations</b>	<b>Common to all used applications</b>  A0017, A0024, A0025  B0007, B0008, B0009  D0010, D0023  G0001

1

E0002 Assessment element card  Issue: What amounts of resources are used when delivering the assessed technology and its comparators (resource-use measurement)?  Topic: Resource utilization						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	2
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	2
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	2
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	2
Clarification	<b>Common to all used applications</b>  Report the parameters required to estimate overall costs (E0009). Include the					

	<p>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>Health-care registers and databases, RCT's with resource utilization 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>

1

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 utilization						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	3
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	3
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	3
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	3

<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>For each technology report 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. Providing the results in tabular form is recommended.</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 cost s.</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>

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2

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)?						
Topic: Measurement and estimation of outcomes						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
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 using them in alternative forms such as QALYs.</p> <p>Report the approach(es) and data source(s) used to estimate the outcomes associated with the technologies.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Estimation of the incremental or other effects can be based on information provided in the Clinical effectiveness domain (e.g., mortality data). 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 effectiveness 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}.</p> <p>Williams {60}; Johannesson et al. {61}.</p>					

<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>A0004, A0005, A0006, A0009</p> <p>C0008, C0002, C0004, C0006,</p> <p>D0001, D0003, D0005, D0006, D0007, D0011, D0012, D0013, D0029</p> <p>F0003, F0010, F0011</p> <p>H0100</p>
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>A0004</p> <p>C0008</p> <p>D0001, D0005, D0006, D0007, D0012, D0029</p>

1

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 (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	5
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	5
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	5
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	5
<b>Clarification</b>	<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, typically, one or more of the following outcomes or</p>					

	<p>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>
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Relevant sources of data and evidence are specified in the relevant issues under the domains Safety , Clinical effectiveness and Costs and economic evaluation (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 the Safety , Clinical effectiveness and Costs and economic evaluation domains.</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> <p>Briggs et al. {26}.; Glick et al. {29}; Johannesson et al. {61}.</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>E0001, E0002, E0005, E0009</p>
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>E0001, E0002, E0005, E0009</p>

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2

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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	6
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	6
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	6
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	6
Clarification	<p><b>Common to all used applications</b></p> <p>The effects of uncertainty should be reported separately for parameter, structural and methodological uncertainty, whenever possible. 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>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>Relevant sources of evidence are specified under relevant issues under domains Safety and Clinical effectiveness , as well as from within the Costs and economic evaluation 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}.</p> <p>Bojke et al. {74}; NICE {69}; Briggs et al. {26}.</p>					

<b>Content relations</b>	<b>Common to all used applications</b>  E0006
<b>Sequential relations</b>	<b>Common to all used applications</b>  E0006

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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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	7
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	7
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	7
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	7
<b>Clarification</b>	<b>Common to all used applications</b>  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.  The methods used in any sub-group analysis should be reported in detail here.					
<b>Methodology and sources</b>	<b>Common to all used applications</b>  Relevant sources of evidence are specified under relevant issues under domains Safety and Clinical effectiveness , as well as from within the Costs and economic evaluation					



	domain.
<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> <p>Sculpher et al. {56}; Cleemput et al. {57}</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>C0005,</p> <p>E0006</p> <p>H0012</p>
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>E0006</p>

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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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	8
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	8
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	8
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	8

<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 predicts health effects</li> <li>- Whether model includes all aspects of resource use and costs considered important</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>The process of validation and the types of validation addressed in the model should be reported 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 under domains Safety and Clinical effectiveness , as well as from within the Costs and economic evaluation 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}.</p> <p>Eddy {38}</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>E0001, E0002, E0005, E0009, E0010, E0011</p>
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>E0001, E0002, E0005, E0009, E0010, E0011</p>

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## 1 ***Ethical analysis***

### 2 **Description**

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

4 The term “ethics” is broadly used to describe activities relating to the understanding and study of  
5 “the moral life”. The term “morality” encompasses beliefs, standards of conduct, principles and  
6 rules which may guide personal and professional behaviour and the behaviour of  
7 institutions. Morals are standards that are widely shared, and that form some degree of social  
8 consensus { 1 }.

9 The ethical domain considers prevalent social and moral norms and values relevant for the  
10 technology in question. It involves an understanding of the consequences of implementing or not  
11 implementing a health care technology in two respects: with regard to the prevailing societal values  
12 and with regard to the norms and values that the technology itself constructs when it is put into  
13 use. The moral value societies attribute to the consequences of implementing a technology is  
14 affected by socio-political, cultural, legal, religious and economic differences. However, many  
15 ethical considerations are common to all countries and societies.

16 In addition to the ethical aspects of using technology, the domain also covers moral and ethical  
17 issues related to the consequences of performing the health technology assessment (HTA). These  
18 are for example questions about the ethical consequences of the choice of endpoints and whether  
19 there are any ethical problems in the economic evaluation. There are, however, also various ethical  
20 considerations that should be taken into account when choosing what technologies to assess and  
21 when planning to conduct the assessment. This is to ensure that the assessments themselves are  
22 designed and conducted in such a way that key ethical principles are considered and respected.  
23 These types of consideration are not part of this domain but presented in the introduction to the core  
24 model.

25 The ethical domain includes six different topics, which together cover nineteen issues. These are  
26 presented in table 1. The issues stem from the general values of the population, the aims of the  
27 healthcare system and from values arising from use of a technology.

28

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

Topic	Issue	Assessment element ID
Beneficence/nonmaleficence	What is the severity level of the condition that the technology is directed to?	F0100
Beneficence/nonmaleficence	What are the known and estimated benefits and harms for patients when implementing or not implementing the technology?	F0010
Beneficence/nonmaleficence	What are the benefits and harms of the technology for other stakeholders (relatives, other patients, organisations, commercial entities, society, etc.)?	F0011
Beneficence/nonmaleficence	Are there any other hidden or unintended consequences of the technology and its applications for different stakeholders (patients/users, relatives, other patients, organisations, commercial entities, society etc.)?	F0003
Autonomy	Is the technology used for patients/people 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 user'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 end-points, cut-off values and comparators/controls in the assessment?	F0017
Ethical consequences of the HTA	Does the economic evaluation of the technology contain any ethical problems?	F0102
Ethical consequences of the HTA	What are the ethical consequences of the assessment of the technology?	F0103

## 1 Why is this domain important?

Technologies 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 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 to date has 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 as the one it is intended to replace but does so with better specificity, sensitivity, safety and at lower cost 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 differ between technologies, and for the same technology for a rapid and full assessment depending on the purpose and context of its use.

It should be noted that in taking ethical considerations into account in HTA, two separate but interconnected activities must be conducted. One is the identification of moral issues relevant to draw conclusions—and in some settings to make decision— about use of the technology, and the other is ethical analysis relevant to HTA. The analysis will generally consist of using structured methods for exposing the relevant often competing moral values in the HTA, and weighing their relative merits. Those drawing conclusions about the use of the technology will need to apply the framework(s) in the course of the HTA to decide which of these possibly competing values should dominate.

### **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, and because
- 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 all 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 have 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 as the clinical or cost-effectiveness evidence emerges. In this way, the results and insights gathered 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 and social aspects. These domains may overlap 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 those of primary outcomes at patient level (e.g. avoidance of death at patient level, avoidance of impaired working ability at societal level). The implementation of 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 for example be:

- 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 so, at what costs? The aim is also relevant for the trade-offs between safety and benefit of the test. For example, the willingness to undergo risky tests is probably lower by healthy people in front of a screening offer, than by 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 {EFF}clinical effectiveness domain{END} 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 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 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 totally healthy people (see {SAF}safety domain{END}). 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, “information only” issue. This perception ignores the potential consequences of specific test results,

1 specially the consequences of false results. Positive test results may initiate a chain of further diagnostic  
2 measures and/or treatments which usually have higher direct risks than the initial test, exposing the  
3 healthy individual (e.g. the false positive) to additional unnecessary risks. On the other side, false negative  
4 results may cause delays or even withholding of an appropriate treatment, this unnecessarily prolonging  
5 suffering or reducing example survival chances. Thus, the starting point is that more diagnostic tests  
6 produce more risks, and it is the benefits that must be proven. In order to balance harms and benefits, not  
7 only the direct risks but also the consequences of all four possible tests results (false positive (FP), false  
8 negative (FN), true positive (TP), true negative (TN)) should be known and understood. Second, diagnostic  
9 tests may change care on ways that are difficult to foresee. Diagnostic tests are crucial parts of care  
10 pathways and treatment processes. A diagnosis, or a positive triage test, often has ethical and practical  
11 consequences in requiring further tests, treatments or other modes of care. The latter being of particular  
12 importance, if the condition diagnosed is untreatable (e.g. the genetic test for Huntington's disease.) Thus  
13 increasing diagnostic tests alone may lead to far-going changes in the requirements placed on health care  
14 systems, and also on individual patients and professionals.

15 Third, diagnostic tests may change the way we see diseases and illnesses. A diagnostic technology may not  
16 become a pure replacement of an existing test especially if the new test is substantially different from the  
17 old one (e.g. different biomarkers for the same disease, genetic test instead of biochemical markers,  
18 imaging instead of laboratory tests). This may shift the diagnosed population towards milder cases  
19 (increasing prevalence). A change in the diagnosed population may, in turn, require different therapeutic  
20 approaches – and thus also new effectiveness studies.

21 Fourth, diagnostic technologies tend to obtain substantial symbolic value (for example, genetic tests and  
22 advanced imaging technologies like PET, MRI and ultrasound for prenatal screening). These tests may have  
23 profound consequences on individuals' self-image and behaviour. Fifth, diagnostic test information may be  
24 of different value to different stakeholder groups. Information on contagious diseases and other health  
25 conditions, and the results of predictive (genetic) tests are not only of interest and importance for the  
26 patient and the treating physician. It is an ethical issue to whom diagnostic test information must and may  
27 be communicated. Along with this issue goes the danger of "labelling" a healthy person as unhealthy by  
28 communicating predictive test results.

#### 29 **4) Normative issues in assessing effectiveness and accuracy**

30 First, the proper end-points for assessment must be determined. Endpoints can be used based on:

- 31 - Technical or diagnostic accuracy
- 32 - Reduced risk / increased safety
- 33 - Diagnostic or therapeutic impact (health improvement)
- 34 - Other patient outcome (knowledge, increased autonomy, lifestyle modification, worry)

35 More than one endpoint may be legitimate and expected. For example, a new test may increase safety of  
36 testing but reduce patient outcome and influence costs and social justice. The decision of using a  
37 technology with various end-points may be morally challenging and requires value-decisions at planning,  
38 analysing and reporting stages of a HTA. Transparency on how, on what grounds and by whom these value-  
39 decisions are done is needed.

For pragmatic reasons it is often necessary to concentrate the technical assessment on some of the endpoints on which 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 on cut off values and balancing accuracy measures (e.g. sensitivity versus specificity) requires value decisions relating 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 that the test will be used on and what the consequences of different diagnostic alternatives are. Even if a ROC curve is interpreted so that the point closest to the upper left corner equals “best accuracy” (see {EFF}effectiveness domain{END}), this may not be the most ethically acceptable cut-off to use (see “context related requirements for accuracy” under the Effectiveness domain). The patient population determines the rates of different outcomes, so the balancing of harms and benefits will depend on the population the test will be used on.

## **Screening-specific content**

Screening technologies bring many ethical questions to participants, their relatives, the health care system and the society as stated in the criteria for a screening programme {5, 6}. The screening technology should target a sufficiently important health problem both to the individual and to society to be able 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 disease is possible if actually not yet suspected. For primary screening, the test is being given to an asymptomatic individual and this raises significant ethical issues. In secondary screening, the population has already come into contact with the healthcare system because symptoms have arisen. In secondary screening for conditions with known adverse effects there may therefore be a greater imperative to identify and treat the condition, because 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 to determine 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 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 the screening must be guaranteed as well as the treatment that follows if the patient is found to have the disease. Ethical analysis needs to be applied to the consequences of “false positive” and “false negative” test results as well as consequences of possible over-diagnosis and over-treatment have to be carefully evaluated and weighed against the expected benefits. There



should be a suitable test or examination for screening, for which 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 to the population. Equity of access is a further consideration. The evaluation should also consider whether participating in the screening programme might stigmatize the participants or the individuals that test positive.

Ethical evaluation of a screening programme has multiple perspectives as it may encompass the health care 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, screening health care professionals) need to be identified both before and during the HTA process. For each stakeholder, possible consequences of proceeding with or refraining from the implementation of the screening technology have to be identified.

## **Pharmaceutical-specific content**

Issues on possible medicalization and unintended harms have to be identified and analysed when novel pharmaceuticals are marketed for health conditions for which no universal and individually applicable definition for having a disease exists. In cases where pharmaceuticals are used for secondary prevention it is also important to discuss the ethical consequences of the criteria for starting a preventive medication.

When pharmaceuticals replace an existing invasive treatment option (e.g. continuous medication vs. surgery), the decision on treatment option can have a large impact on the patient's quality of life and also interfere with their social and family life.

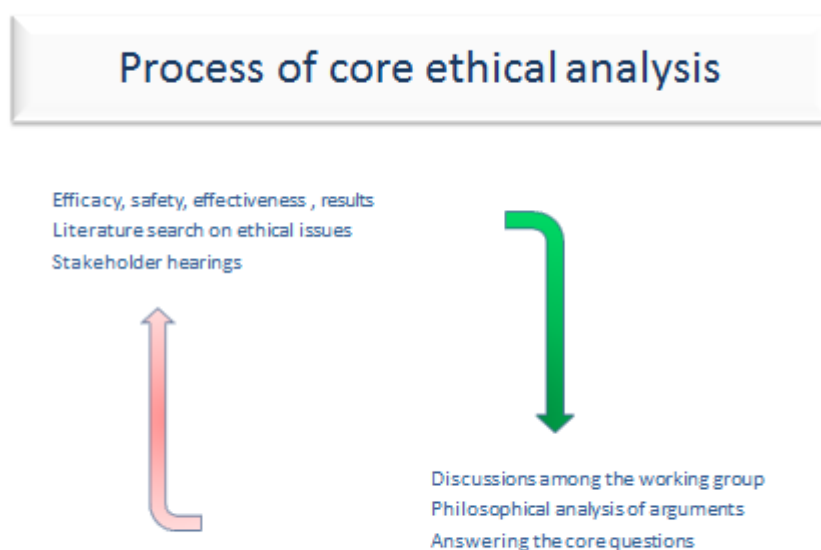
## **Methodology**

### **Process for answering research questions**

Even though there is wide consensus that ethical analysis should be a mandatory element of HTA, there has been no generally accepted, structured method for performing ethical analysis. The INAHTA ethics working group has identified and defined various methodological approaches that are used by HTA agencies {8}. These are presented in the section about 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 it infringes the discretionary room for appraising the technology by (national or regional) decision-makers.



- 1 For each core HTA project it is recommended that there is a person, preferably an ethical expert,  
2 responsible for facilitating and reporting the ethical analysis. However, the ethical analysis of the  
3 process of HTA should also be done together with scientific and clinical experts.
- 4 The choice of approach and process to conduct a formal analysis of ethical aspects depends on a  
5 number of interacting factors:
- 6 a) The type of technology being assessed
  - 7 b) The role and authority of the HTA organisation in the national decision-making procedure
  - 8 c) The time and resources available for the assessment.
  - 9 d) The methodological expertise and experience with ethical analysis that are available within the  
10 organisation
- 11 The relative weight placed on the ethical analysis and the selection of methods depends heavily on  
12 the technology being evaluated {2, 10}. The more the technology presents new, severe or  
13 fundamental value conflicts, or challenges to everyday norms or beliefs, the more emphasis should  
14 be placed on the ethical analysis. For example, technologies with strong "prima facie" moral  
15 implications (like genetic testing or aggressive cancer therapies in children), technologies  
16 concerning diseases with strong interest groups involved (for example cochlear implants) or other  
17 "extraordinary" new technologies that appear to challenge commonly held values or everyday  
18 beliefs (like home care nurse robots) require a more elaborative ethical analysis.
- 19 Technologies used for vulnerable patient groups (critically ill, children, individuals with impaired  
20 cognitive capacity etc.) also require special ethical analysis with regard to the patients' diminished  
21 autonomy. The same consideration goes for the technologies for which there is a specific belief.
- 22 HTA organisations differ in their resources and mandate for decision-making. While some only  
23 provide synthesis of evidence, others conduct appraisal of evidence and formulate recommendations  
24 or produce clinical practice guidelines. Decision making bodies and agencies providing guidance  
25 may have more explicit requirements for transparency for their stakeholders than academic or other  
26 bodies carrying out HTA. They may also have legal duties requiring them to avoid discrimination  
27 and promote equality. This may affect their approach to ethical analysis. If the HTA organisation is  
28 clearly separated from decision-makers, it may be enough to describe the different norms, values,  
29 attitudes and arguments that should be considered by the decision-makers.



1

2 **Figure 1. The iterative process of ethical analysis**

3 **Gathering information**

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

5 The focus of the assessment, the specific questions to be answered, the study inclusion criteria, and  
6 the primary outcome points for the analysis of the consequences of implementing a technology are  
7 defined by the entire working group, and may be incorporated into a formal scope or decision  
8 problem document. These choices are value laden and they need to be carefully scrutinized before  
9 proceeding to literature review as they can have a major impact on the content and conclusions of  
10 the HTA report.

11 It is important to consider whether there are issues of potential ethical significance related to the  
12 disease or health problem, even before any factual considerations about consequences of  
13 implementing or not implementing the related technology. For example, some types of technologies  
14 may introduce gender bias or be used in conditions that are considered by some to be “self-  
15 inflicted”, which could lead to debates about access to treatment. Furthermore, some technologies  
16 involve complex relationships, interests and outcomes. For example, prenatal screening tests may  
17 raise fundamental questions about the value of life and autonomy, and highlight competing interests  
18 of the embryo, mother, father, siblings or future possible siblings.

19 Some issues in the assessment elements table deal with the direct consequences of the  
20 implementation of a technology (e.g. can the technology harm the patient?). Others relate to  
21 questions of value that need to be addressed when deciding on implementation, such as the impact  
22 of the technology on availability of healthcare resources for different patient groups, or the balance  
23 of benefit and harm for the population as a whole. Competing ethical considerations generally do  
24 not lead to clear conclusions and therefore judgement 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 for stakeholders' different viewpoints (see Methods for ethical analysis – different approaches).

The perspective 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 care-givers, 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 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 in 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, for example, 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 implementing or not implementing it 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 sources of literature 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 effectiveness assessments. 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}.

## 1 Expert and stakeholder opinion

2 Discussions among the working group and with experts are effective in identifying important  
3 ethical issues related to the technology. The questions in the assessment elements table of this  
4 domain are a good starting point for discussions with experts and other stakeholders, but additional  
5 content-specific ethical issues or challenges may also be identified during the  
6 discussions. Qualitative analysis of the expectations and fears of various stakeholders may reveal  
7 questions that cannot be identified by the content or methodological expert group or from the  
8 literature review. This information can be derived from stakeholder meetings or by conducting  
9 primary studies.

## 10 Methods for ethical analysis – different approaches

11 In this section, the various methodological approaches used by HTA agencies that were identified  
12 by INAHTA ethics working group are shortly described. They have also been complemented by the  
13 EUnetHTA ethics working group. Presenting concrete examples of how to apply these methods is  
14 beyond the limits of this document. For guidance on how to conduct privacy impact assessment, see  
15 Privacy Impact Assessment (link:  
16 [http://www.ico.org.uk/for\\_organisations/data\\_protection/topic\\_guides/privacy\\_impact\\_assessment](http://www.ico.org.uk/for_organisations/data_protection/topic_guides/privacy_impact_assessment)).

## 17 Casuistry

18 Casuistry means solving morally challenging situations ("cases") by referring to relevantly similar  
19 "paradigmatic" cases for which an undisputed solution has been found {13-16}.

20 The methodology of casuistry comprises three steps. First, the case at hand is sorted to a broad  
21 category of problems, "topics" (e. g. medical indications, patient preferences, quality of life,  
22 contextual features). Details should be described in a standardised way (who, what, where, when,  
23 why, how, by what means). Second, common sense moral rules, "maxims", related to the case are  
24 explored (e.g. "the wish of the patient has to be respected"). If the maxims are contentious, the  
25 moral principles that underlie them in the case at hand are explored. Third, the case at hand is  
26 compared with a set of paradigmatic cases on the same topic that have been solved in agreement  
27 previously. Comparing the details of the case at hand, including the underlying maxims and  
28 principles, with the details of the paradigmatic case then may suggest a solution for the current  
29 problem {17}.

30 In HTA, especially for coverage decisions, a casuistic approach (precedence method) is suggested  
31 as at least a part of the ethical analysis. It means first establishing an inventory of past coverage  
32 decisions. The aim is to generate a typology of paradigmatic, covered technologies, which would  
33 represent the basic moral principles that underlie decision-making in the respective health care  
34 system. Next, the relevant qualitative and quantitative characteristics of the new technology are  
35 identified, and the technology is compared to similar, preceding paradigmatic cases. Ideally their  
36 solution may then be applied to the new technology. However, in addition to applying the solutions  
37 of past precedents to current cases, it is also necessary to reflect on the possibility that the value  
38 base has changed since the paradigmatic decisions were made. It may be that this reflection leads to  
39 a need to reconsider previous decisions.

40 In pure casuistry, cases are approached without referring to ethical principles, norms or theories.  
41 The process might resemble coherence analysis in that coherence between solutions to similar cases

is searched for, or interactive approaches that aim for consensus of relevant stakeholders. A pragmatic, “moderate” form of casuistry as described above can include an element of principlism in that referring to ethical maxims and principles is done if comparison to previous cases does not provide clear enough solution. It also includes an element of wide reflective equilibrium, in that applying past precedents to new cases might reveal a need to reconsider 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 *prima facie* relevant. It is a procedural, pragmatic approach, i.e. 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 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 summarized in regard 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 society or parts of it (deeply held, fundamental values and views central to individuals and societies self-image)

CA is a reflective procedure (internal monologue / group discussion) trying to help achieve 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.). Higher consistency of the whole is the norm, on which conflicting ideas are evaluated, edited and possibly abandoned. Thus and in contrast to interactive approaches (see below), opinions of important stakeholders can but need not be taken into account.

Reaching consistency might not succeed, so the end result might as well be identification of 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 CA is an essential part of all ethics analysis. It may be especially useful early on in the HTA process, to help identify central issues in need of further scrutiny.

## 1 Interactive, participatory HTA approach (iHTA)

iHTA aims for 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 to approach ethical problems, not any ideal solution to these problems. In contrast to coherence analysis, however, iHTA also aims to improve the validity of the whole HTA process through empowering and involving the stakeholders to participate. Although iHTA aims for consensus, this may not always be reached together with the stakeholders. It may also be decided that the conclusions are drawn from the stakeholder hearing by the method experts {19-23}.

The iHTA process begins by asking what kind of values are at stake, whose values they are, and who the important stakeholders are. Second, an interactive procedure to clarify these values is chosen, depending on presumed severity of value conflicts and 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 to assess the (health) effects of the technology, but can also be reported as such.

iHTA informs, but does not dictate, the normative ethical conclusions needed in reporting the results of the HTA. The iHTA can bring into the expert group 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. But the description of possibly differing valuations of different stakeholders, discovered with the iHTA process can be important for the application of the results.

## 22 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 four principles, representing 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 and
- Justice: a group of norms for distributing benefits, risks and costs fairly.

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 they are not absolute, because they can 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, as the principles are abstract, they must always first be specified according to the current context. Then, if all principles cannot be realised fully (as is most often the case), the specified principles must be balanced with each other. A principle should only be overridden if:

- Better reasons can be offered to act on the overriding one,
- The moral objective which justifies the infringement must have a realistic chance of being achieved,
- The infringement must be the only way to realize one principle at the cost of the other,
- The form of the infringement must be commensurate with achieving the primary goal,
- Any negative effects of the infringement must be minimized and
- The decision must be impartial in regard 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).

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 in fact is technology-in-context, then both technology and its context can be influenced or adjusted to improve the outcomes of using technology. The societal processes underlying technology development can be explained to some extent by the values relevant in different contexts.

From the ethics point of view, the SST approach emphasizes

- a) reflexive focus on the range and values of relevant actors and their conditions of involvement
- b) considering how technology can influence society and how technology can be best managed by society
- c) 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).

## 1 **Wide reflective equilibrium (WRE)**

2 The WRE {27-30} is an ideal, perpetual goal of justification in modern philosophical inquiry. It is  
3 based on pragmatism and social constructivism, which claim that ethical truths cannot be revealed  
4 or directly experienced, and that there are no static, fundamental a priori valid universal principles.  
5 On one hand, the normative framework of society may change over time. On the other hand,  
6 humans need stability, cognitive coherence and some degree of reconciliation of individual and  
7 social norms and values. WRE is a central methodological part of the ‘four principles’ approach,  
8 discussed above {1}.

9 When using WRE, the reflection starts from the most considered judgments and moral feelings that  
10 have a prima facie credibility. This has to be done behind a ‘veil of ignorance’ (i.e. imagining we do  
11 not know which position we would have in the society our decisions concern) to try to be as  
12 impartial as possible. To approximate WRE, all possible situations, arguments, and judgments need  
13 to be taken into account and brought into a coherent whole through rational reflection (see  
14 coherence analysis above). This might entail that some of our primary considered judgments have  
15 to be adjusted.

16 WRE is an important political and philosophical goal of coherence analysis and discourse ethics in  
17 regard to decision making. However, it is an ideal goal of a theoretical procedure, which may be  
18 difficult to apply in real-world HTA processes. As a goal emphasizing individual and inter-  
19 subjective consensus, WRE may also neglect true conflicts between incommensurable arguments.  
20 Essentially, WRE emphasizes open, honest and impartial discourse, conducted by rational, sensible  
21 actors in democratic, pluralistic societies who want to reach consensus through finding the most  
22 validity of claims.

## 23 ***The “triangular model” based on the human person - centred approach***

24 The triangular model is centred on a substantial conception of human person. It considers the man  
25 as reference-value in the reality, around which all the ethical judgements are coordinated. Based on  
26 a cognitivist approach to the ethics, this model considers that it is possible to get some truths,  
27 concerning man and his/her praxis, recognizable by everyone through a rational activity {31}.

28 The methodology of the triangular model comprises three steps of analysis: 1. data collection; 2.  
29 anthropological aspects, 3. ethical-normative evaluation. The first step, “scientific moment” consists  
30 of an in-depth study of all facts/data, including qualitative and relational ones. The second step,  
31 “anthropological moment”, consists of the anthropological understanding of facts; in other words,  
32 the analysis of eventual values at stake, related to human life, integrity and dignity. According to  
33 this analysis it is possible to find values which should be promoted and defended, and norms which  
34 should guide human action on individual and societal levels. The third, “ethical-normative” step  
35 consists of evaluation of practical choices that should be made.

36 This model highlights a triangular connection between bio-medicine, anthropology and ethics,  
37 settled on two levels: the explanation of a certain topic (descriptive step), followed by a normative  
38 phase, in which we can get conclusions within a debate of the meta-empirical perspectives i.e.  
39 relating to the steps 2 and 3 described above. It is evident that such a comprehensive process needs  
40 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, to promote or safeguard him/herself {31}.

#### **Axiological (Socratic) approach**

The axiological approach is based on the insight that science and technology is a social activity governed by a wide variety of norms and values. Health technology is applied in a social setting where there is interplay of different kinds of norms and values, HTA should highlight and address the norms and values involved in the implementation and use of a health technology. The reason why it is also called a Socratic method, is that 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 in 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 in regard 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. Summarize the analysis and highlight the most important value issues.

The aim with 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}, newborn screening {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.

## 1 Analyzing and synthesizing evidence

### 2 *Qualitative synthesis*

3 When the ethically relevant issues have been identified and analysed the results have to be  
4 synthesized and reported transparently so that they can be considered when deciding whether to  
5 implement a technology. No single solution to every ethical problem exists, nor is it possible to list  
6 ethical issues according to a commonly agreed weighted value. Answers to the core set of issues  
7 may also reflect the variation in norms and values found within most societies. The synthesis of  
8 ethical analysis has to be performed in an open way. Either the interests of various stakeholders are  
9 kept as "unweighted" as possible, or the weighing is done transparently i.e. describing the procedure  
10 and participants of the analysis. Ideally, the decision on "whose values are to be weighted" need to  
11 be in the hands of the decision makers. There can be different decision makers for different types of  
12 technologies within the same country and between countries. The ideal way to present the synthesis  
13 of the analysis may vary accordingly.

14 Ethical analysis on the consequences of implementing or not implementing the technology may be  
15 handled using an open framework {47}. The possible consequences of proceeding with or  
16 refraining from the implementation of the technology can be listed separately for each stakeholder  
17 in an open table as the answers for various parties may differ largely (table 1). The identified issues  
18 are not value-weighted prescriptively against each other. In fact the table offers a transferable list of  
19 aspects that need to be considered in the final decision making process.

20 **Table 1. A framework for ethical analysis**

Stakeholder	Benefits when proceeding with implementation	Adverse consequences when proceeding	Benefits when refraining from implementation	Adverse consequences when refraining
Patient				
Family and important others				
Health care providers				
Society				
Others				

21 It is important to identify also those areas where values may differ significantly between the various  
22 stakeholders (e.g. attitude towards the care of patients with non-treatable diseases, extremely costly  
23 interventions or conditions perceived as 'self-inflicted'). The main areas of ethical controversy  
24 should be clearly stated in the final document.

## 1 **Reporting and interpreting**

2 The results of the ethical analysis will usually be reported as a separate chapter, in order to assure  
3 transparent reporting of value issues. The ethical implications of implementing or refraining from  
4 the implementation of technology need, however, to be discussed in a balanced way so that the  
5 health policy makers have a wider view on all possible consequences of their decision. The open  
6 framework as presented in table 2 can be a helpful tool in this process. The decision to implement a  
7 new technology requires careful decision on the balance between benefit and harm, cost-  
8 effectiveness, impact on (re)allocation of resources, etc. Discussing the context-specific ethical  
9 issues within the respective domain (e.g. effectiveness, safety, and costs) may thus also help the  
10 decision makers to identify various scenarios.

## 11 ***Transferability of ethical analysis***

12 The ethical analysis and its outcome have to be described in an open way so that their transferability  
13 across different national or local settings can be judged. Many of the ethical implications are  
14 common to various nations but some value laden issues are likely to be country- or community-  
15 specific, and will crucially relate to factors such as the ‘social contract’, the country’s healthcare  
16 financing system and the country’s GDP growth prospects. Analyses related to ethical principlism,  
17 coherence or paradigmatic approaches are likely to be more easily transferable than argumentation  
18 based on interactive approaches relying on local values, stakeholder attitudes and available health  
19 care resources.

20

## 1 Assessment elements

F0100 Assessment element card						
Issue: What is the severity level of the condition that the technology is directed to?						
Topic: Beneficence/nonmaleficence						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	1
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	1
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	1
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	1
Clarification	<b>Common to all used applications</b>  Knowing the severity 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.					
Methodology and sources	<b>Common to all used applications</b>  Literature search. Expert opinion					
References	<b>Common to all used applications</b>  48					
Content relations						
Sequential relations	<b>Common to all used applications</b>  A0002  A0007					

	A0005
	A0024
	A0025

1

F0010 Assessment element card						
Issue: What are the known and estimated benefits and harms for patients when implementing or not implementing the technology?						
Topic: Beneficence/nonmaleficence						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	2
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	2
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	2
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	2
Clarification	<p><b>Common to all used applications</b></p> <p>Decisions concerning implementation of new technologies generally require careful consideration of the balance between benefits and harms. Examples of questions that can be asked 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> <p><b>Specific to Pharmaceuticals (2.1) - PUBLIC DRAFT</b></p> <p>.</p>					

<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Information from other domains (links). Literature search. Expert opinion. Stakeholder hearing</p>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>47</p>
<b>Content relations</b>	
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>D0001,</p> <p>D0029,</p> <p>H0001, H0004, H0005,</p> <p>H0006, C0008, C0005,</p> <p>A0010</p> <p>D0017</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>D0027, D0028 D0031, D0024, D0030, D1019</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>D0024, D0030, D1019 D0027, D0028, D0031, D0024, D0030, D1019</p>

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2

F0011 Assessment element card						
Issue: What are the benefits and harms of the technology for other stakeholders (relatives, other patients, organisations, commercial entities, society, etc.)?						
Topic: Beneficence/nonmaleficence						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	3
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	3
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	3
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	3
Clarification	<p><b>Common to all used applications</b></p> <p>Can the technology have positive effects for other stakeholders? Can the technology harm any other stakeholders? 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 other stakeholders. 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 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 (link) in the process description can be used to describe benefits and harms.</p> <p><b>Specific to Pharmaceuticals (2.1) - PUBLIC DRAFT</b></p> <p>.</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>1, 47</p>
<b>Content relations</b>	
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>D0029,</p> <p>H0001, H0002,</p> <p>C0020, C0040,</p> <p>A0006,</p> <p>E0006,</p> <p>D0017</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>I0008</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>I0008</p>

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### F0003 Assessment element card

**Issue:** Are there any other hidden or unintended consequences of the technology and its applications for different stakeholders (patients/users, relatives, other patients, organisations, commercial entities, society etc.)?

**Topic:** Beneficence/nonmaleficence

Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
	Screening Technologies (2.1) - PUBLIC DRAFT	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. Ethical analysis of the technology should 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. The intended purpose and uses of the technology should be evaluated against the likely uses and consequences of the technology in reality.</p> <p>The mode of delivery, the need of laboratory tests or clinical follow-up to ensure safe and effective dose, and way of delivery (at home, outpatient or in-patient) may have 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. IVF and development of genetic testing has led to questions of preimplantation genetic diagnostics (PGD)). As pre-symptomatic screening tests have become available, the health care system has to be prepared to handle moral issues raised by true positive and false negative findings.</p> <p>The mode of delivery, the need of laboratory tests or clinical follow-up to ensure safe and effective dose, and way of delivery (at home, outpatient or in-patient) may have 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</p>					

	<p>disorder or changing the border values when the concept of normality also changes).</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 (2.1) - PUBLIC DRAFT</b></p> <p>Diagnostic technologies may also have effects on relatives. Not only genetic tests, but all diagnoses of hereditary disorders, also provide knowledge of relatives. Diagnostic information may also affect social relations (e.g. STD)".</p> <p><b>Specific to Pharmaceuticals (2.1) - PUBLIC DRAFT</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 of other pharmaceuticals). Expensive pharmaceuticals (orphan disorders, new cancer treatments) and prescribing pharmaceuticals according to genetic profiles challenges 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 (2.1) - PUBLIC DRAFT</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 of relatives. Screening results may also affect social relations.</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>49, 50</p>
<b>Content relations</b>	
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>None</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>D0030, D0022, D0023, I0008, C0006</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>D0022, D0023, I0008, C0006 D0030, D0022, D0023, I0008, C0006</p>

F0005 Assessment element card						
Issue: Is the technology used for patients/people that are especially vulnerable?						
Topic: Autonomy						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	5
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	5
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	5
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	5
Clarification	<p><b>Common to all used applications</b></p> <p>The right and justification to use the technology for persons who are vulnerable has to be clarified. Persons that are vulnerable could for example be pregnant women as to protect their unborn child, 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>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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	6
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	6
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	6
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	6
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 patients' right to autonomy directly or indirectly by influencing/subtracting the decisional capacity. However, patients have in most cases a right to autonomy, i.e. right to be self-governing agents. This means 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 fecal 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 if side effects take place and how these can affect the living quality or choices (eg 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>					

	49, 52
<b>Content relations</b>	
<b>Sequential relations</b>	<b>Common to all used applications</b>  H0013

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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 (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	7
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	7
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	7
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	7
Clarification	<p><b>Common to all used applications</b></p> <p>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</p>					

	serious side effects, may have an effect on personality or lead to increased need of sleep or overweight. They should also be informed of that the mode of delivery or action may affect their daily life (eg. no car driving allowed, restricted travelling).
<b>Methodology and sources</b>	<b>Common to all used applications</b>  . Expert opinion. Stakeholder hearing
<b>References</b>	<b>Common to all used applications</b>  51
<b>Content relations</b>	
<b>Sequential relations</b>	<b>Common to all used applications</b>  H0013, H0007, H0008,  C0008, B0014,  I0002,  C0005

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2

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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	8
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	8
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	8
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	8
Clarification	<p><b>Common to all used applications</b></p> <p>Technologies may change the relationship between physician and patient, 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 health care professionals (eg. screening for drug abuse when use is denied). Technologies that align 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>49, 53</p>					
Content relations						

<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>G0010</p>
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<p><b>F0008 Assessment element card</b></p> <p><b>Issue: Does the implementation or use of the technology affect human dignity?</b></p> <p><b>Topic: Respect for persons</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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	9
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	9
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	9
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	9
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Especially technologies that are applied for 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 use of the technology may also threaten their dignity.</p> <p>Some technologies may cause labelling healthy people as sick (eg 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>					
<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>					



	49, 54
<b>Content relations</b>	
<b>Sequential relations</b>	

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F0009 Assessment element card						
Issue: Does the implementation or use of the technology affect the user's moral, religious or cultural integrity?						
Topic: Respect for persons						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	10
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	10
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	10
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	10
Clarification	<p><b>Common to all used applications</b></p> <p>The technology can challenge integrity by preventing (or tempting 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 users' selves. 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 will not tolerate blood transfusion, pharmaceuticals used for abortion in cultural groups that will not tolerate 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,</p>					

	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.
<b>Methodology and sources</b>	<b>Common to all used applications</b>  Literature search. Expert opinion. Stakeholder hearing
<b>References</b>	<b>Common to all used applications</b>  49, 50
<b>Content relations</b>	
<b>Sequential relations</b>	<b>Common to all used applications</b>  H0011, H0013

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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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	11
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	11
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	11
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	11
<b>Clarification</b>	<b>Common to all used applications</b>					

	The sphere of privacy can be invaded both virtually and physically. 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?
<b>Methodology and sources</b>	<b>Common to all used applications</b>  Literature search. Expert opinion. Stakeholder hearing
<b>References</b>	<b>Common to all used applications</b>  51
<b>Content relations</b>	
<b>Sequential relations</b>	<b>Common to all used applications</b>  B0010, D0011,  I0007, I0009,  I0005

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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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	12
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	12
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	12
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	12
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 reallocation of human resources, funding and training. A large reallocation of resources may seriously jeopardize 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 prioritization explicit or implicit?</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Diagnostic technologies sometimes acquire significant symbolic value (e.g. fetal ultrasound, PSA) that may create demands for tests that are not justified on health grounds.</p> <p><b>Specific to Pharmaceuticals (2.1) - PUBLIC DRAFT</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 (eg. large variation in prescribing ADHD medication for children by various countries).</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Screening technologies sometimes acquire significant symbolic value (e.g. fetal ultrasound, PSA) that may create demands for tests that are not justified on health grounds.</p>					

<b>Methodology and sources</b>	<b>Common to all used applications</b>  Expert opinion.
<b>References</b>	<b>Common to all used applications</b>  49, 55, 56
<b>Content relations</b>	
<b>Sequential relations</b>	<b>Common to all used applications</b>  G0007,  E0001,E0002, E0009

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<p><b>F0013 Assessment element card</b></p> <p><b>Issue: How are technologies with similar ethical issues treated in the health care system?</b></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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	13
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	13
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	13
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	13
<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 health care system may help to adopt coherent and just health policies, either by applying past precedents to current cases, or showing that past cases need reconsideration. Similarity is to be defined individually for each technology. The idea is to concentrate only on the similarities relevant for solving the ethical problems found important for the current HTA</p>					

	project. The similar ethical problems can be related to similarities in the technology's medical, technological, economic, social, organisational or legal nature.
<b>Methodology and sources</b>	<b>Common to all used applications</b>  Literature search. Expert opinion
<b>References</b>	<b>Common to all used applications</b>  49
<b>Content relations</b>	
<b>Sequential relations</b>	

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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 (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	14
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	14
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	14
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	14
<b>Clarification</b>	<b>Common to all used applications</b>  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, and employment, insurance) prevent access? Potential inequalities and discrimination should be justified. Issues of access to a technology as well as labelling and potential discrimination of persons receiving and not					

	<p>receiving treatment should be considered.</p> <p>Are special groups discriminated?. Ethical and social issues have often been considered in academic articles and discussions in the HTA field, but they have rarely been translated into practice.</p>
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Implement the best available evidence about social restrictions, social pressure, social attitudes</p>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>See social domain</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>SHARED with SOC domain H0012</p> <p>Legal domain</p>
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>G0009, G0101</p> <p>A0012</p> <p>I0011</p>
<b>Other domains</b>	<p>Also in: Social aspects</p>

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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 (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	15
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	15
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	15
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	15
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. 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 health care.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Literature search. Law, rules and regulations. Expert opinion. Stakeholder hearing</p>					
References	<p><b>Common to all used applications</b></p> <p>49, 57</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>SHARED with legal domain?</p>					
Sequential relations	<p><b>Common to all used applications</b></p> <p>H0012</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: Legislation						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Important	None	No	16
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	None	No	16
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	None	No	16
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	None	No	16
Clarification	<b>Common to all used applications</b>  Is legislation and regulation to use the technology fair and adequate? Use of the technology may lead to ethical issues that make current regulations inadequate. Screening and diagnostic technologies are commonly differently regulated than treatments, especially medications. Ethical reflection is essential in order to assess what kind of legislation, regulation or amendments is needed (see also legal domain).					
Methodology and sources	<b>Common to all used applications</b>  Law, rules and regulations. Stakeholder hearing. Expert opinion					
References	<b>Common to all used applications</b>  49, 58					
Content relations	<b>Common to all used applications</b>  SHARED with legal domain?					
Sequential relations	<b>Common to all used applications</b>  B0010, I0011,					

	I0009,  I0002,  I0026  <b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b>  I0008  <b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b>  I0008
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F0017 Assessment element card						
Issue: What are the ethical consequences of the choice of end-points, 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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	17
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	17
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	17
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	17
Clarification	<p><b>Common to all used applications</b></p> <p>Is there a risk that the chosen end points, cut-off values or comparators/controls may give 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 fully possible so other endpoints may have 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</p>					

	have serious consequences.
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Other domains:, safety, effectiveness. Expert opinion, Stakeholder hearing</p>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>49</p>
<b>Content relations</b>	
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>See methodological description in EFF and SAF</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>B0018 D1004 D1005 D1006</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>D1004 D1005 D1006 B0018 D1004 D1005 D1006</p>

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F0102 Assessment element card						
Issue: Does the economic evaluation of the technology contain any ethical problems?						
Topic: Ethical consequences of the HTA						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	18
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	18
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	18
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	18
Clarification	<b>Common to all used applications</b>  It is important to consider whether there are any ethical problems related to the data or assumptions that have been used in the economic valuation. An example is whether or not indirect costs have been valued in a fair and adequate way.					
Methodology and sources	<b>Common to all used applications</b>  Literature search, Expert opinion					
References	<b>Common to all used applications</b>  9, 51					
Content relations						
Sequential relations	<b>Common to all used applications</b>  See methodological description in ECO					

F0103 Assessment element card						
Issue: What are the ethical consequences of the assessment of the technology?						
Topic: Ethical consequences of the HTA						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	19
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	19
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	19
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	19
Clarification	<b>Common to all used applications</b>  At what time of the lifetime of the technology is it assessed? Who will (not) get access to the new technology, as a result of the conclusions of the HTA? What are the consequences of assessing the technology with respect to prioritisation?					
Methodology and sources	<b>Common to all used applications</b>  Expert opinion, Stakeholder hearing					
References	<b>Common to all used applications</b>  49					
Content relations						
Sequential relations						

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## 1 **Organisational aspects**

### 2 **Description**

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

4 The domain of organisational aspects (later in the text *organisational domain*) considers how  
5 different kind of resources (e.g. material artefacts, human skills and knowledge, money, attitudes,  
6 work culture) have to be mobilised and organised when implementing a technology, and the  
7 consequences they may further produce in the organisation and the health care system as a whole.  
8 The issues include e.g. work processes and patient/participant flow, quality and sustainability  
9 assurance, centralization, communication and co-operation, managerial structure, and acceptance.

10 There are three levels on which to consider organisational aspects: Intra-organisational (e.g. how  
11 information about new technology is provided to the patients in the organisation), inter-  
12 organisational (e.g. how the communications between different organisations occur), and health  
13 care system level (e.g. how to set national objectives). There are various stakeholders, besides staff  
14 and patients/participants, at various levels, e.g. payers, providers and suppliers. These groups have  
15 usually different aims and expectations of the technology.

16 The elements that constitute an organisation have been defined in many ways in different  
17 approaches: for example the physical structure, social relations, technology and organisational  
18 culture. The structure of an organisation defines its assignment of tasks, reporting systems and the  
19 mechanisms of interaction and coordination. In addition, other elements of society and its culture  
20 influence an organisation and its function. Different types of organisations exist, e.g. the profit  
21 centre organisation, the matrix organisation and the network organisation. {1}

22 The complexity of health care systems and processes challenges the assessment of organisational  
23 aspects. Due to the multiplicity of objectives and criteria in organisational analysis, it will be less  
24 pre-determined and more variable than for example economic and clinical effectiveness analyses. In  
25 addition, the findings are expected to be more context-dependent and less transferable than e.g. in  
26 the effectiveness and safety domains of an HTA. The choice of the areas of assessment should be  
27 guided by the information needs of the end users of HTA (e.g. regional health authorities' focus  
28 may differ from that of hospital managers). Furthermore, different health care systems and national  
29 prescribing rules must be taken into account to deal with transferability issues. Since organisational  
30 aspects vary across countries, it could limit exportation of HTA information from one country to  
31 another.

#### 32 **Topics and issues in this domain**

33 The organisational domain includes five topics and each topic contains 2 to 6 issues (questions),  
34 resulting in altogether 14 issues (table 1). These topics and issues represent probably the most  
35 important organisational issues, but their relevance depends on the specific technology and needs to  
36 be considered within each assessment. In the context of some technologies one might identify other,  
37 more relevant topics and issues, and if such are found, the Model should be amended.

38 The issues of the organisational domain are more generic than those of many other domains of the  
39 HTA Core Model. This is because organisational aspects are difficult to define in detail in advance.  
40 For example the issue concerning patient/participant flow is a question about describing the steps of

1 the patient path including e.g. intervention and waiting times. Therefore, one issue compiles a  
2 coherent full picture of the path instead of focusing on the details in separate issues, as may be more  
3 relevant in some other domains. Contents of the issues are explained in more detail in the  
4 Clarification section of Assessment element table (AE table 2).

5 While defining the issues, it had to be taken into account that the viewpoint of the organisational  
6 domain consists of different levels of health care (mikro-, meso- and macro-level).

7 **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 mobilized for patients/participants and important others?	G0002
Health delivery process	What is the process ensuring proper education and training of the staff?	G0003
Health delivery process	What kind of co-operation and communication of activities have to be mobilised?	G0004
Health delivery process	How is the quality assurance and monitoring system of the new technology organised?	G0012
Structure of health care system	How does de-centralisation or centralization requirements influence the implementation of the technology?	G0005
Structure of health care system	What are the processes ensuring access to care of the new technology for patients/participants?	G0101
Process-related costs	What are the processes related to purchasing and setting up the new technology?	G0006
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 the other interest groups taken into account in the planning / implementation of the technology?	G0011

1

## 2 Why is this domain important?

3 In many countries the organisational aspects have not been a visible part of HTA until a few years  
4 ago: focus has been more on the clinical aspects {2-4}. The growing focus on organisational issues  
5 in HTA indicates a recognition that many decisions on resource allocation in provision of  
6 technologies are of crucial importance. Organisational aspects in an HTA influence the behaviour of  
7 managers and health professionals {5}. Also policymakers on the national level need information  
8 on organisational aspects when making decisions on the use of technologies. Organisational aspects  
9 in HTA may clarify most of the challenges and barriers in implementing health technologies and  
10 hence they could influence the impact of health technology assessment.

## 11 Relations to other domains

12 The organisational domain is related to all other domains: health problem and current use (e.g.  
13 utilisation, management), description and technical characteristics (e.g. investments), safety (e.g.  
14 occupational safety), effectiveness (e.g. adherence), cost and economic evaluation (e.g. budget  
15 impact), ethical aspects (e.g. acceptance), social aspects (e.g. patient/participant aspects), and legal  
16 (e.g. privacy). The relations of the issues are marked in the AE table 4.

17 Some relations between issues are sequential. For example the domain of Health Problem and  
18 Current Use of Technology includes issues concerning the utilisation of a technology, the number  
19 of people including the target group and estimates of the utilisation of the technology. The results  
20 for these questions should be known before answering most of the Organisational domain's issues.  
21 In addition, issues concerning any required quality assurance of the technology, which is included  
22 in the domain of Description and Technical Characteristics, are important in the organisational  
23 domain. Here, the organisational domain's point of view is different from that in the Health  
24 Problem and Current Use domain: instead of describing content of any necessary quality assurance  
25 of a new technology, it describes the process required for organising these.

26 The domain of Organisational aspects is related to the Costs and Economic Evaluation domain, as  
27 some of the information on organisational aspects can be beneficial in economic analysis. For  
28 example, the patient/participant flow of a new technology, which is described in the Organisational  
29 domain, could offer information on parameters used in economic analysis. For this reason, a

dialogue between the Costs and Economic Evaluation domain and the Organisational aspects domain should be initiated at an early stage, so that the Cost and Economic Evaluation 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 needs organizational changes and leads to organizational changes that should be taken into account. The implementation of a new diagnostic test can substantially increase (or decrease) number of patients needed to be treated, thus changing relations between different organizations 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 incorporating 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 an assessment of a complex organization where organisational changes and relations within and between organisations are considered.

The screening technology under assessment can have various objectives and thus various implications for organisational aspects assessment. For example, when assessing mammography screening program, the focus can be either on a new screening test (digital mammography), or on the population eligible for screening (screening for women less than 50 years old), or varying the screening interval (1 to 3 years), or 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 extent of the use of screening as defined in the Health Problem and Current Use domain, is of importance to the Organisational domain. In the Description and Technical Characteristics domain issues concerning definitions of the screening test and further investigations (diagnostic tests) are important in the organisational domain, too. The domain of Costs and Economic Evaluation often benefits from determination of e.g. management of screening programmes, training of personnel 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. It deals as well with the distribution, and the 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 the single pharmaceutical on the organization of the care pathway and its interaction with pre-existing health technologies.

## 1 Methodology

### 2 Process for answering research questions

3 Process of assessment of organisational aspects starts with defining relevant scope of the analysis  
4 and relevant topics and issues for the technology being assessed. After this, theoretical perspective  
5 that fits the co-production approach has to be chosen. When identifying the research problems and  
6 questions it has to be taken into account that organisational analysis deals with the overall policy  
7 questions and the organisational set-up.

8 The first step is to make a systematic literature search focusing on the organisational aspects. If  
9 there are no systematic reviews available, primary studies and other sources of information (e.g.  
10 guidelines) should be used. If there are no relevant studies, own research should be conducted e.g.  
11 in the form of surveys or interviews. If there is no resources or time for own research, at least health  
12 care professionals or content experts should be consulted.

13 The researchers working on this domain should consider their basic approach early in the project as  
14 several other domains depend on the answers of this domain (e.g. ECO domain). Sometimes it  
15 could be sensible to make a joint survey with Technology description and Current use domains  
16 early in the project as a pragmatic approach to finding answers to key questions. Other domains  
17 could contribute to the survey questions so that they provide useful information for all domains. A  
18 common survey has to be considered carefully as it could be time consuming and require lot of  
19 resources.

### 20 Gathering information

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

22 Several sources of information are needed to find answers to the questions of Organisational  
23 domain. To reduce publication bias, it is recommended that a wide range of sources of information  
24 should be searched {6}. These should include published literature, as well as grey literature, hand  
25 searching of journals, contacting experts and scanning reference lists of relevant papers. In addition,  
26 own research is often an important source of information. The retrieved information of  
27 organisational domain may often be rather general in nature and not disease- or product-specific.

#### 28 Databases and search strategies

29 Some important databases and other sources of information possibly useful for the analysis in this  
30 domain are listed below. We recommend also using the Summarized Research in Information  
31 Retrieval for HTA (SuRe Info, available at <http://vortal.htai.org/?q=sure-info>) which provides  
32 research-based information relating to the information retrieval aspects of producing health  
33 technology assessment.

34 The databases needed in the Organizational domain depend on the topic of the assessment. Usually,  
35 the most used databases are MEDLINE/Pubmed, CRD DARE, Cinahl, Cochrane Library and GIN.

36 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://eunethhta.dimdi.de/PopDB/>
  - ClinicalTrials.gov at <http://www.clinicaltrials.gov/>
  - Prospero (International prospective register of systematic reviews) at [http://www.crd.york.ac.uk/NIHR\\_PROSPERO/](http://www.crd.york.ac.uk/NIHR_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);
  - OAlster (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
- 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  
[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
- Industry
- Expert opinions: Contacts or interviews with appropriate experts and agencies
- National and regional guidelines
- National and regional norms and regulations

#### Own primary research

Own research is needed in situations where adequate information is not found in the literature search, and also if there's a specific need for information on some specific geographic area (and the information is not found in the literature). As the organisational domain is multiply related to other domains, it could be helpful to co-operate with other domains while conducting own research. Relations, especially sequential relations (e.g. with Costs and Economic Evaluation domain) have to be taken into account before starting own research.

#### Some aspects to consider 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:



- 1 o Discussions with experts or officials
- 2 o Expert surveys or interviews
- 3 o Research using administrative databases
- 4 o Register-based research

- 5
  - Industry

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

9 When starting primary research, the aim of the research has to be clarified. The list of assessment  
10 elements helps specify the aim and content of the research. The research questions will influence  
11 the choice of research design (quantitative or qualitative). Quantitative research could be descriptive  
12 (survey or case series) or analytical (observational or experimental). Qualitative research uses  
13 inductive reasoning and it could be used together with quantitative research designs (mixed  
14 method). There are several possible study methods to choose from, e.g. interviews, questionnaires,  
15 observation, an analysis of written material. The target group(s) of own research has to be planned  
16 carefully. For example tailored questionnaires or interviews to different groups of professional  
17 could be needed for getting information about work processes.

18 Usually, it will be difficult to isolate and measure the output effects of given organisational  
19 initiatives. More realistic is to describe the various process dimensions in relationship between a  
20 technology and organisational behaviour. The natural starting point of an analysis of change in  
21 processes will be to map the current work processes and patient-flow. Therefore, the methods for  
22 data collections involve: qualitative methods such as interviews or observations, or quantitative  
23 methods such as surveys. { 1 }

24



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

2 Evaluation of public health interventions is usually complex, as multiple interventions, outcomes,  
3 participants, settings and stakeholders are often necessary components. Because of the complexity,  
4 no single research method is likely to be appropriate and a range of different study designs are used.  
5 A framework for the design and assessment of complex interventions has been proposed which  
6 offers guidance on the various phases, including establishing the theoretical basis (mechanisms of  
7 action) for the intervention. A sound theoretical base is considered vital to the design of complex  
8 interventions and in explaining likely mechanisms for success. However, in practice many  
9 interventions and assessments lack explicit theoretical underpinning. {7}

10 In a complex system, such as health care, the boundaries are typically fuzzy and activities of  
11 different agents are not predictable. Multiple approaches to the assessment are needed in these  
12 kinds of systems {8}. Through different theoretical frameworks we can understand how various  
13 organisational functions operate.

14 One approach to address health care systems is to divide them into micro-level (patient interaction),  
15 meso-level (health care organization and community) and the macro-level (health policy). All these  
16 levels have been taken into account while defining the issues of the organisational domain. Most of  
17 the issues are relevant at all levels (e.g. approval of a new technology) and some mostly in one  
18 level, (e.g. issues related to the staff, which affect mostly the hospital level). There are issues related  
19 to the patients/participants in nearly all topics.

20 The relation between technology and organisation can be tackled in different ways. At least two  
21 different and incompatible views on causality and transferability can be differentiated with respect  
22 to the organisational issues: the diffusion model and the translation model, see Appendix 3 {1, 9}.

23 The definition of organisational analysis in this document is based on the loose approach called co-  
24 production of technology and its context and especially on the translation model. Its main thesis is  
25 that a technology needs a context or a network to function. In addition to the translation model,  
26 other approaches that form the co-production approach are for example constructive technology  
27 assessment {10, 11}, the systems approach {12} and social construction of technology {13}.

28 Both organisational and administrative perspective can be used in the organisational analysis {14}  
29 Administrative analysis uses a managerial perspective (e.g. decision making, co-ordination and  
30 managerial tools) and organisational analysis deals with changes in relation to the executing  
31 /producing function (e.g. organisational conditions, change processes).

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

33 A wide range of disciplines needs to be applied to research on the organization and delivery of  
34 health services {15}. It can be challenging for researchers from various disciplines to think outside  
35 their own paradigms {4}. Multidisciplinary research is a key element in the organisational domain  
36 and qualitative study is the mostly used study type. (Table 2). In this kind of research approach the  
37 scope of relevant evidence is not known in advance and therefore the search method is usually  
38 iterative. The collected information of iterative search can be systematic only if the search steps  
39 have been documented carefully.

- 1 There are several ways how to formulate the research question of organisational aspects. Within  
2 quantitative research the review question is usually based on PICO (Patient, Interventions, Control,  
3 Outcomes), see Appendix 3. Within qualitative evidence synthesis SPICE (Setting, Perspective,  
4 Intervention/Interest, Comparison, Evaluation) {16} or PICO (Population, phenomena of Interest,  
5 Context, outcome) would be more eligible for formulating a research question {17}.
- 6 What kind of study design gives the most reliable answer to a research question depends on the  
7 question itself. Both quantitative and qualitative studies and their synthesis are essential in the  
8 organisational domain. Although the most important sources of information are observational and  
9 qualitative studies, it is also relevant to check if there are controlled or quasi-experimental studies  
10 available. Other types of relevant information for organisational issues can be found in national and  
11 international guidelines, statistics and registers and handbooks.

12 **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

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

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

## 5 **Tools for critical appraisals**

6 Quality assessment of the information retrieved in the organisational domain may be difficult, as  
7 there is often no standard way of doing it and due to the fact that many aspects and facets must be  
8 taken into account when information is evaluated in terms of its quality. The validity of the  
9 information may differ considerably depending on the source (see table 2) and type of information  
10 requested (quantitative or qualitative; registers, administrative data etc.).

11 There are different study types used in gathering information for the organisational domain and  
12 therefore the range of quality assessment and appraisal instruments available to assess studies is  
13 wide. Examples of the tools of critical appraisals of different study types are shown in the appendix  
14 3. Some of the appraisal instruments are generic and others targeted to specified contexts.

15 For quantitative studies assessment of quality is clearer than for qualitative studies. It has been  
16 claimed that quality of a qualitative study cannot be determined by prescribed instruments {18}.  
17 Therefore using checklist or scales on quality assessment of observational or especially of  
18 qualitative studies is not always relevant.

19 The Canadian CADTH has recently reviewed quality assessment tools and provides useful insights  
20 into the topic and details beyond what is included in this chapter {19}.

## 21 ***Critical Appraisal of Quantitative and Qualitative Evidence***

22 Within quantitative reviews, there is a range of study designs that may be incorporated. A common  
23 approach is to state a preferred hierarchy of types of studies: Experimental e.g. randomised  
24 controlled trials (RCTs); Quasi experimental e.g. non-randomised controlled trials; Observational  
25 (Correlational) – e.g. cohort, case control studies; Observational (Descriptive) – e.g. case series and  
26 case study; and Expert opinion. By stating also the level of evidence, the quality of evidence would  
27 be more appropriately assessed  
28 [http://www.joannabriggs.edu.au/About%20Us/About%20Us/JBI%20Approach/Levels%20of%20E](http://www.joannabriggs.edu.au/About%20Us/About%20Us/JBI%20Approach/Levels%20of%20Evidence%20FAME)  
29 [vidence%20FAME](http://www.joannabriggs.edu.au/About%20Us/About%20Us/JBI%20Approach/Levels%20of%20Evidence%20FAME)

## 30 **Quality Assessment of Trials**

31 The RCT (Randomized Controlled Trials) and quasi-RCT represents one of the most frequent  
32 research studies where quantitative data on results of applying a certain health technology can be  
33 found. Quality of this information should be assessed on aspects such as: random assignment of  
34 patients, blinded allocation of patients, blinded evaluation of outcomes, similar control and  
35 treatment groups, confounders, outcomes measurement, statistical analysis etc. See Critical  
36 Appraisal Checklists for RCT {17}.

37

## 1 **Quality Assessment of Epidemiologic studies**

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

5 Several checklists or scales exist for critical appraisal of observational studies, but no consensus  
6 exists about using those. In choosing the checklist, it has to be taken into account how easy the scale  
7 is to use and how long it takes to complete each instrument. The most appropriate scales are  
8 Newcastle Ottawa Scale\*, the checklist of AHQR (System to Rate the Strength of Scientific  
9 Evidence) and checklist of STROBE\*\* on reporting observational studies (see Appendix 3).

10 *\*Newcastle Ottawa scale (see Appendix 3) may not be appropriate in the quality assessment of*  
11 *studies examining disease prevalence or burden of disease. It is more appropriate for studies*  
12 *assessing the link between diseases and risk factors.*

13 *\*\*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*  
14 *as a check list for study quality, although it is an instrument meant for assessing the quality of*  
15 *reporting (see Appendix 3).*

## 16 **Quality Assessment of case control or cohort studies**

17 Case-control of cohort studies can be used to identify if the benefits observed in randomised trials  
18 translate into effectiveness across broader populations in clinical settings and provide information  
19 on adverse and risks. See Critical Appraisal Checklists for cohort or case-controlled studies and for  
20 descriptive or case series studies {17}.

## 21 **Quality Assessment of observational studies**

22 There are several checklists or scales on critical appraisal of observational studies but no consensus  
23 about using those. In choosing a checklist, it had to be taken into account how easy the scale is to  
24 use and how long it takes to complete each instrument. Some of the most appropriate scales are  
25 Newcastle Ottawa Scale, the checklist of AHQR (System to Rate the Strength of Scientific  
26 Evidence) and checklist of STROBE on reporting observational studies (see Appendix 3).

## 27 **Quality Assessment of guidelines**

28 AGREE is a tool for assessing quality of clinical practice guidelines. Grading the quality of  
29 evidence and strength of recommendations could be done by GRADE (see Appendix 3).

## 30 **Quality Assessment of manufacturers' data**

31 The information provided by manufacturers might be limited by issues of confidentiality and  
32 marketing. This source can be useful in order to answer questions concerning the requirements for  
33 use of the technology, development status or forthcoming innovations of the technology.  
34 Manufacturers may also provide information on on-going research and on scientific literature not  
35 yet published. Scientific information provided by manufacturers needs to be evaluated for validity  
36 and applicability. Own analysis of administrative data often requires authorization from the data  
37 owner, which in some countries might be difficult to obtain due to issues of privacy protection and  
38 confidentiality.

## 1 **Quality assessment of expert opinion**

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

9 The focus on limiting bias to establish validity in the appraisal of quantitative studies is not possible  
10 when dealing with text and opinion. In appraisal of text, the opinions being raised are vetted, the  
11 credibility of the source investigated, the motives for the opinion examined, and the global context  
12 in terms of alternate or complementary views are considered. Validity in this context therefore  
13 relates to what is being said, the source and its credibility and logic; and consideration of the overt  
14 and covert motives at play.

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

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

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

- 20 • How representative is the register? (European, national, regional, local?)
- 21 • What kind of information is coded?
- 22 • What are the inclusion/exclusion criteria for data entered?
- 23 • What is the quality of information?
- 24 • How complete is the coverage?

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

28 **Statistics and routinely collected data:** Routinely collected administrative data (e.g. DRGs,  
29 discharge databases, reimbursement claims databases) can be useful, when available. For example  
30 sickness funds collect large amounts of information which could be used to analyse utilisation of  
31 technology. By definition, these data have been collected for other purposes than research and they  
32 cannot be used to answer scientific questions without previous processing. Analysis of this kind of  
33 data might be very time consuming, since data need to be “prepared” before analysis, and hence the  
34 data may not be feasible to use within an HTA project. The use of routinely collected statistics has  
35 several limitations. The reliability of the diagnosis varies and usually it is not possible to  
36 differentiate between different stages of the disease. Even the validity of the coding of causes of  
37 death may be variable, and in some countries it is known to be very limited. Several national and  
38 international sources of statistics exist which can be used to assess the incidence, prevalence,  
39 mortality, or burden of disease. These statistics are usually available in aggregated form and  
40 increasingly through the internet.

1 Own analysis of administrative data often requires authorization from the data owner, which in  
2 some countries might be difficult to obtain due to issues of privacy protection and confidentiality.  
3 Researchers of this domain should be aware of the *Policy for HTA Core Model and core HTA*  
4 *information* that defines specific rules for using non-public data.

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

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

10 Appraisal should consider appropriateness of research method(s), sampling, data collection and  
11 analysis. Although several quality assessment instruments are available, there is disagreement about  
12 the appropriate criteria for critical appraisal of qualitative research or whether quality assessment  
13 should be done at all (appendix 3).

14 For example, within a Cochrane Intervention review a critical appraisal of qualitative studies is an  
15 essential step. According to Cochrane guidance, critical appraisal involves (i) filtering against  
16 minimum criteria, involving adequacy of reporting detail on the data sampling, - collection and -  
17 analysis, (ii) technical rigour of the study elements indicating methodological soundness and (iii)  
18 paradigmatic sufficiency, referring to researchers' responsiveness to data and theoretical  
19 consistency. In choosing an assessment instrument the review team needs to consider the  
20 appropriateness of their choice in the context of their review and be aware that whether or not a  
21 study meets the standard might depend on the instrument used. {20}.

### 22 **Analyzing and synthesizing evidence**

#### 23 **Data extraction**

24 There are several issues defined in the HTA Core Model, particularly in this domain, where  
25 systematic data retrieval is not necessary (see Table 1). Unsystematic gathering of information from  
26 books, surveys, introduction sections of reviews and articles, registers and the internet until  
27 saturation is reached may be enough. However, one should consider the risk of selection bias due to  
28 insufficient or selective inclusion of information sources and data, and reflect the possible  
29 limitations in the domain discussion chapter.

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

36 In reviews of qualitative studies, data extraction is typically a more iterative process. Review  
37 authors may move between reading primary papers, data extraction and synthesis / interpretation in  
38 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}. One example of data extraction form for qualitative studies is SUMARI (System for the Unified Management, Assessment and Review of Information) made by Joanna Briggs institute {17}. SUMARI is designed to assist health and other researchers and practitioners to conduct systematic reviews with evidence of Feasibility, Appropriateness, Meaningfulness and Effectiveness and to conduct economic evaluations of activities and interventions. It is composed by 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 either 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 to ensuring comprehensiveness and encouraging a more reflexive analysis of data than as a pure test of validity. {22}

### ***Evidence tables***

The information of evidence tables may include attributes of study design, patient characteristics, patient outcomes and derived summary statistics.

Until now the HTA Core Model has not contained any standard tables for summarizing the evidence that supports 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 to 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>

## 1 **Meta-analysis**

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

## 4 **Synthesis of qualitative research**

5 Synthesizing qualitative evidence is a process of combining evidence from individual qualitative  
6 studies to create new understanding by comparing and analysing concepts and findings from  
7 different sources of evidence with a focus on the same topic of interest. It can be an aggregative or  
8 interpretive process which requires authors to identify and extract evidence, categorizing the  
9 evidence, and combining categories to develop synthesized findings. It is important to understand  
10 why people feel or behave in certain ways and not just make a description of it {23}.

11 There is a range of methods available for synthesizing diverse forms of evidence, for example meta-  
12 ethnography, grounded theory, thematic synthesis, narrative synthesis, realist synthesis and content  
13 analysis. Some of the methods maintain the qualitative form of the evidence (such as meta-  
14 ethnography) and some involve converting qualitative findings into a quantitative form (such as  
15 content analysis). {7}

16 Synthesis methods are classified in different ways and it has been argued whether it is acceptable to  
17 conduct syntheses of qualitative evidence at all, and whether it is acceptable to synthesize  
18 qualitative studies derived from different traditions. {7, 24, 25}

19 Qualitative and quantitative findings could be synthesized in two ways: multilevel synthesis  
20 (separate and combined synthesis) and parallel (separate and juxtaposed synthesis) {23}.  
21 Quantitative and qualitative studies can be synthesized together; one example is a systematic review  
22 on teenage pregnancy and social disadvantage {20}.

## 23 **Reporting and interpreting**

24 Transparency in information retrieval is crucial when reporting core HTA information; the sources  
25 and methods of retrieval, systematic or not, and quality assessment criteria (also when missing)  
26 should be explicitly stated for each issue.

27 A reader of core HTA information might be interested to know the incidence of the condition and  
28 the extent of use of the technology in other countries, particularly when there is no information  
29 available from own country. Therefore, both European level and national data can be of importance,  
30 and can be reported. Tables, graphs and figures make abundant numerical information, e.g. trends in  
31 epidemiology, more digestible.

32 Overview of guidelines synthesizing the main recommendations on management practises would be  
33 illustrative.

34 The transferability of the research identified in literature searches will have to be assessed very  
35 carefully, since this domain is in general to be considered highly context-specific. It is possible that  
36 the results from the literature review can be considered to be hypothesis-generating and useful for  
37 planning primary research in the own context.



## 1 Screening-specific content

2 Policy measures, such as the choice between organised and opportunistic screening, or the  
3 reimbursement/funding strategies are implemented at the macro-level and are likely to be assessed  
4 more appropriately by observational/qualitative studies. The organisation of screening services  
5 delivery at the institutional (meso-level) might be studied using qualitative research designs, but  
6 experimental studies may offer valuable and crucial information. Similarly, at the micro-level of the  
7 interaction between provider and patients both experimental and qualitative evidence are important  
8 when assessing screening technology. Of course there are interactions across the three levels and  
9 different actors may be involved at more than one level (i.e. the provider is involved both at the  
10 meso- and at the micro-level).

## 11 Pharmaceutical-specific content

12 Pharmaceuticals can be used at home or in the hospital and this determines to some extent the  
13 success of treatment. In the hospital, a pharmaceutical is administered by trained and skilled  
14 personnel. At home and at events that take place during the hospital stay pharmaceuticals are  
15 administered by the patient himself, by relatives or in some cases by ambulatory trained personnel.  
16 It is necessary to evaluate whether patients are able to administer the prescribed treatment at home,  
17 read labels, understand dose instructions, and open containers or packaging.

18

## 1 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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
Clarification	<p><b>Common to all used applications</b></p> <p>Current tasks and work processes should be described. This help to make a picture of 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>It should be explained what kind of changes a new technology could have: it might replace or reduce some activities.</p> <p>This issue is about patient path way by the point of view of patient/participant. Patient path should be described step by step. This includes also the waiting times for diagnosis and/or treatment and waiting time for analysis of the technology.</p> <p>Preparations that patients/participants need to do before and after (e.g. diet before bariatric surgery) must be taken into account, as well as need for self/home monitoring.</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>The implementation of a new diagnostic test can substantially increase (or decrease) number of patients needed to be treated, thus changing relations between different organizations and influencing the health care system as a whole.</p> <p><b>Specific to Pharmaceuticals (2.1) - PUBLIC DRAFT</b></p> <p>The differences of the work processes between the new medicine and the comparator have</p>					

	<p>to be specified. For example new medicine does not need routine laboratory unlike the comparator.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>It has to be described 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 notifying results, recalls, reminders ).</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> <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>{1, 14}</p> <p>{1, 14}</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>: A0013, A0014,A0024, B0004, C0063, D0020, D0021, D0023, F0001, F0007, I0002, I0009</p>
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>A0007, A0023, A0011</p> <p>Order of doing; to be answered prior to: E0001</p>

1

2

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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	2
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	2
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	2
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	2
Clarification	<p><b>Common to all used applications</b></p> <p>This issue is about patient path way by the point of view of patient/participant. Patient path should be described step by step. This includes also the waiting times for diagnosis and/or treatment and waiting time for analysis of the technology.</p> <p>Preparations that patients/participants need to do before and after (e.g. diet before bariatric surgery) must be taken into account, as well as need for self/home monitoring.</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>{1, 14}</p>					
Content relations						
Sequential relations	<p><b>Common to all used applications</b></p> <p>A0010, H0003</p>					

Order of doing; to be answered prior to: E0001

1

G0002 Assessment element card						
Issue: What kind of involvement has to be mobilized for patients/participants and important others?						
Topic: Health delivery process						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Important	None	No	3
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	None	No	3
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	3
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	3
Clarification	<p><b>Common to all used applications</b></p> <p>This issue is about the role of patients/participants. A new technology may require distribution of tasks among the people involved in the treatment and care. Patients/participants and their important others may be more actively involved in own care and treatment – or tasks they used to carry out may be taken over by health professionals.</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</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 (2.1) - PUBLIC DRAFT</b></p> <p>The way patient get the medicine and how he is involved in the follow-up (monitoring by patients/participants or by their important others).</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>The screening has to be organised in the way that the test and the further investigations are easily attainable e.g. mobile mammography.</p>					
Methodology and sources	Common to all used applications					

	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).
<b>References</b>	<b>Common to all used applications</b>  {14}
<b>Content relations</b>	<b>Common to all used applications</b>  B0014, H0003, H0010, H0006, H0007, H0008, H0009, H0013
<b>Sequential relations</b>	<b>Common to all used applications</b>  A0007 Order of doing; to be answered prior to: H0002

1

G0003 Assessment element card						
Issue: What is the process ensuring proper education and training of the staff?						
Topic: Health delivery process						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	4
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
<b>Clarification</b>	<b>Common to all used applications</b>  New technology may require new kind of professionals or new tasks for existing personnel. This issue is about how the organisation can manage to ensure proper education. It had to take into account how training affects the management and effectiveness.  Implementing a technology can change the job and thus have influence on job satisfaction.					

	<p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>When implementing new screening, proper education of the staff had to be ensured. For example implementing screening of foetal abnormalities the education and competence of ultrasound nurses take time.</p>
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Literature search, guidelines, reports and documents of the hospital or hospital districts and own study: interview or questionnaires of different actors of the process.</p>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>{1, 14, 26}</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>A0013, A0014, B0012, C0063, D0023, E0001, E0002, F0007, legal?</p>
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>B0013</p> <p>Order of doing; to be answered prior to: E0003</p>

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2

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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	5
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	5
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	5
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	5
Clarification	<p><b>Common to all used applications</b></p> <p>Co-operation and communication is crucial for fluent patient pathway. Implementing a technology can demand new co-operation and communication in- and outside the organization, e.g. other hospitals, pharmacies and manufactures. Therefore structure of co-ordination is important. Also, interaction and communication with patients/participants and their important others could change. Adaptation of self/home monitoring needs close co-operation and fluent communication.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Screening needs close co-operation and fluent communication between all actors of 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 making up a new screening. The information must be fluent and electronic communication (software) is crucial. Adequate communication with participants and their important others must be taken into account. Different kinds of "patient information" could be defined for screening. For example: 1. "promotional/educational information" with the aim to involve target population and to promote 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.). 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 hospital and hospital districts,</p>					



	guidelines, own study: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory, participants).
<b>References</b>	<b>Common to all used applications</b>  {1, 14} {27}
<b>Content relations</b>	<b>Common to all used applications</b>  B0014, B0015, C0063, D0023, H0010, H0007, H0008, H0009, H0013, I0002
<b>Sequential relations</b>	

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G0012 Assessment element card						
Issue: How 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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	6
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	6
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	6
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	6
<b>Clarification</b>	<b>Common to all used applications</b>  A new technology usually have an effect on current quality assurance not only inside the organization but also outside in different health care levels. To assure the quality, a monitoring system with standards and indicators are needed. There could be variations how quality assurance and monitoring system has been implemented. It had to be taken into account who is responsible for quality assurance and for monitoring system and how follow up has been arranged.  It had to take into account how quality assurance and monitoring system affects the					

	<p>management and effectiveness.</p> <p>There could be international, national, regional and/or (cross) organisational demands for quality assurance (e.g. quality standards and monitoring) and for registration.</p> <p><b>Specific to Pharmaceuticals (2.1) - PUBLIC DRAFT</b></p> <p>What information have 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 is may be necessary for innovative pharmaceuticals.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Screening involves asymptomatic participants and therefore quality control is crucial. Quality control needs to be systematic at every step of the screening process steps and throughout the screening programme. Acceptable delay from screening test to test positive result and finally to treatment must be specify. Special attention has to be paid to the control when the programme is provided by several providers (e.g. a combination of private and public health care organisations) when test and further investigations are separated.</p>
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>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. .</p>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>{14}</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>B0010, B0012, B0020, C0007, E0001, E0002,</p>
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>B0020</p> <p>Order of doing: to be answered prior to E0003</p>

G0005 Assessment element card						
Issue: How does de-centralisation or centralization requirements influence the implementation of the technology?						
Topic: Structure of health care system						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	7
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	7
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	7
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	7
Clarification	<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 economical 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 (2.1) - PUBLIC DRAFT</b></p> <p>In what health care level the medicine is implemented?</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Sometimes screening test (for example maternal ultrasound) needs special experience from personnel which is possible after education and sufficient amount of patients/participants. Centralisation could make screening or further investigation more difficult to access. For example timing is important in foetal screening. Decentralisation makes screening more attainable but the quality can weaken.</p>					
Methodology and sources	<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 hospital and hospital districts, health information databases (DRG etc.), own study: questionnaires and interviews of</p>					

	different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory, participants).
<b>References</b>	<b>Common to all used applications</b>  {1, 14, 26, 27}
<b>Content relations</b>	
<b>Sequential relations</b>	<b>Common to all used applications</b>  B0004, F0012

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G0101 Assessment element card						
Issue: What are the processes ensuring access to care of the new technology for patients/participants?						
Topic: Structure of health care system						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	8
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	8
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	8
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	8
<b>Clarification</b>	<b>Common to all used applications</b>  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.  Access to care by wide definition includes availability, accessibility, accommodation, affordability and acceptability.  This issue is related to the issue of acceptability of new technology (G0010)					

<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>
<b>References</b>	
<b>Content relations</b>	
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>A0001, H0012</p>

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G0006 Assessment element card						
Issue: What are the processes related to purchasing and setting up the new technology?						
Topic: Process-related costs						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	9
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	9
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	9
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	9
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Implementing the required changes in e.g. premises may be costly for organisations. High costs can influence the decision to introduce the new technology. There may be division of costs such that some organisation(s) is(are) responsible for the acquisition costs and others for the running costs. Investments by, at all stages of the process, should be taken into consideration.</p>					

	<p><b>Specific to Pharmaceuticals (2.1) - PUBLIC DRAFT</b></p> <p>This includes e.g. devices, special room and software needed for the new medicine.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>When building up a new screening programme, there's need for many investments (e.g. equipment, education and implementation support, training).</p>
<b>Methodology and sources</b>	<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 study: questionnaires and interviews of different actors of the screening process (monitoring authorities, hospitals, hospital districts, laboratory</p>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>{14}</p>
<b>Content relations</b>	
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>B0007, B0008, B0009,</p> <p>Order of doing: to be answered prior to E0001</p>

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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 (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	10
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	10
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	10
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	10
Clarification	<p><b>Common to all used applications</b></p> <p>Whenever a technology is introduced, there will be an impact on health care budgets. Budget impact analysis attempts to examine the likely impact of introducing a technology on financial outlays 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. For example: What kind of incentives does the budget impact impose on different actors? How might this potentially impact on each organization? 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 (2.1) - PUBLIC DRAFT</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. hospital fee for further investigations. It should be noticed that when initiating a new screening programme, initial cost outlays may be necessary.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Literature search, reports questionnaires and interviews of different actors of the screening process (monitoring authorities, hospitals, hospital districts, laboratory), information from manufacturers.</p>					

<b>References</b>	<b>Common to all used applications</b>  {14, 28}
<b>Content relations</b>	<b>Common to all used applications</b>  A0011, A0020, B0007, B0009,D0023,
<b>Sequential relations</b>	<b>Common to all used applications</b>  Order of doing; to be answered prior to:E0001

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<p><b>G0008 Assessment element card</b></p> <p><b>Issue: What management problems and opportunities are attached to the technology?</b></p> <p><b>Topic: Management</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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	11
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	11
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	11
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	11
<b>Clarification</b>	<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. Data/information management systems connected to each of these points have to take account.</p> <p>This issue includes also risk management and safety issues (e.g. safety of personnel).</p>					



<b>Methodology and sources</b>	<b>Common to all used applications</b>  Literature search, guidelines, reports and documents of hospitals, own study: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory).
<b>References</b>	<b>Common to all used applications</b>  {28} {29}{14}
<b>Content relations</b>	<b>Common to all used applications</b>  A0011, A0012, A0015, A0016, A0017, A0025, B0020, C0063, D0021, H0009, I0009
<b>Sequential relations</b>	

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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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	12
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	12
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	12
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	12
<b>Clarification</b>	<b>Common to all used applications</b>  Provide information on who are the key actors in deciding on the use of the technology. Do most important decisions take place on the national level (e.g. population screening) or for example by individual professionals (e.g. surgical method for a specific disease)? How is the decision made; are there some documented criteria?					

	<p>Information about the possible variations in the decision level and criteria has ethical implications.</p> <p>This issue is related to the issue of work processes (G0001)</p> <p><b>Specific to Pharmaceuticals (2.1) - PUBLIC DRAFT</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 class of pharmaceuticals for a targeted patient group or sub-groups. How companion diagnostic should be used to identify eligible patient should be specified and explained.</p> <p>Criteria must be specified for higher risk groups of patients such as elderly and children.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Decisions about the people eligible for screening is done in the beginning of the screening. Usually, it has 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 result 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 study: 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>Kristensen 2007 {24}</p> <p>{14}</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>A0011</p> <p>A0012</p> <p>:B0016, D0021, F0012, I0012, H0012</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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	13
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	13
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	13
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	13
Clarification	<p><b>Common to all used applications</b></p> <p>Acceptance should be looked at by different perspectives: by organisation, by personnel and by patients/participants. Organisational view can be separated out intra-organisational (primary care), inter-organisational (secondary care) and health care system level. In all these actors/views acceptance could vary. Alternative ways to introduce a new technology into the organisation could influence problems e.g. resistance among staff and dysfunction of processes.</p> <p>Acceptability is related to access to care.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Acceptance could vary in the same screening process for example in foetal screening someone accepts ultrasound but not chromosomal (serum) test. Example of organisational acceptance: Sometimes screening could consist of elements which are not suitable for the image of the organisation. Screening is voluntary and for persons eligible for screening both decisions are right decisions: to participate or not. Giving understandable information on pros and cons of screening is important. Communicational skills of personnel may have an influence on acceptance of screening.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Literature search, own study: 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>					

	{14}
<b>Content relations</b>	<b>Common to all used applications</b>  F0001, F0003, F0007, H0006, H0007, H0011, H0012
<b>Sequential relations</b>	

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G0011 Assessment element card						
Issue: How are the other interest groups taken into account in the planning / implementation of the technology?						
Topic: Culture						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	14
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	14
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	None	No	14
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	None	No	14
<b>Clarification</b>	<b>Common to all used applications</b>  It may be useful to know who are the possible stakeholders, as well as what kind of co-operation exists and what kind of interaction is needed. The stakeholders could be e.g. the pharmaceutical industry and companies offering technologies for screening, authorities (national / regional), registry, administrative parties, municipalities, policy makers / decision makers, staff groups, GPs/primary care physicians and patient organisation. One can 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?					
<b>Methodology and sources</b>	<b>Common to all used applications</b>  Literature search, reports and documents of hospitals, own study: questionnaires and interviews of different actors of the screening process (monitoring authorities, hospitals,					

	hospital districts, screening units, laboratory, manufacturers, registry, participants).
<b>References</b>	<b>Common to all used applications</b> {1, 14, 27}
<b>Content relations</b>	<b>Common to all used applications</b> A0022, B0015, F0003, F0011,
<b>Sequential relations</b>	

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5



## 1 ***Social aspects***

### 2 **Description**

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

4 The social domain takes the patient or individual as a point of departure in an HTA. A technology  
5 may be practiced in hospital, primary care or at home. Implications for patients may though extend  
6 far beyond the original setting of the technology.

7 Patients and carers give specific meanings and significance for health technologies. Perceptions are  
8 attached to feelings of hope, fear, or perhaps uncertainty as well as values of society {1-5}. The  
9 social analysis is interested in all these aspects.

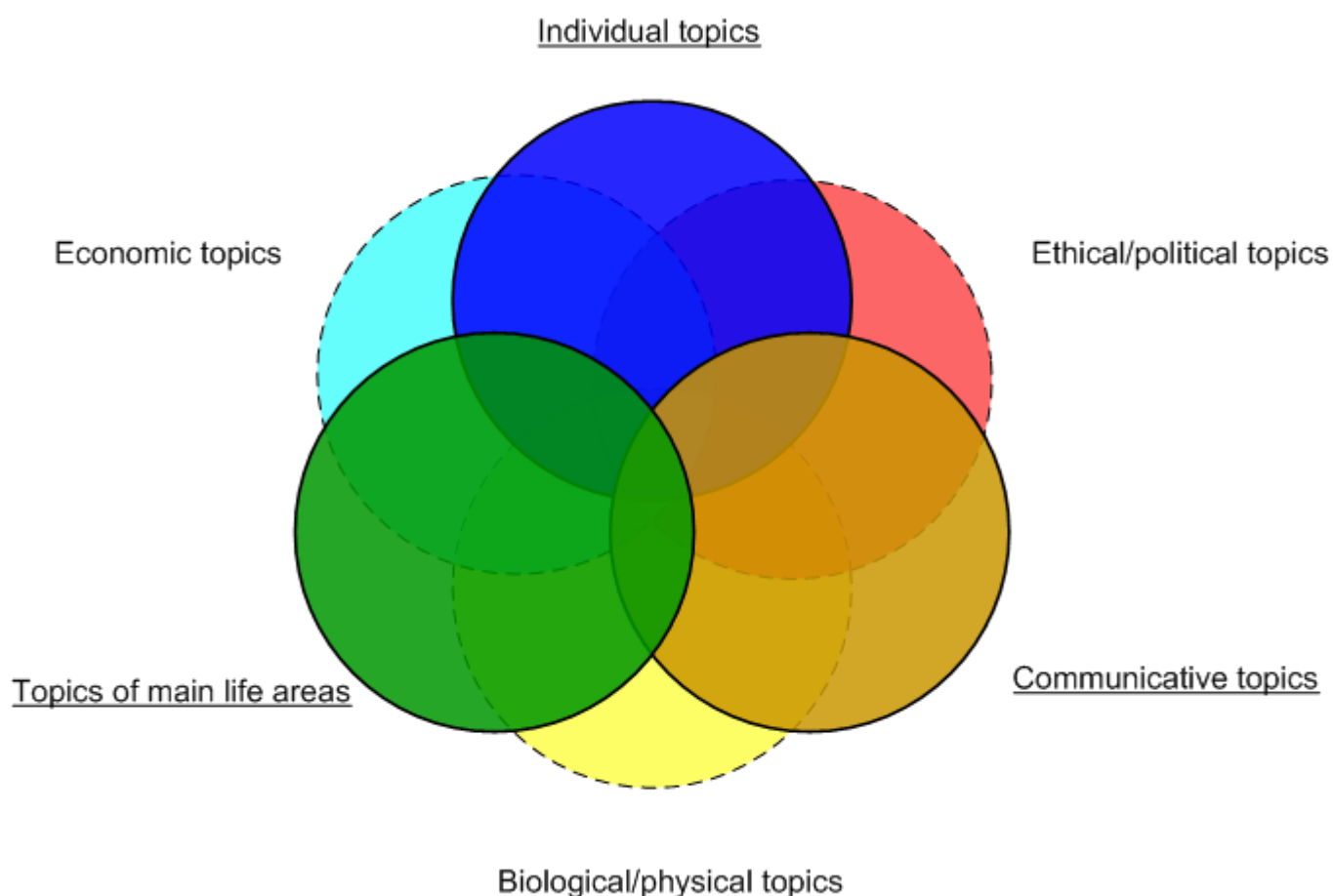
10 The analysis of social aspects of health technology can include at least two kinds of questions. The  
11 first set of issues focuses on the kinds of resources (people, support, money and so on) that have to  
12 be enacted and mobilised from the point of view of a patient before, during and after the  
13 implementation of the technology. The other set of issues focuses on the experiences, actions and  
14 reactions of patients with respect to the technologies as well as on the changes and consequences  
15 that the enactment of the technologies may further generate. These are for example changes that  
16 occur with respect to a person's working capacity, social relationships, coping with illness and  
17 treatment, or attitudes towards a person who uses the technology.

18 Social aspects of the technology can also be considered at a higher analytical level {6}. It can be  
19 related to the impacts of the technology on the health care system or on the interactions among  
20 different institutions (e.g. hospitals, clinics, health insurance, schools, etc.).

21 Analysis may also be related to the society as a whole, for instance, in examining collective  
22 attitudes and behaviours, culture, traditions, norms and values in relation to the technology in  
23 question {7}. However, issues that are primarily targeted at the individual level (i.e. has the patient  
24 and possible his or her important others as the focal point) are the main focus of the social domain.  
25 The social domain is furthermore closely related to organisation domain and ethics domain.

26 The theoretical approach used when analysing social aspects of a technology is imperative to the  
27 outcome of the analysis {8-9}. Whether the analysis is based on for example a critical, hermeneutic  
28 or constructivist theory affects the results of the study and awareness of which approach is used  
29 therefore important to the study. Examples of models that can be useful when conducting a social  
30 analysis can be found in appendix 3.

31 Figure 1 provides a view of different social aspects that are relevant from a patient's perspective  
32 {1}. The model intends to show and map different aspects, which could be considered of relevance  
33 for a specific HTA analysis. Social domain chooses mainly to focus on the individual topics,  
34 communicative topics, and topics of major life areas such as family life, work life, and leisure time.  
35 These topics are underlined in figure 1.



1

2 **Figure 1. Social aspects of relevance from a patient perspective in HTA. Modified from {1}.**

3 The scope of social analysis (and thus the choice of analytical level) is based on what issues are  
4 relevant to a given technology.

5 The social domain contains 12 issues. The issues are related to the three topics of individual, overall  
6 society level and information exchange. Table 1 below shows the topics and issues of the social  
7 domain.

8

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

Topic	Issue	Assessment element ID
Individual	What kind of changes do patients or citizens expect?	H0100
Individual	Who are the important others that may be affected, in addition to the individual using the technology?	H0002
Individual	What kind of support and resources are needed for the patient or citizen as the technology is introduced?	H0003
Individual	What kind of changes may the use of the technology generate in the individual's role in the major life areas?	H0004
Individual	How do patients, citizens and the important others using the technology react and act upon the technology?	H0006
Individual	Are there factors that could prevent a group or person from gaining access to the technology?	H0012
Individual	What is the socio-economic impact of the technology to the patient and his/her important others?	H0014
Major life areas	What kinds of reactions and consequences can the introduction of the technology cause at the overall societal level?	H0011
Major life areas	Which social areas does the use of the technology influence?	H0001
Major life areas	What influences patients' or citizens' decisions to use the technology?	H0009
Major life areas	How does the technology affect inequalities in health?	H0015
Information exchange	What is the knowledge and understanding of the technology in patients and citizens?	H0007
Information exchange	What are the social obstacles or prospects in the communication about the technology?	H0013

## 1 Why is this domain important?

2 The patient is not just a passive target for interventions in health care. He is also a human being  
3 with different roles – a family member, a citizen, an employee, a consumer etc. {1}. His life takes  
4 place in various arenas: everyday life, homes, schools, workplace, health services, etc. The use of  
5 the technology may change the roles, skills and positions in both negative and positive ways. A  
6 new role can strongly affect all the arenas of one's everyday life and all the important others.  
7 Considerations of power, empowerment and stigmatisation are therefore essential {10-13}.

8 The technology does not produce the good results alone. Social analysis reveals the resources  
9 needed in individual's daily activities in order to achieve satisfactory results. Being satisfactory  
10 depends on the technology and its defined outcomes. The use of technology always produces some  
11 kind of changes or consequences in different spheres of social life, which should be anticipated.  
12 These can be positive or negative, or even unexpected {14-16}. The different meanings individuals  
13 give to a technology and its implication are important to recognize {17-18}.

14 At a higher level, health technologies may lead to resource mobilization or a change in the relation  
15 between individuals and institutions inside or outside the health care system. This dynamic is of  
16 relevance to an HTA. The social reality surrounding a health technology represents a certain  
17 cultural context and a certain health care system. Since norms, culture and national characteristics  
18 of social systems, health care systems and policies vary across countries, one should nevertheless be  
19 sensitive to the limits of exportation of HTA from one country to another.

20 The European Union has identified social aspects as a special target for health investments {19}.  
21 Investing in people's health as human capital helps improve the health of the population in general  
22 and reinforces employability, thus making active employment policies more effective, helping to  
23 secure adequate livelihoods and contributing to growth. Including social aspects in an HTA is  
24 consequently important in order to analyze the overall benefit of a technology.

25 Irrespective of the technology in question, the use of health technology always requires that the user  
26 mobilizes some kind of resources in his or her daily activities (for example some kind of action  
27 from him/herself or support from other people) in order to achieve satisfactory results with the  
28 technology. An assessment of patient and social aspects both in and outside the clinical encounter is  
29 therefore necessary. Overall, the social analysis reveals the resources needed when using a  
30 technology and the consequences of its use in patients life spheres so that those who will use the  
31 technology can anticipate them {14-16}.

## 32 Relations to other domains

33 Only in an analytical perspective is it possible to narrow the focus to one topic, for example  
34 communicative topics {20}. Having said that, the social domain choose mainly to focus on the  
35 individual topics, communicative topics, and topics of major life areas such as family life, work life,  
36 and leisure time. These topics are underlined in figure 1. Other topics of relevance for a social  
37 analysis such as the patient perspectives concerning ethical/political topics are mainly discussed in  
38 the ethical domain. Patient-related patient perspectives on biological/physical topics are discussed  
39 in the effectiveness and safety domains, and patient-related perspectives on economic topics are  
40 included in the economic domain. Socio-economic aspects related to the individual are covered in  
41 the SOC domain, while issues related to the socio-economic benefits at a societal level are covered  
42 in the ECO domain. Issues related to the impact on the individuals working with the technology are

discussed in the organisational domain. In some situations these topics could also be relevant to incorporate in the analysis of the social domain.

Patient perspectives are present in several other domains:

- Ethical analysis domain
- Effectiveness and safety domains
- Costs and economic evaluation domain
- Organisational domain
- Legal domain.

The information from social domain can guide the other domains e.g. in defining important endpoints for assessment. Coordination is needed across the domains to cross feed and avoid overlap when producing a core HTA.

## **Screening-specific content**

Equity in access is essential for the participation in the screening and thus the success of the screening program. The delivery modes of screening may have an impact on this. Self-sampler devices and the possibility to mail the sample instead of clinic visit and telephone reminder messages can affect participation, as well as mass media campaigns.

Correct and balanced information on benefits and harms of screening is essential for an individual to be able to make informed decision to participate screening.

## **Pharmaceutical-specific content**

In case pharmaceuticals replace a more invasive self-limiting treatment (e.g. a radical cystectomy) the pharmaceuticals can have a large impact on the social areas of the patient (e.g. social interaction, employment, independence, stigma). Also individuals' perceptions and views on certain pharmaceutical as well as the consequences it may cause for their social lives can largely influence patterns of use of pharmaceuticals, thus explain if it is used successfully.

## **Methodology**

## **Process for answering research questions**

For each HTA project a person needs to be defined to be responsible for performing and reporting the social analysis. The social analysis is both theoretically and empirically complex and demanding. Hence, advanced skills in social analysis are required from the person conducting this part of the HTA. Co-operation and interaction between the HTA team members is essential because of complexity of the social analysis. It is recommendable to consult outside experts on the specific theme from within the field of social science.

An assessment of patient and social aspects should not be a separate process within an HTA. Relevant social issues for a technology at hand could be identified together when considering e.g. ethical and organizational aspects {21}. Some issues may also be studied as patient related outcomes (PRO), and may as such be related to effectiveness and safety domains. When these issues are brought into the analysis of social aspects, focus is on the interrelation between biological, individual and social aspects. Patient related outcomes can result in central thematic issues/topics, which should be taken into consideration and which can have major impact on the content and conclusions of a HTA report. For example does a given technology have other patient related consequences than intended?

Overall, the scope of patient related and social analysis of the HTA 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 being assessed and adjust the work on the social domain with the work being done within the affiliated domains. The assessment elements table contains more specific issues on this topic.

The content of the study plan depends on the technology in question. To be able to judge what issues are relevant to a given technology, a preliminary small analysis is required:

1) Define the relevant scope of the analysis:

- Consider, what is the extension of the technology nationally as well as internationally? How widely is the technology already being used or practised? Information provided by the health problem and current use of technology domain may provide valuable information.

2) Define the relevant set of research elements:

- Decide, which topic(s) and issues of the social aspects with respect to the patient and the technology are of particular relevance in the assessment of the technology in question (see figure 1 and Table: 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. You may need to conduct some preliminary literature searches.
- Consider, what would be the specific theoretical perspective within the co-production approach for the analysis.
- Change the relevant assessment elements to precise study questions on the basis of the chosen theoretical perspective.

When the scope of the social analysis, exact research questions, and relevant methodologies are clear, you can proceed to write a concrete study plan. The study plan should moreover describe the different phases and strategies of the assessment process.

When designing the process of answering the relevant research questions, it is important to have the end-goal of the analysis in mind in order to assure the usefulness of the study {22}.

Even if the assessment process may differ with respect to each technology, the main phases of the assessment process can be defined. The following phases may need to be gone through in the following order and to the extent that is necessary to find answers to the relevant issues:

- 1) Search for literature reviews, or if no literature reviews are available
- 2) Conduct a literature review, or if relevant studies are not available,
- 3) Conduct a primary study, or if there's no time or other resources for primary study,
- 4) Consult health care professionals and content experts (proxy informants) for their opinions.

## **Gathering information**

Find out whether there are systematic reviews concerning the social issues in question. Probably you will not find a systematic review on social issues or a large amount of relevant literature may not be analyzed in systematic reviews. This is especially the case with qualitative research. Hence, conduct a systematic review complemented with what may be termed 'thematic mapping' {23}.

Thematic mapping means mapping out relevant sub-themes for the core set of questions to be investigated and describing each. It further implies estimation of the quantity, quality and applicability of literature existing for each relevant subtheme. Thematic mapping may often begin with the development of a systematic search strategy, but evolve into snowball sampling (citation analysis). It may be time saving to consult experts on the different sub-themes, rather than letting the key person of the social analysis map out all relevant subthemes alone.

Perform searches in psychological/sociological databases such as Psychinfo, Sociological Abstracts and ISI Web of Science, as well as in medical databases such as Pubmed, Medline, Embase, Cinahl etc. The search process is equal to a systematic review practice (see also effectiveness domain), except that studies with different research paradigms will be considered. Since qualitative studies are highly relevant for the social aspects, they should be considered along quantitative studies with various observational designs. All studies, also qualitative studies should be quality evaluated before inclusion. Guidelines for standards on qualitative research vary and are currently debated and developed. For further guidance, see e.g. {24} or {20}.

Describe what kind of knowledge is available in the literature, and what questions cannot be answered on basis of the existing literature. Then consider how the included studies can be utilized and what their weaknesses are. Do they give sufficient insight into social processes?

In thematic mapping, a thorough description of relevant themes and dimensions is more important than whether all relevant studies are found. Examples of themes may be descriptions of how illness changes family relations, patient roles, people's interaction with technology, unforeseen and unintended social consequences, risk management etc. Such thematic synthesis may be incorporated into the systematic review document or kept apart depending on the nature of studies found. Guidance for making synthesis of qualitative literature can be found in method books {25-27}. A critical interpretive synthesis on literature considering access to healthcare by vulnerable groups provides one example {28}.

When estimating the applicability of literature found in the systematic review process, it is important to consider to what extent the results can be translated in a valid way. Hence, contextual factors must be taken into account.

38



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

2 Some important databases and other sources of information possibly useful for the analysis in this  
3 domain are listed below. We recommend also using the Summarized Research in Information  
4 Retrieval for HTA (SuRe Info, available at <http://vortal.htai.org/?q=sure-info>) which provides  
5 research-based information relating to the information retrieval aspects of producing health  
6 technology assessment.

7 Issues on the social aspects of technologies can be subject of the following fields:

- 8 • Medical Anthropology,
- 9 • Medical Decision-Making,
- 10 • Medical Sociology,
- 11 • Science and Technology Studies,
- 12 • Governance of Innovation Studies,
- 13 • Medical Ethics,
- 14 • Social Psychology,
- 15 • Communication science, and
- 16 • Health Services Research
- 17 • Health Sociology

18 Examples of relevant scientific journals: Health Expectations, Medical Anthropology Quarterly,  
19 Social Science and Medicine, Anthropology and Medicine, Sociology of Health and Illness,  
20 Qualitative Health Research, Values in Health, Medical Decision Making.

## 21 **Databases and search strategies**

22 Psychological/sociological databases such as

- 23 • Psycinfo,
- 24 • ASSIA (Applied Social Sciences Index and Abstracts),
- 25 • Sociological Abstracts and
- 26 • ISI Web of Science
- 27 • Social Services Abstracts,
- 28 • Social Care on line / Caredata
- 29 • SocINDEX

30 Euroethics (European Database Network on Ethics in Medicine, including:

- 31 • Biogea (Italy),
- 32 • Cendibem (Spanish),
- 33 • CRIB (Belgium),
- 34 • ETHINSERM (France),
- 35 • ETHMED (Austria, Germany, Switzerland),
- 36 • EUROETHIK (Germany),
- 37 • MIKS (Sweden).

38 Medical databases such as

- 39 • Medline,



- Embase,
- Cinahl.

Suggested search terms include: "social aspects of", "medical decision making process", "patient education", depending on the PICO question.

Other sources of qualitative studies can be

- Citizens and patients associations
- WHO, OECD, ILO, UNESCO homepages and databases
- Citizens and patients associations
- Patients' (virtual) forums
- Structured systematic content analysis of Patients' (virtual) forums
- Structured systematic content analysis of Mass media

The use of qualitative sources should always be done in caution do to the high possibility for the subjective bias.

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

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

If reports regarding patient reported outcomes and treatment satisfaction with the technology are available these should be included in the information collected.

### **Tools for critical appraisals**

Quality assessments should evaluate {29}:

- the purpose of the study and relevance to 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) and
- the account of the knowledge generated given the methods (relevance for practice)

### ***Observational studies***

If no relevant studies could be identified, it could be worth while to carry out primary studies concerning the relevant issue/s for the specific technology under assessment. In this case it must always be taken into consideration whether the need is of a primary HTA study, or whether the need of new knowledge has dimensions that speak for a larger research project rather than an HTA. The study design should be based on the ideas corresponding to those described in the domain description. HTA of social issues does not have as its starting point a hierarchy of study methods. The study design has to be structured individually in every primary assessment study. Every kind of study method can in principle be used: interviews, surveys, observation, participant observation, analysis of written material and documents, etc. {30-31}.

The timing of the study of the social aspects must be considered thoroughly. Depending on the specific technology under study, the appropriate time point for assessing the patient experience will differ. Both ethical and practical considerations must be taken into account when deciding on whether to study people before, during the application or use of technology or ask them of their experience afterwards. This choice may have considerable significance for the results. Any intervention does something to practice, and it must be clear from the social study, whether the effects of the intervention are part of the specific context that the people under study behave in, or whether the social study reflects daily practice.

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

## **Analyzing and synthesizing evidence**

Qualitative studies often involve generating evidence in the form of certain themes, concepts and trends. Thematic mapping means mapping out relevant sub-themes, and the assessment of the quantity, quality of existing literature related to them. Applicability of published information depends on its ability to give insight into social processes. Examples of sub-themes may be: how does illness or risk perceptions change family relations, roles, people's interaction with technology, unforeseen and unintended social consequences, or risk management. A thorough description of relevant themes and dimensions is more important than finding all relevant studies. It is also important to define the questions that cannot be answered on basis of the existing literature.

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

In assessing qualitative studies it should be noted that generalizability of findings in statistical terms is often not the aim. In qualitative works study samples are rarely randomly selected because the logic of generalizability is here different. The aim is to provide in-depth ('thick') descriptions or to address particularities rather than to provide generalizable findings {32}.

Another point is that researchers' judgment sometimes applies to the interpretations provided by qualitative studies. Although the researcher describes a certain issue from the point of view of participants, s/he simultaneously unpacks the issue in such a way that broader meanings and connections can be elicited. Therefore, the presence of researcher's perspective does not per se discredit the study. So long as the judgment is made consciously and articulated explicitly in the study, it may not be considered as a source of bias {33}.

Guidelines for standards on qualitative research vary and are currently debated and developed. For further guidance, see e.g. {24} or {20} . Another tool can be found in {33}, page 241 and {34}.

## 1 **Evidence tables**

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

## 5 **Meta-analysis**

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

## 8 **Data extraction table**

Publication details: First author, year

Social topic(s)/issue(s): to be categorized by the reviewer

Nature of the study: aims/objectives, user/carer 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 practitioners, policy makers or patients

Features the studied intervention (when applicable): aim of the intervention, intervention process  
(description of how was the intervention/service delivered)

Outcomes and results: outcome measures, details of findings, strengths/limitations of the study,  
author's conclusions.

Reviewers' comments: e.g. remarks of quality issues

## 9 **Qualitative synthesis**

10 The synthesis of qualitative studies can be done according to different methods such as meta-  
11 ethnography {35} or narrative analyses {36}. Guidance for making synthesis of qualitative  
12 literature can be found in method books {25-27}. A critical interpretive synthesis on literature  
13 considering access to healthcare by vulnerable groups provides one example {28}.

## 14 **Reporting and interpreting**

15 For transparency purposes it is very relevant to clearly divide facts from interpretation when  
16 reporting. This is especially true for the social domain as many relevant issues are subject to  
17 interpretation from various parties and perspectives.

18 It is therefore also very relevant to clearly state the perspectives of the issue, e.g. the patient, the  
19 health care professional, family/social environment, citizens, public health authorities or the health  
20 care system.

21

## 1 Assessment elements

H0100 Assessment element card						
Issue: What kind of changes do patients or citizens expect?						
Topic: Individual						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
Clarification	<p><b>Common to all used applications</b></p> <p>What do the patients expect to get out of the intervention before, during and after the intervention? Are there temporary changes that should be explained?</p>					
Methodology and sources						
References						
Content relations	<p><b>Common to all used applications</b></p> <p>ETH</p>					
Sequential relations						

2

H0002 Assessment element card						
Issue: Who are the important others that may be affected, in addition to the individual using the technology?						
Topic: Individual						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	2
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	2
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	2
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	2
Clarification	<p><b>Common to all used applications</b></p> <p>Describe who are the important other people that are involved in the use of technology in addition to the patients (parents, children, friends, people at work place etc)</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Describe who are the important other people that are involved in the use of technology in addition to the patients (parents, children, friends, people at work place etc)</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Describe who are the important other people that are involved in the use of technology in addition to the patients (parents, children, friends, people at work place etc)</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</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>None</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals</p>					

	<p>and content experts can be consulted.</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals and content experts can be consulted.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Search for existing literature review, or collect primary studies and if possible conduct a literature review, or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals, patients, citizens, or important others can be consulted.</p>
<b>References</b>	
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>ETH and LEG</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Ethical and Legal domains</p>
<b>Sequential relations</b>	

1

2

H0003 Assessment element card						
Issue: What kind of support and resources are needed for the patient or citizen as the technology is introduced?						
Topic: Individual						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	3
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	3
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	3
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	3
Clarification	<p><b>Common to all used applications</b></p> <p>This issue is about any kind of support and resources (practical, physical, emotional, personal social, nurturing, financial etc.) that need to be mobilized, and organized - or might be released - in order for the patient to use the technology with satisfactory results. It covers all arrangements or adjustments that may be needed (e.g. alteration of special tasks, working time, adjustments in the physical environment, emotional support).</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>This issue is about any kind of support and resources (practical, physical, emotional, personal social, nurturing, financial etc.) that need to be mobilized, and organized - or might be released - in order for the patient to use the technology with satisfactory results. It covers all arrangements or adjustments that may be needed in the major life areas (e.g. alteration of special tasks, working time, adjustments in the physical environment, emotional support).</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>This issue is about any kind of support and resources (practical, physical, emotional, personal social, nurturing, financial etc.) that need to be mobilized, and organized - or might be released - in order for the patient to use the technology with satisfactory results. It covers all arrangements or adjustments that may be needed in the major life areas (e.g. alteration of special tasks, working time, adjustments in the physical environment, emotional support).</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>This issue is about any kind of support and resources (practical, physical, emotional,</p>					

	<p>information, personal, social, nurturing, financial etc.) to ensure the access and satisfactory results. It covers all arrangements or adjustments that may be needed in the major life areas (e.g. alteration of special tasks, working time, adjustments in the physical environment, emotional support, attitudes, reasons for (non)-participation.</p>
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>None</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals and content experts can be consulted.</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals and content experts can be consulted.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Search for existing literature review, or collect primary studies and if possible conduct a literature review, or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals, patients, citizens, or important others can be consulted.</p>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>(35): environmental factors: support and relationships (chapter 3: e310-399); " activities and participation, chapter 6: d698, structural arrangements of patient's environment. (17, 15, 14)</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>ICF(32) environmental factors: support and relationships (chapter 3: e310-399); activities and participation, chapter 6: d698, structural arrangements of patient's environment (10, 12, 13)</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>ICF(32) environmental factors: support and relationships (chapter 3: e310-399); activities and participation, chapter 6: d698, structural arrangements of patient's environment (10, 12, 13)</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>ICF 2001: environmental factors: support and relationships (chapter 3: e310-399); " activities and participation, chapter 6: d698, structural arrangements of patient's environment. Dreier 2000, Rapp 1999, Kaufert 2000</p>



<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>ORG</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Organisational</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Organisational</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Organisational and Costs domains</p>
<b>Sequential relations</b>	

1

H0004 Assessment element card						
Issue: What kind of changes may the use of the technology generate in the individual's role in the major life areas?						
Topic: Individual						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
Clarification	<p><b>Common to all used applications</b></p> <p>This issue is about the patient's social roles and ability to manage and maintain relations with other people in a socially appropriate manner in major life areas.</p>					

	<p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>This issue is about the patient's social roles and ability to manage and maintain relations with other people in a socially appropriate manner in major life areas.</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>This issue is about the patient's social roles and ability to manage and maintain relations with other people in a socially appropriate manner in major life areas.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>This issue is about the patient's social roles and ability to manage and maintain relations with other people in a socially appropriate (associated by the social norms and values defining the role) manner in major life areas.</p>
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>None</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals and content experts can be consulted.</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals and content experts can be consulted.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Search for existing literature review, or collect primary studies and if possible conduct a literature review, or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals, patients, citizens, or important others can be consulted</p>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>(35): activities and participation, interpersonal interactions and relationships (chapter 7, d710-779), community, social and civic life (chapter 9:d910-d999). (5, 7, 35, 36)</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>ICF(32) activities and participation, interpersonal interactions and relationships (chapter 7, d710-779), community, social and civic life (chapter 9:d910-d999), (5, 7, 33, 34)</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p>

	<p>ICF(32) activities and participation, interpersonal interactions and relationships (chapter 7, d710-779), community, social and civic life (chapter 9:d910-d999), (5, 7, 33, 34)</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>ICF 2001: activities and participation, interpersonal interactions and relationships (chapter 7, d710-779), community, social and civic life (chapter 9:d910-d999). Douglas 1996, Goffman 1990, Hoffman 2005, Becker 1997</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>ETH and SAF</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Ethical. Effectiveness, safety</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Ethical. Effectiveness, safety</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Ethical, Effectiveness, Safety and Legal domains</p>
<b>Sequential relations</b>	

1

2

H0006 Assessment element card						
Issue: How do patients, citizens and the important others using the technology react and act upon the technology?						
Topic: Individual						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	5
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	5
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	5
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	5
Clarification	<p><b>Common to all used applications</b></p> <p>This issue is about the patients and her important others' attitudes, perceptions, preferences, satisfaction and relations to the technology. This covers whether, from a patient perspective, any positive or negative issues arise as a consequence of using the technology e.g. feelings of unity or empowerment and existential experiences (e.g. insecurity, worries, hope, anxiety, stigmatisation, social status, courage to face life, satisfaction, changes in self-conception).</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>This issue is about the patients and her important others' attitudes, perceptions, preferences, satisfaction and relations to the technology. This covers whether, from a patient perspective, any positive or negative issues arise as a consequence of using the technology e.g. feelings of unity or empowerment and existential experiences (e.g. insecurity, worries, hope, anxiety, stigmatisation, person's value as a human being or social status, courage to face life, satisfaction, changes in self-conception).</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>This issue is about the patients and her important others' attitudes, perceptions, preferences, satisfaction and relations to the technology. This covers whether, from a patient perspective, any positive or negative issues arise as a consequence of using the technology e.g. feelings of unity or empowerment and existential experiences (e.g. insecurity, worries, hope, anxiety, stigmatisation, person's value as a human being or social status, courage to face life, satisfaction, changes in self-conception).</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p>					

	<p>Micro sociological aspect: This issue is about the attitudes, perceptions, preferences, and satisfaction of the patients, citizens using the technology and their important other in relation to the technology. This covers whether, from a patient perspective, any positive or negative issues arise as a consequence of using the technology e.g. feelings of unity or empowerment and existential experiences, e.g. insecurity, worries, hope, anxiety, stigmatisation, person's value as a human being or social status, courage to face life, satisfaction, changes in self-conception.</p>
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>None</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals and content experts can be consulted.</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals and content experts can be consulted.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Search for existing literature review, or collect primary studies and if possible conduct a literature review, or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals, patients, citizens, or important others can be consulted.</p>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>(35): body functions: mental functions (chapter 1:b110-b199), environmental factors: attitudes (chapter 4:, e410-499), (3)</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>ICF(32) body functions: mental functions (chapter 1:b110-b199) environmental factors: attitudes (chapter 4:, e410-499) , (3)</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>ICF(32) body functions: mental functions (chapter 1:b110-b199) environmental factors: attitudes (chapter 4:, e410-499) , (3)</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>ICF 2001: body functions: mental functions (chapter 1:b110-b199), environmental factors: attitudes (chapter 4:, e410-499), Whyte 1997</p>

<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>EFF</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Effectiveness</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Effectiveness</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Effectiveness and Ethical Domains</p>
<b>Sequential relations</b>	

1

<p><b>H0012 Assessment element card</b></p> <p><b>Issue: Are there factors that could prevent a group or person from gaining access to the technology?</b></p> <p><b>Topic: Individual</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 (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	6
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	6
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	6
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	6
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>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, and employment, insurance) prevent access? Potential inequalities and discrimination should be justified. Issues of access to a</p>					

	<p>technology as well as labelling and potential discrimination of persons receiving and not receiving treatment should be considered.</p> <p>Are special groups discriminated?. Ethical and social issues have often been considered in academic articles and discussions in the HTA field, but they have rarely been translated into practice.</p>
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Implement the best available evidence about social restrictions, social pressure, social attitudes</p>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>See social domain</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>SHARED with SOC domain H0012</p> <p>Legal domain</p>
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>G0009, G0101</p> <p>A0012</p> <p>I0011</p>
<b>Other domains</b>	<p>Also in: Ethical analysis</p>

1

2

H0014 Assessment element card						
Issue: What is the socio-economic impact of the technology to the patient and his/her important others?						
Topic: Individual						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	No				
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	No				
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	7
Clarification	<p><b>Common to all used applications</b></p> <p>Socio-economic aspect from a patient perspective are important to assess when a technology would be best utilized in the treatment path to ensure optimal benefit for patients. For example regarding avoiding exclusion from workforce, loss of income, ability to avoid getting socio-economic deprived and excluded from social activities.</p>					
Methodology and sources						
References	<p><b>Common to all used applications</b></p> <p>-22</p>					
Content relations	<p><b>Common to all used applications</b></p> <p>ECO</p>					
Sequential relations						



H0011 Assessment element card						
Issue: What kinds of reactions and consequences can the introduction of the technology cause at the overall societal level?						
Topic: Major life areas						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	7
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	7
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	7
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	8
Clarification	<p><b>Common to all used applications</b></p> <p>This issue is about the broader society. What social reactions can be expected for example from religious groups, specific patients and citizens organisations and associations and from any other stakeholder groups (social burden with accepted versus stigmatising diseases)? Are special (social) risk groups defined (ethnic, age etc.) and their possible reactions assessed?</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>Search for existing literature review, or collect primary studies and if possible conduct a literature review, or, if relevant data is not available, conduct a stakeholder analysis and a qualitative/quantitative primary study; if there's no time the systematic collection of opinion of some of the involved stakeholders and interest groups can be done. Patients, citizens and important others can be consulted.</p>					
References						
Content relations	<p><b>Common to all used applications</b></p> <p>Ethical, organizational and Legal domains</p>					
Sequential relations						

H0001 Assessment element card						
Issue: Which social areas does the use of the technology influence?						
Topic: Major life areas						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	8
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	8
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	8
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	9
Clarification	<p><b>Common to all used applications</b></p> <p>Map the major life areas of the patient and the important others (family life, day care, school, work, leisure time, lifestyle, or other daily activities), where the technology is going to be used or where its use may have a direct or indirect influence.</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Map the major life areas of the patient and the important others (family life, day care, school, work, leisure time, lifestyle, or other daily activities), where the technology is going to be used or where its use may have a direct or indirect influence.</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Map the major life areas of the patient and the important others (family life, day care, school, work, leisure time, lifestyle, or other daily activities), where the technology is going to be used or where its use may have a direct or indirect influence.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Map the major life areas of the patients or citizens using the technology, and their important others. Major life areas include family life, day care, school, work, leisure time, lifestyle, or other daily activities. The use of the technology can affect the final decision of the individual about participating.</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>None</p>					

	<p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals and content experts can be consulted.</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals and content experts can be consulted.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Search for existing literature review, or collect primary studies and if possible conduct a literature review, or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals, patients, citizens, or important others can be consulted.</p>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>None</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Hansen 2007</p>
<b>Content relations</b>	
<b>Sequential relations</b>	

1

2

H0009 Assessment element card						
Issue: What influences patients' or citizens' decisions to use the technology?						
Topic: Major life areas						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	9
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	9
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	9
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	11
Clarification	<p><b>Common to all used applications</b></p> <p>What kind of societal influences lead patients to decide to participate? How do the provisional perceptions about the outcome influence the use of the technology</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>This issue clarifies the possible implications from the patient's perspective to decision making e.g. limitations (dependent, passive user) and possibilities (empowered, active user) as a consequence of using the technology.</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>This issue clarifies the possible implications from the patient's perspective to decision making e.g. limitations (dependent, passive user) and possibilities (empowered, active user) as a consequence of using the technology.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>What kind of societal influences lead patients to decide to participate? How do the provisional perceptions about the outcome influence the use of the technology?</p>					
Methodology and sources	<p><b>Common to all used applications</b></p> <p>None</p>					

	<p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals and content experts can be consulted.</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals and content experts can be consulted.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Search for existing literature review, or collect primary studies and if possible conduct a literature review, about what works and what does not.</p>
<b>References</b>	
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>ETH</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Organisational. Ethical</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Organisational. Ethical</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Ethical and Effectiveness Domains</p>
<b>Sequential relations</b>	

1

2

H0015 Assessment element card						
Issue: How does the technology affect inequalities in health?						
Topic: Major life areas						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	No				
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	No				
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	10
Clarification	<p><b>Common to all used applications</b></p> <p>Investing in reducing health inequalities is a target of the European Commission because it contributes to social cohesion and breaks the vicious spiral of poor health contributing to, and resulting from, poverty and exclusion.</p>					
Methodology and sources						
References	<p><b>Common to all used applications</b></p> <p><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>TEC and CUR</p>					
Sequential relations						

H0007 Assessment element card						
Issue: What is the knowledge and understanding of the technology in patients and citizens?						
Topic: Information exchange						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	10
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	10
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	10
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	12
Clarification	<p><b>Common to all used applications</b></p> <p>This issue explores the patient's and important others' understanding of the technology in order to describe and decide what guidance and help (e.g. patient information leaflets, counselling processes, need of follow up consultation or help from other professionals) they need before, during and after the use of the technology.</p> <p>What kind of access do patients' and significant others' have to ask questions? How do they receive answers? How is information provided and received?</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>This issue explores the patient's and important others' understanding of the technology in order to describe and decide what guidance and help (e.g. patient information leaflets, counselling processes, need of follow up consultation or help from other professionals) they need before, during and after the use of the technology.</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>This issue explores the patient's and important others' understanding of the technology in order to describe and decide what guidance and help (e.g. patient information leaflets, counselling processes, need of follow up consultation or help from other professionals) they need before, during and after the use of the technology.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>This issue explores the understanding of the technology in order to describe and decide what guidance and help (e.g. patient information leaflets, counselling processes, need of follow up consultation or help from other professionals) is needed before, during and after</p>					

	the use of the technology.
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>None</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals and content experts can be consulted.</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals and content experts can be consulted.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Search for existing literature review, or collect primary studies and if possible conduct a literature review, or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals, patients, citizens, or important others can be consulted.</p>
<b>References</b>	
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>CUR and SAF</p> <p><b>Specific to Diagnostic Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Current use. Safety</p> <p><b>Specific to Medical and Surgical Interventions (2.1) - PUBLIC DRAFT</b></p> <p>Current use. Safety</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>Health problem and current use, Safety, and Organisational Domains</p>
<b>Sequential relations</b>	



H0013 Assessment element card						
Issue: What are the social obstacles or prospects in the communication about the technology?						
Topic: Information exchange						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	11
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	11
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	11
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	13
Clarification	<b>Common to all used applications</b>  E.g. limitations to decision making in participating or using the technology (dependent, passive user), and possibilities (empowered, active user)..					
Methodology and sources	<b>Common to all used applications</b>  Search for existing literature review, or collect primary studies and if possible conduct a litterateur review,or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals, patients, citizens, or important others can be consulted.					
References						
Content relations	<b>Common to all used applications</b>  Organisational and Ethical Domains					
Sequential relations						

1

2

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21

## 1 ***Legal aspects***

### 2 **Description**

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

4 The objective of the legal domain is to assist the HTA doers in detecting rules and regulations which need to  
5 be taken into consideration when evaluating the implications and consequences of implementing a health  
6 technology. Rules and regulations have been established to protect the patients' rights and societal  
7 interests. They may be part of patient rights legislation, data protection legislation, or provisions  
8 concerning health care personnel and their rights and duties in general. The market access authorisation or  
9 -regulation processes have not been in the direct focus of HTA earlier, but this may be subject to change in  
10 the future.

11 **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	What kind of legal requirements are there for counselling the user or patient or obtaining informed consent from her?	I0005
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 such additional information that is not directly related to the current care of the patient and may violate her right to respect for private life?	I0007
Privacy of the patient	What do laws/ binding rules require from informing relatives about the results?	I0008
Privacy of the patient	What do laws/ binding rules require from 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 from appropriate processes or resources regarding guaranteeing equal access to the technology?	I0011
Equality in	What are the consequences of various EU level and national	I0012

health care	regulations to the equal access to the technology?	
Authorisation and safety	What authorisations and register listings does the technology have?	I0015
Authorisation and safety	What do laws/ binding rules require from the safety of the technology and how should this be addressed when implementing it?	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 of the legal or binding rules about the width, depth and length of the manufacturers guarantee	I0021
Regulation of the market	What kind of legal price control mechanisms are there relevant to the technology?	I0023
Regulation of the market	What kind of regulation exists for 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 of conflicts of interest concerning the preparation of binding rules and their implementation?	I0037

- 1 **Why is this domain important?**
- 2 Proper knowledge of relevant legal questions has significant consequences for the decision-
- 3 making, often perceived as part of the so called socio-legal issues {1,2}. Legal issues in HTA will be
- 4 increasingly important, since norms of professional ethics are continuously codified into statutes,
- 5 and European Union is producing ever more health technology -related legislation. The rapid
- 6 innovation processes of new technologies put the policy and decision makers in situations where
- 7 they need to know the legal implications of implementing and not-implementing a technology and
- 8 what are the roles and responsibilities of different actors, e.g. patients, providers and payers. The
- 9 perspective should include the levels of international, EU and national legislations, keeping in mind
- 10 the national characteristics, which limit the transfer of legal information from one country to
- 11 another. The legal domain helps in identifying the legal barriers which hinder the export and

1 import of HTA results {3,4,5,6}. It gives insight into the areas of health care legislation where  
2 harmonisation is needed, and provides tools for legislative and policy reforms.

### 3 **Relations to other domains**

4 Content relations were identified with 40 issues in 6 domains: in CUR-domain 2 issues, TEC 8, SAF  
5 11, ETH 11, ORG 5, and in SOC-domain 3 issues. Most of them (n=39) were also sequence  
6 relations, which means that results of those issues are needed before a particular issue in legal  
7 domain is answered. The relations are detailed in the assessment elements table.

8

## 1 Methodology

### 2 Process for answering research questions

3 The aim within the legal domain is not, and indeed cannot be, to give or even propose a binding  
4 legal solution to a given question. Instead, the aim is to guide the HTA doers in recognising the  
5 relevant legal questions they need to consider when evaluating the technology and providing  
6 advice for decision makers. For each relevant question identified in the Model an answer should  
7 be provided which helps the national HTA doer to adapt the information to their local context.  
8 Some issues may be similarly regulated in all countries, while other issues, e.g. those guided by EU  
9 directives may imply more national variability, which the HTA Core Model user can not address  
10 fully when providing the answer. What is most important is that the level of transferability of the  
11 information is clearly stated in the result card.

### 12 What kind of information is required?

13 Relevant directives, treaties and recommendations by the European Union and the European  
14 Council provide the HTA doers the basic framework for responding to the questions in the legal  
15 domain. Helpful documents on interpretation of laws are e.g. preparatory acts of legislation and  
16 judgements of courts. These primary sources of legal information often need to be complemented  
17 by various so-called soft law instruments, agreements and documentation by the technology  
18 supplier, and legal scientific literature.

19 There are three levels of legislation to consider: international, European Union and national  
20 legislations.

21 1. **International law**, particularly generated by the Council of Europe. The Council of Europe is an  
22 international organisation promoting co-operation between all countries of Europe in the  
23 areas of legal standards, human rights, democratic development, the rule of law and cultural  
24 co-operation. It is an entirely separate body from the European Union (EU). The conventions of  
25 the Council of Europe are not statutory acts of the Organisation: they owe their legal existence  
26 to the consent of those member States that sign and ratify them. In 1950, for instance, the  
27 Council of Europe established the European Convention for the Protection of Human Rights  
28 and Fundamental Freedoms (ECHR), commonly known as the European Convention of Human  
29 Rights, which is currently ratified and thus binding for all 47 member countries of the Council  
30 of Europe, among them all 28 member states of the EU. The most important document in the  
31 field of medicine is the Human Rights and Biomedicine Convention with its Additional  
32 Protocols. E.g. privacy and information rights are governed by its Article 10, which  
33 supplements the right to know with its counterpart, the right “not to know.”

34 [The Council of Europe Treaty Series](#) groups together all the conventions concluded within the  
35 organisation since its foundation in 1949. [The recommendations of the Committee of](#)  
36 [Ministers](#) since 1978 cover several issues of health policy. However, these have not been  
37 ratified by all European countries, so their applicability needs to be checked in each case. In  
38 addition, it may be necessary to investigate whether the [European Court of Human Rights](#)  
39 (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 **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. An **EU Regulation** is a legal act that becomes immediately enforceable as law in all member states simultaneously. There are relevant regulations and directives listed in the table below, 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 for example 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> </ul>
<ul style="list-style-type: none"> <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> </ul>
<ul style="list-style-type: none"> <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>
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>
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> .
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> .
Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on <b>in vitro diagnostic medical devices</b> .
<b>Medicinal products</b>

## Legal aspects

<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> </ul>
<ul style="list-style-type: none"> <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> </ul>
<ul style="list-style-type: none"> <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>
<b>Health care professionals</b>
<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>
<b>Product safety</b>
<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>
<b>International Treaties and recommendations from the Council of Europe</b>
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>
<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 of Human Origin</b> 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>

1

- 2 3. The level of **national legislation**. As EU Directives leave member states with a certain amount  
3 of flexibility, member states adapt the directives taking into account the differing national

situations. Much of the health care -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

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 in Medline, combining the term "legal" with the medical search terms. Libraries' electronic databases can be further used to search for relevant international and national monographs and articles on the issue in question. Journals such as 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.

[A summary of EU pharmaceutical legislation](#)

[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 Organization (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 Organization (WIPO) [WIPO Lex](#). Electronic database which provides access to intellectual property (IP) laws and treaties of the Members of WIPO, the World Trade Organization (WTO) and the United Nations (UN).

1 PATENTSCOPE (<http://patentscope.wipo.int/search/en/search.jsf>). A WIPO with more than 32 million patent documents  
2 including international patent applications submitted under the Patent Cooperation Treaty (PCT).

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#### 4 **Reporting and interpreting**

5 In each result card the results should be preferably reported in the order of power of influence of  
6 the legal sources. The authors should make a reasonable effort to produce a result which is  
7 beyond the interest of one's own country. General or EU-level information is therefore preferred,  
8 but national information can also be useful to other jurisdictions, as long as the sources are  
9 transparently reported and the generalizability or transferability of the result considered.

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## 1 Assessment elements

I0002 Assessment element card						
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?						
Topic: Autonomy of the patient						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	1
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	1
Clarification	<p><b>Common to all used applications</b></p> <p>Describe the rules and recommendations about what patients should know of the implications of using or not using the technology. The right of the patient to not-to-know may also be important, as well as patient's right to complain. 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 potential to provide information that is not directly relevant to the condition being tested, and in emergency situations in which the patients does not usually have sufficiently time to consider the treatment decision.</p> <p><b>Specific to Screening Technologies (2.1) - PUBLIC DRAFT</b></p> <p>As screening programs are targeted for symptom free and healthy people, it is particularly important that the individuals are aware of the potential benefits and harmful consequences of attending 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</p>					

	<p>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>	<p><b>Common to all used applications</b></p> <p>EU Charter of fundamental rights (2000/C 364/01) Art 3;</p> <p>Biomedicine Convention Art 5</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>B0014, B0015, C0002, C0005, C0007, C0008, F0004, F0006, F0010, F0016, G0004</p>
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>B0014, B0015, C0002, C0005, C0007, C0008, F0004, F0010, G0004</p>

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<p>I0005 Assessment element card</p> <p>Issue: What kind of legal requirements are there for counselling the user or patient or obtaining informed consent from her?</p> <p>Topic: Autonomy of the patient</p>						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Important	None	No	2
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	None	No	2
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	None	No	2
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	None	No	2
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Describe the rules and recommendations regarding informed consent or advance directive related to this kind of technology. The concept of informed consent includes also the</p>					

	possibility to consider, without pressure, other therapeutic options, if these are available, or watchful waiting with treatment of symptoms. See also I0002.
<b>Methodology and sources</b>	<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 especially 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>Content relations</b>	<p><b>Common to all used applications</b></p> <p>F0004, G0004, I0002</p>
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>F0004, I0002</p>

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<p>I0034 Assessment element card</p> <p>Issue: Who is allowed to give consent for minors and incompetent persons?</p> <p>Topic: Autonomy of the patient</p>						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Important	None	No	3
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	None	No	3
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	None	No	3
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	3



<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>What kind of informed consent procedure is required by the law/binding rules? See also I0005.</p>
<b>Methodology and sources</b>	<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>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Convention on Human Rights and Biomedicine, Art 6 and 7</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>F0005, I0005</p>
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>F0005, I0005</p>

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I0007 Assessment element card						
<p>Issue: Is there a possibility that the use of the technology produces such additional information that is not directly related to the current care of the patient and may violate her right to respect for private life?</p> <p>Topic: Privacy of the patient</p>						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	4
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	4
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	4
Clarification	<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 mean challenges to this principle. As an example Z vs. Finland (ECHR February 25, 1997): This is about a case of an HIV infected person, where the HIV positive test was an incidental finding, not-related to her healthcare intervention.</p>					
Methodology and sources	<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>					
References	<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>					
Content relations	<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>
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<p><b>I0008 Assessment element card</b></p> <p><b>Issue: What do laws/ binding rules require from informing relatives about the results?</b></p> <p><b>Topic: Privacy of the patient</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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	5
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	No				
	Pharmaceuticals (2.1) - PUBLIC DRAFT	No				
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	5
<b>Clarification</b>	<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, according with the existing legislation, must be thought through beforehand: is the information to be revealed to or withheld from the relatives in question. The question is on what conditions (if any) can the privacy of the original patient 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 relatives (closest) demand the results. Similar cases could occur in sudden, unexpected deaths and in some cases of highly infectious diseases.</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>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>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Directive 95/46/EC; Convention on Human Rights and Biomedicine Art 10.</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>B0014, F0011, G0004, H0002</p>
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>B0014, F0011, H0002</p>

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<p>I0009 Assessment element card</p> <p>Issue: What do laws/ binding rules require from appropriate measures for securing patient data and how should this be addressed when implementing the technology?</p> <p>Topic: Privacy of the patient</p>						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	6
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	5
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	5
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	6
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Provide an overview of the legal requirements, regarding policies and procedures, and</p>					

	examples of practical local solutions, of securing the kind of patient data that will be generated when using of the technology. 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?
<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>	<p><b>Common to all used applications</b></p> <p>Directive 95/46/EC; Convention on Human Rights and Biomedicine Art 10,</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>B0010, F0101, F0016</p>
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>B0010, F0101, F0016,</p>

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<p><b>I0011 Assessment element card</b></p> <p><b>Issue: What do laws/ binding rules require from appropriate processes or resources regarding guaranteeing equal access to the technology?</b></p> <p><b>Topic: Equality in health care</b></p>						
<b>Application-</b>	<b>Application</b>	<b>Used</b>	<b>Importance</b>	<b>Transferability</b>	<b>Core</b>	<b>Order</b>

## Legal aspects

<b>specific properties</b>	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	7
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	6
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	6
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	None	Yes	7
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>In general, equality in health care is spoken out in the EU Charter of Fundamental Rights and it is also one of the central principles of the Biomedicine Convention. Moreover, in many Constitutions equality of citizens covers also access to health care. However, there may be experiences nationally of some specific difficulties in equal access to the technology, and probably also proposed solutions, which could be helpful for decision makers in other countries too.</p>					
<b>Methodology and sources</b>	<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>Panaiteescu vs. Romania (ECtHR April 10, 2012).</p> <p>Costa and Pavan vs. Italy (ECtHR August 28, 2012)</p>					
<b>References</b>	<p><b>Common to all used applications</b></p> <p>EU FR Charter Art 35, Biomedicine Convention Article 3, CM Recommendation R (2006) 18</p>					

<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

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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 (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	8
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	7
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	7
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	8
<b>Clarification</b>	<b>Common to all used applications</b>  The possible consequences of the EU Directive of cross border health care could be considered here. There may be legally defined processes nationally, including reimbursement and pricing, determining the implementation and level of access of a technology. This information may give useful insight also beyond one's own country.					
<b>Methodology and sources</b>	<b>Common to all used applications</b>  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.					

<b>References</b>	<b>Common to all used applications</b>  Charter of Fundamental Rights of the European Union (2000/C 364/01). Art 35
<b>Content relations</b>	<b>Common to all used applications</b>  A0021, B0004, F0012, F0013, G0009, G0101, H0012, H0015
<b>Sequential relations</b>	<b>Common to all used applications</b>  A0021, B0004, F0012, F0013, G0009, H0012, H0015

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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 (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	9
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	8
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	8
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	9
<b>Clarification</b>	<b>Common to all used applications</b>  Describe here 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. Information of register listings 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).					



<b>Methodology and sources</b>	<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 (2.1) - PUBLIC DRAFT</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>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>In vitro diagnostic directive (98/79/EC); EUDAMED; FDA, EMA</p>
<b>Content relations</b>	<p><b>Common to all used applications</b></p> <p>A0020, B0010, C0002, C0007, C0060</p>
<b>Sequential relations</b>	<p><b>Common to all used applications</b></p> <p>A0020, B0010, C0002, C0007, C0060</p>

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I0017 Assessment element card						
Issue: What do laws/ binding rules require from the safety of the technology and how should this be addressed when implementing it?						
Topic: Authorisation and safety						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	10
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	9
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	9
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	10
Clarification	<p><b>Common to all used applications</b></p> <p>What are 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? The findings of the safety and organisational domain should be considered 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 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 (2.1) - PUBLIC DRAFT</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>					

<b>References</b>	<b>Common to all used applications</b>  Directive 93/42/EEC, Directive 2001/95/EC
<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

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<b>I0019 Assessment element card</b>  <b>Issue: What should be known about the intellectual property rights and potential licensing fees?</b>  <b>Topic: Ownership and liability</b>						
<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 (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	11
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	10
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	10
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Complete	Yes	11
<b>Clarification</b>	<b>Common to all used applications</b>  This information is important because infringement of intellectual property rights can reduce the use of the technology and have implications in the wording of the acquisition contract of a new technology, and possibly also licencing fees.					
<b>Methodology and sources</b>	<b>Common to all used applications</b>  Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions.					

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

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I0021 Assessment element card						
Issue: What should be known of the legal or binding rules about the width, depth and length of the manufacturers guarantee						
Topic: Ownership and liability						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	12
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Complete	Yes	11
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Optional	Complete	No	11
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Optional	Complete	No	12
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 manufacturers guarantee. User guide plays 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 relevant to the technology?						
Topic: Regulation of the market						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	13
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	12
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	12
	Screening Technologies (2.1) - PUBLIC DRAFT	No				
Clarification	<p><b>Common to all used applications</b></p> <p>Describe the adopted economic measures to control public health expenditures when adopting technologies. This information, although not transferable, gives insight to decision maker 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>					

	G0007
<b>Sequential relations</b>	<b>Common to all used applications</b>  G0007

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<p>I0024 Assessment element card</p> <p>Issue: What kind of regulation exists for acquisition and use of the technology?</p> <p>Topic: Regulation of the market</p>						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	14
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	13
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	13
	Screening Technologies (2.1) - PUBLIC DRAFT	No				
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 (2.1) - PUBLIC DRAFT</b></p> <p>Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001</p>					

	on the Community code relating to medicinal products for human use
<b>References</b>	<b>Common to all used applications</b>  Directive 2004/18/EC
<b>Content relations</b>	<b>Common to all used applications</b>  G0006, G0007
<b>Sequential relations</b>	<b>Common to all used applications</b>  G0006, G0007

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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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	15
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	14
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	14
	Screening Technologies (2.1) - PUBLIC DRAFT	No				
<b>Clarification</b>	<b>Common to all used applications</b>  Describe here the general legal principles of the restrictions of marketing health technologies to lay people.					
<b>Methodology and sources</b>	<b>Common to all used applications</b>  Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the					



	<p>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 (2.1) - PUBLIC DRAFT</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>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Directive 1989/105/EEC, directive 2001/83/EC</p>
<b>Content relations</b>	
<b>Sequential relations</b>	

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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 (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	16
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	15
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	15
	Screening Technologies (2.1) - PUBLIC DRAFT	No				
<b>Clarification</b>	<b>Common to all used applications</b>					

## Legal aspects

	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.
<b>Methodology and sources</b>	<b>Common to all used applications</b>  Consulting legal expert, possibility to analogical interpretation of law, Court decisions, literature
<b>References</b>	
<b>Content relations</b>	<b>Common to all used applications</b>  B0002, B0003, F0003, F0016
<b>Sequential relations</b>	<b>Common to all used applications</b>  B0002, B0003, F0003, F0016

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I0037 Assessment element card						
Issue: Are there relevant concerns of conflicts of interest concerning the preparation of binding rules and their implementation?						
Topic: Regulation of the market						
Application-specific properties	Application	Used	Importance	Transferability	Core	Order
	Diagnostic Technologies (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	17
	Medical and Surgical Interventions (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	16
	Pharmaceuticals (2.1) - PUBLIC DRAFT	Yes	Critical	Partial	Yes	16
	Screening Technologies (2.1) - PUBLIC DRAFT	Yes	Important	Partial	Yes	13

<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Relevant concerns of partiality or conflicts of interest regarding binding guidance may give useful insight to decision makers about the importance of implementing a technology.</p>
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p>Literature</p>
<b>References</b>	<p><b>Common to all used applications</b></p> <p>Decision No 1926/2006/EC of the European Parliament and of the Council of 18 December 2006 establishing a programme of Community action in the field of consumer policy (2007-2013)</p> <p><a href="http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32006D1926&amp;from=DE">http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32006D1926&amp;from=DE</a> (2.4.2014)</p> <p>Directive 2001/20/EC of the European Parliament and the Council 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).</p> <p><a href="http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF">http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF</a> (2.4.2014).</p> <p>World medical association declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, (especially A5) <a href="http://www.wma.net/en/30publications/10policies/b3/17c.pdf">http://www.wma.net/en/30publications/10policies/b3/17c.pdf</a> (2.4.2014)</p> <p>Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research Strasbourg, 25.I.2005.</p> <p>The Treaty of Lisbon amending the Treaty on European Union and the Treaty establishing the European Community entered into force on 1 December 2009. , especially Chapter III Article 12) <a href="http://conventions.coe.int/Treaty/en/Treaties/Html/195.htm">http://conventions.coe.int/Treaty/en/Treaties/Html/195.htm</a> (2.4.2014).</p>
<b>Content relations</b>	
<b>Sequential relations</b>	

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## 1 **Appendices**

### 2 **Appendix Intro-Eth: Ethical considerations within HTA process**

3 Every HTA process should be performed considering the following ethical issues:

- 4 • The driving forces (and valued interests) to perform the assessment at this stage should be  
5 identified, including the stakeholders and the whole HTA organisation. *Are there particular interests*  
6 *that make this technology subject to assessment (pressure from producers, patient groups or*  
7 *professionals, costs)?*
- 8 • The morally relevant reasons for performing / not performing a HTA on this topic should be  
9 identified. *Is the topic a significant public health issue? Is the technology likely to benefit public*  
10 *health? Are HTA resources wisely spent on this topic? Is the topic a priori morally contentious? Is*  
11 *there fear of presenting unpopular results? Has the technology already been implemented without*  
12 *proper, objective evaluation? Is the technology being used beyond its actual target group? Have the*  
13 *costs exceeded the resources?*
- 14 • The interests of the producers of the technology should be identified. *Developers and producers are*  
15 *interested in promoting their technology which influences the distribution and use of technologies.*  
16 *What are the financial interest in respect to "well doing".*
- 17 • It should be identified whether there are related technologies that are morally contentious, or if  
18 the technology is a novel, innovative mode of care. *It is important to identify, from the beginning,*  
19 *whether there are ethically relevantly similar technologies in use. They may provide useful casuistic*  
20 *background for the ethical analysis. On the other hand, novel, innovative technologies may pose*  
21 *unexpected ethical problems and value conflicts, which may justify extra emphasis placed on ethical*  
22 *analysis.*
- 23 • The interests of the content expert group should be discussed openly so that the work can be  
24 conducted in an objective and independent way. *It is morally important to evaluate the relationship*  
25 *between professionals and the industry with respect to the development and use of the technology*  
26 *in question. What are their final interests? Is the technology of relevance for the professional*  
27 *identity and development?*
- 28 • The choice of end points in the assessment has to be carefully considered. *The choice of end points*  
29 *lead to questions that are of moral relevance. What is the aim of the technology - to reduce*  
30 *mortality, increase functional status, improve quality of life, lengthen disease-free time, save*  
31 *money? Are there other stakeholders with possible gains or losses that should be evaluated? The*  
32 *decision on endpoints has also an impact on the inclusion criteria of original studies and thus may*  
33 *not reflect the entire existing literature on the technology in question.*
- 34 • The morally relevant issues related to the selection of meta-analysis and studies to be included in  
35 the HTA have to be identified *The choice of endpoint affects the inclusion criteria for original studies*  
36 *to be accepted. What to do when the quality criteria are not filled by any existing studies or when*  
37 *no RCT studies exist - especially when the technologies are already being used? When is it necessary*  
38 *to continue with the HTA even if no RCTs are available?*
- 39 • The scope of the HTA and choice of research methods (e.g. inclusion of other aspects of assessment  
40 than effectiveness in the literature searches). *The literature searches focused only on the*  
41 *effectiveness of the technology in question seldom give access to articles relevant to other domains*  
42 *of assessment (e.g. the ethical, social or organizational analysis). Ethically relevant issues may be*  
43 *identified during the entire HTA process and the literature searches are thus possible first after their*  
44 *identification. The literature search should cover other related technologies with similar ethical*  
45 *challenges. The detailed presentation of questions and experiences related to a (ethically relevantly)*  
46 *similar technology are important, as they may help decision makers identify relevant issues and*  
47 *adopt coherent policies.*

## 1 **Appendix Intro-Scr: Screening technologies**

2 Depending on background and training, people may give different meaning to the word "screening".  
3 The following observations and definitions were agreed on originally for version 1.0 of the  
4 screening application and retained for version 2.0.

### 5 **Why do we need a dedicated Model application for screening technologies?**

6 Screening involves testing to identify people at high risk of having a specific disease (diagnosis). As  
7 there is already a HTA Core Model application for diagnostic technologies that covers testing  
8 procedures, why do we need additional application for screening? The following properties of  
9 screening were identified that justify the need of a dedicated application of the HTA Core Model.

- 10 – As preventive or early diagnostic intervention, screening is targeted to a large number of  
11 healthy or asymptomatic people – in contrast to diagnostics where people typically already have  
12 some symptoms or signs of illness.
- 13 – Screening tests are usually applied in a population with low disease prevalence, i.e. mostly  
14 healthy people. Therefore, the diagnostic tools often perform very differently from clinical settings  
15 (i.e. very low positive predictive value). The same technology has different performance when used  
16 in diagnosis than in screening.
- 17 – Effectiveness depends on participation rate of the target population.
- 18 – Screening issues usually benefit from careful ethical and legal considerations, due to the risk  
19 of false positives and false negatives, the consequences related to the under-or over-diagnosis and -  
20 treatment, and earlier diagnosis in cases where prognosis improvement is negligible. Equity of  
21 access is always an issue in screening programs.
- 22 – There are several organizational issues specific for screening as it
  - 23 • involves active contact of the target population by the health service
  - 24 • is multidisciplinary and involves multiple providers
  - 25 • requires quality control and a continuous monitoring system.
- 26 – There are many specific characteristics and methodological issues which have to be taken  
27 into account when evaluating economic impact of a screening program. For example, most of the  
28 costs of a screening program are incurred within a relatively short time period and the benefits (e.g.  
29 life years gained) further in the future. This means that decisions about whether to discount the  
30 future costs and effects or not, and which discount rate(s) to use, need to be carefully considered.

### 31 **Multiple definitions for screening**

32 There are **two main streams** of considering screening as a public health intervention.

- 33 – The first, mostly adopted in Europe, considers screening as a program in which
  - 34 • the target population and adequate screening interval are determined in advance;
  - 35 • all individuals in a certain category (e.g. all women of a certain age) are involved;
  - 36 • 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 standardized.

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 gynecological 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

## **LITERATURE:**

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## 1 Appendix Intro-2.1: Changes in the ontology

2 The following table indicates the changes made the ontology of HTA Core Model version 2.0 when making  
 3 the version 2.1. This includes formatting of questions and merging or removal of assessment elements.  
 4 Whenever the clarification of a question has been changed, the respective changes are displayed in the  
 5 assessment element cards after the table.

ASSESSMENT ELEMENT	CHANGES
<b>TEC</b>	
A0020 What is the marketing authorisation status of the technology?	<p>Element copied from CUR to TEC</p> <p>Question changed to: For which indications has the technology received marketing authorisation or CE marking?</p> <p>Clarification edited (see element card)</p>
B0002 What is the approved indication and claimed benefit of the technology and the comparator(s)?	Question changed to: What is the claimed benefit of the technology in relation to the comparators?
B0004 Who performs or administers the technology and the comparator(s)? AND B0005 In what context and level of care are the technology and the comparator used?	<p>Merged into one element.</p> <p>Question changed to:            NEW B0004 Who administers the technology and the comparators and in what context and level of care are they provided?</p> <p>Clarification edited (see element card)</p>
A0021 What is the reimbursement status of the technology across countries?	<p>Element copied from CUR to TEC</p> <p>Question changed to: What is the reimbursement status of the technology?</p>
B0010 What kind of data and records are needed to monitor the use of the technology and the comparator? AND B0011 What kind of registers are needed to monitor the use the technology and comparator?	<p>Merged into one element and copied to SAF domain. Question changed to:            NEW B0010 What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?</p> <p>Clarification edited (see element card)</p>
<b>CUR</b>	
A0001 For which health conditions and for what purposes is the technology used?	Question changed to: For which health conditions and populations, and for what purposes is the technology used?
A0002 What is the disease or health condition in the scope of this assessment?	Clarification edited (see element card).
A0005 What are the symptoms and burden of disease for the patient at different stages of the disease?	<p>Question changed to: What are the symptoms and the burden of disease or health condition for the patient?</p> <p>Clarification edited (see element card)</p>
A0006 What are the consequences of the disease or	Question chanded to: What are the consequences

the health condition for the society (i.e. the burden of the disease)?	of the disease or health condition for the society?  Clarification edited (see element card)
A0007 What is the target population in this current assessment of the technology?	Question changed to: What is the target population in this assessment?  Clarification edited (see element card)
A0011 How much is the technology utilised currently and in the future?	Question changed to: How much are the technologies utilised?  Clarification edited (see element card)
A0020 What is the marketing authorisation status of the technology?	Element copied from CUR to TEC and question changed (see details in TEC)
A0021 What is the reimbursement status of the technology across countries?	Element copied from CUR to TEC and question changed (see details in TEC)
EFF	
D0001 What is the expected beneficial effect of the intervention on overall mortality? AND D0002 What is the expected beneficial effect on the disease-specific mortality?	Merged into one element: NEW D0001 What is the expected beneficial effect of the technology on mortality?  Clarification edited (see element card)
D0003 What is the effect of the technology on the mortality due to causes other than the target disease?	Clarification edited (see element card)
D0005 How does the technology affect symptoms and findings (severity, frequency) of the target condition?	Question changed to: How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?  Clarification edited (see element card)
D0006 How does the technology affect the progression (or recurrence) of the target condition?	Question changed to: How does the technology affect progression (or recurrence) of the disease or health condition?  Clarification edited (see element card)
D0011 What is the effect of the technology on patients' body functions?	NOTE: question in element card is missing a question mark, added now.  Clarification edited (see element card)
D0016 How does use of the technology affect activities of daily living?	Question changed to: How does the use of the technology affect activities of daily living?  Clarification edited (see element card)
D0012 What is the effect of the technology on generic health-related quality of life?	Clarification edited (see element card)
D0013 What is the effect of the technology on disease specific quality of life?	Question changed to: What is the effect of the technology on disease-specific quality of life?  Clarification edited (see element card)
SAF	
C0001 What kind of harms can use of the technology cause to the patient; what are the	Merged into one element: NEW C0008 How safe is the technology in relation

incidence, severity and duration of harms? AND C0008 How safe is the technology in relation to the comparator(s)?	to the comparator(s)?  Clarification edited (see element card)
C0005 Are there susceptible patient groups that are more likely to be harmed through use of the technology?	Question changed to: What are the susceptible patient groups that are more likely to be harmed through the use of the technology?  Clarification edited (see element card)
C0007 Are there special issues in the use of the technology that may increase the risk of harmful events?	Question changed to: Are the technology and comparator(s) associated with user-dependent harms?  Clarification edited (see element card)
B0010 What kind of data and records are needed to monitor the use of the technology and the comparator? AND B0011 What kind of registers are needed to monitor the use the technology and comparator?	Merged into one element and copied to SAF from TEC (see details in TEC).

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1 **CUR**

**A0002 Assessment element card**

**Issue: What is the disease or health condition in the scope of this assessment?**

**Topic: Target Condition**

**Clarification**

**Common to all used applications**

~~Relevant for all assessments. Especially when effectiveness depends on the subtype, stage or severity of the disease.~~ Use the target condition and ICD codes defined in the scope of the project and consider adding details such as: description of anatomical site, disease aetiology and pathophysiology, types of disease or classification according to origin, severity, stages, or risk level, and different manifestations of the condition. The following properties of the target condition are defined in separate assessment elements: risk factors (A0003), natural course (A0004), symptoms (A0005), and burden of disease ~~for the society including prevalence and incidence~~ (A0006).

2

**A0005 Assessment element card**

**Issue: What are the symptoms and the burden of disease or health condition for the patient?**

**Topic: Target Condition**

**Clarification**

**Common to all used applications**

~~This issue is especially relevant when the patient or individual is expected to undergo a substantial change in pain, disability, psychosocial issues, or other determinants of quality of life. This element should d~~Describe the patient's relevant symptoms before intervention with the technology, their severity and whether they are persistent, intermittent, or undulating, taking into account different stages of the disease. Patients' perceptions of the burden of the disease are not always in line with the clinical seriousness of the disease or its societal burden.

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.

3

### A0006 Assessment element card

**Issue: What are the consequences of the disease or health condition for the society?**

**Topic: Target Condition**

**Clarification**

**Common to all used applications**

~~Prevalence and incidence of the disease that is prevented or treated by using the technology; disease-specific mortality and disability, life years lost, and/or disability-adjusted life years, quality of life, QALYs.~~ Describe consequences and burden of the disease or health condition by providing information on prevalence or incidence of the disease that is prevented or treated by using the technology; disease-specific mortality and disability, life years lost and/or disability-adjusted life years, quality of life, QALYs.

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### A0007 Assessment element card

**Issue: What is the target population in this assessment?**

**Topic: Target Population**

**Clarification**

**Common to all used applications**

Relevant for all assessments: both safety and effectiveness depend largely on the subpopulation towards which the intervention is targeted. The technology may be used for all patients with the condition, or only those in the early stages, or at a specific severity level, or for those at moderate risk of having the condition.

Personalised medicine divides the target population into even smaller units when targeting the intervention to specific subgroups based on e.g. genetic profile. Use the target population defined in the scope of the project, and consider adding further details and description of who defined the selected subgroups and why.

Point out e.g. if certain populations should be excluded from the analysis.

2

### A0011 Assessment element card

**Issue: How much are the technologies utilised?**

**Topic: Utilisation**

<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Provide national estimates for current and future utilisation rates, <u>for the indication under assessment</u>, for both the technology under assessment and its comparators. Variations in utilisation reflect market access, sales figures, actual usage in hospital level and adherence to the use of the technology by both professionals and patients. Data on current and previous utilisation reflect the phase of the technology (experimental, emerging, established or obsolete). This also has implications for the availability of evidence and the level of uncertainties.</p> <p><b>Specific to Screening Technologies (2.0)</b></p> <p>What is the current rate of screening adherence?</p>
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### A0020 Assessment element card

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

**Topic: Regulatory Status**

<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>There are both international and national market authorisation systems. <u>For pharmaceuticals the systems are established but for devices and procedures less so.</u> An overview of the status with regard to key processes, e.g. CE marking, EMA/FDA approval is recommended. Also information on national data and an analysis of possible discrepancies can be highly useful.</p> <p><b>Specific to Diagnostic Technologies (2.0)</b></p> <p>Imaging devices may require approval. Substances needed for obtaining images may require additional approval (e.g. radiotracers). In some cases the approval for primary screening is different to that for clinical use (FDA recently licensed tests explicitly for screening), but in most cases approval is obtained for diagnostic use and the test is proposed for screening without any other formal approval.</p> <p><b>Specific to Screening Technologies (2.0)</b></p>
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	Imaging devices may require approval. Substances needed for obtaining images may require additional approval (e.g. radiotracers). In some cases the approval for primary screening is different to that for clinical use (FDA recently licensed tests explicitly for screening), but in most cases approval is obtained for diagnostic use and the test is proposed for screening without any other formal approval.
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1 **TEC**

**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**

**Clarification**

**Common to all used applications**

Describe the following aspects:

-Which professionals (nurses, doctors, and other professionals) apply and make decisions about starting or stopping the use of the technology?

-Do the patients themselves, or their carers, administer the technology?

-Who can select the patients, make referrals, decide to initiate the use of the technology, or interpret the outcome?

-Are there certain criteria (skills, function, training requirements) for the patients or professionals who will administer the technology?

Describe the level of care in which the technology is used: self care, primary care, secondary and tertiary care. If secondary or tertiary care, describe whether it is intended to be used in the outpatient or inpatient setting.

Its role in the management pathway can be as a replacement, an add-on or for triage

2

**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**

**Clarification**

**Common to all used applications**

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 ~~could be consulted~~.

	<p><u>Describe the general importance of having a registry to monitor the use of this particular technology and the comparator. Are there existing registries that should be used, or should a registry be established, to collect the necessary data to monitor safety or true life effectiveness? Provide national examples.</u></p> <p><b><u>Specific to Pharmaceuticals (2.0)</u></b></p> <p><u>Refer to SPC and EPAR.</u></p> <p><u>Sometimes registries are connected with the risk sharing scheme that innovative pharmaceuticals require in some countries. Notice also the requirements of pharmacovigilance monitoring.</u></p>
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1 EFF

D0001 Assessment element card	
Issue: What is the expected beneficial effect of the technology on mortality?	
Topic: Mortality	
Clarification	<p><b>Common to all used applications</b></p> <p>Mortality is the preferred, objective endpoint for assessments of life- threatening conditions.</p> <p><u>Overall mortality and disease-specific mortality are distinguished.</u> Overall mortality refers to all-cause mortality. It is expressed either as mortality rates (incidence in given population, at given time point and usually risk standardised), or survival (number of people alive for a given period after an intervention). <u>Disease-specific mortality is a proportion of the all-cause mortality. It should be noted that even if a given treatment reduces one type of death, it could increase the risk of dying from another cause, to an equal or greater extent. Disease-specific mortality is typically presented as rates and as age- and risk- adjusted measures such as hazard ratio. It is a frequently used endpoint in screening trials, where it is considered to be subject to bias.</u></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>Consider separately absolute mortality (compared to placebo or waiting list) and mortality relative to the comparator. See also Methodological guideline for REA of pharmaceuticals: Endpoints used for relative effectiveness assessment of pharmaceuticals, clinical endpoints <a href="http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf">http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf</a></p> <p><u>Supplement with relevant data if differences can be expected for specific subgroups.</u></p> <p><b>Specific to Diagnostic Technologies (2.0)</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 Screening Technologies (2.0)</b></p> <p>In diagnostic and screening technologies this issue refers to the expected beneficial</p>

	<p>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><u>Specific to Pharmaceuticals (2.0)</u></p> <p><u>See also Methodological guideline for REA of pharmaceuticals: Endpoints used for relative effectiveness assessment of pharmaceuticals, clinical endpoints</u>  <a href="http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf">http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf</a></p>
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<p><b>D0003 Assessment element card</b></p> <p><b>Issue: What is the effect of the technology on the mortality due to causes other than the target disease?</b></p> <p><b>Topic: Mortality</b></p>	
<p><b>Clarification</b></p>	<p><b>Common to all used applications</b></p> <p>This issue includes all unintended, either positive or negative effects of the technology on mortality. There may be e.g. decrease of mortality of another disease observed or suspected; or increased mortality due to accidents or hazardous medical interventions after false positive or incidental test results.</p> <p><u>Supplement with relevant data if differences can be expected for specific subgroups.</u></p> <p><b>Specific to Diagnostic Technologies (2.0)</b></p> <p>In diagnostic and screening technologies this issue refers to the effect of the test-treatment-chain,</p> <p><b>Specific to Screening Technologies (2.0)</b></p> <p>In diagnostic and screening technologies this issue refers to the effect of the test-treatment-chain,</p>

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### D0005 Assessment element card

**Issue: How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?**

**Topic: Morbidity**

#### Clarification

**Common to all used applications**

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.

Supplement with relevant data if differences can be expected for specific subgroups.

See also Methodological guideline for REA of pharmaceuticals: Endpoints used for relative effectiveness assessment of pharmaceuticals, clinical endpoints  
<http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf>

1

### D0006 Assessment element card

**Issue: How does the technology affect progression (or recurrence) of the disease or health condition?**

**Topic: Morbidity**

#### Clarification

**Common to all used applications**

Report here outcomes such as complete cure, progression-free survival, time-to-event (next stage of disease, relapse). Describe here the duration of treatment effect on symptoms and findings: permanent, short term, long term, intermittent, undulating. Report the results both in absolute terms and relative to the comparator. See also Methodological guideline for REA of pharmaceuticals: Endpoints used for relative effectiveness assessment of pharmaceuticals, clinical endpoints  
<http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf>

Supplement with relevant data if differences can be expected for specific subgroups.

2

### D0011 Assessment element card

**Issue: What is the effect of the technology on patients' body functions?**

#### Topic: Function

##### Clarification

##### Common to all used applications

International classification of function proposes the following categories for body functions: mental, sensory and pain, voice and speech, cardiac, respiratory and immune functions, genitourinary and reproductive functions, movement-related, and skin functions. Report the results both in absolute terms and relative to the comparator.

Supplement with relevant data if differences can be expected for specific subgroups.

##### Specific to Pharmaceuticals (2.0)

See also Methodological guideline for REA of pharmaceuticals: Endpoints used for relative effectiveness assessment of pharmaceuticals, clinical endpoints  
<http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf>

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### D0016 Assessment element card

**Issue: How does the use of the technology affect activities of daily living?**

#### Topic: Function

##### Clarification

##### Common to all used applications

Activities of Daily Living (ADL) is used in rehabilitation as an umbrella term relating to self care, comprising those activities or tasks that people undertake routinely in their every day life. The activities can be subdivided into personal care and domestic and community activities. Report the results both in absolute terms and relative to the comparator.

For further information see guideline Health-related quality of life and utility measures <http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Health-related%20quality%20of%20life.pdf>, and guideline: Endpoints used for relative effectiveness assessment of pharmaceuticals, clinical endpoints  
<http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf>

Supplement with relevant data if differences can be expected for specific subgroups.

1

<b>D0012 Assessment element card</b>  <b>Issue: What is the effect of the technology on generic health-related quality of life?</b>  <b>Topic: Health-related Quality of life</b>	
<b>Clarification</b>	<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 to measure 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). Two basic approaches to quality-of-life measurement are available: generic instruments that provide a summary of HRQL; and specific instruments that focus on problems associated with single disease states, patient groups, or areas of function. Generic instruments include health profiles and instruments that generate health utilities. Each approach has its strengths and weaknesses and may be suitable for different circumstances. See also •Methodological guideline for REA of pharmaceuticals: Health-related quality of life and utility measures.  <a href="http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Health-related%20quality%20of%20life.pdf">http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Health-related%20quality%20of%20life.pdf</a></p> <p><u>Supplement with relevant data if differences can be expected for specific subgroups.</u></p>

2

<b>D0013 Assessment element card</b>  <b>Issue: What is the effect of the technology on disease specific quality of life?</b>  <b>Topic: Health-related Quality of life</b>	
<b>Clarification</b>	<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 to measure 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). Two basic approaches to quality-of-life measurement are available: generic instruments that provide a summary of HRQL; and 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.</p>

See also •Methodological guideline for REA of pharmaceuticals: Health-related quality of life. <http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Health-related%20quality%20of%20life.pdf>

**Supplement with relevant data if differences can be expected for specific subgroups.**

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1 SAF

**C0008 Assessment element card**

**Issue: How safe is the technology in relation to the comparator(s)?**

**Topic: Patient safety**

**Clarification**

**Common to all used applications**

Here one should identify and describe the direct harms of the use and the administration of the technology and the comparator(s). Highlight the differences in the most important risks (i.e. the most severe and frequent harms) of the technology and its comparator(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 & cost effectiveness should be considered.

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 separately harms identified in spontaneous reporting databases. Harms should be reported per indication or target population . The identified harms should be categorised 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 the occurrence of each harm is usually presented in comparison with placebo or no treatment, as percentages or risk ratios. Finally, the harms should be grouped by their severity and frequency and ordered so that the severe and/or frequent harms are presented first. If there are many different harms reported in the literature, concentrate on reporting the most serious and the most frequent harms

**Specific to Pharmaceuticals (2.0)**

The important identified and potential adverse events/reactions presented in Risk Management Plan of the pharmaceutical (RMP) should be considered, as well as the important identified and potential interactions with other medicinal products, foods and other substances, and the important pharmacological class effects.

Special attention should be given to drug interactions. Information in the label warnings and PSUR should be evaluated using literature and registration data.

Distinction should be made 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.

Attention should be paid to the possibility of medication errors. Errors may be

	<p><u>classified 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, or replacement of two pharmaceuticals which look alike or difficulties of handwriting readings that lead to mistakes by patient or professional.</u></p> <p><u>For further information see Endpoints used in REA of pharmaceuticals – Safety <a href="http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Safety.pdf">http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Safety.pdf</a></u></p>
<b>Methodology and sources</b>	<p><b>Common to all used applications</b></p> <p><u>Placebo controlled trials, observational research, FDA database, safety monitoring databases, observational research, registers, statistics registers, statistics,</u></p> <p><u>R</u> <u>research articles, manufacturers' product data sheets, <del>safety monitoring databases.</del></u></p> <p>Other HTA reports or systematic reviews of main comparators.</p> <p>Method: Systematic review. <u>Results should be presented by risk level (i.e. the product of severity and frequency of harm).</u></p>

1

<p><b>C0005 Assessment element card</b></p> <p><b>Issue: What are the susceptible patient groups that are more likely to be harmed through the use of the technology?</b></p> <p><b>Topic: Patient safety</b></p>	
<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Typically, people with comorbidities and co-medication, pregnancy, intolerances, or specific genetic profiles, elderly people, children and immunosuppressed patients. <u>Are there any relevant contra-indications or interactions with other technologies?</u></p>

2

### C0007 Assessment element card

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

**Topic: Patient safety**

<b>Clarification</b>	<p><b>Common to all used applications</b></p> <p>Describe here what is known of the harms caused by the properties or behaviour of professionals, patients or other individuals who apply or maintain the technology. Is there e.g. a noteworthy risk of malfunction of a device, due to deficient user training or personal attitude; or a risk of errors related to reconstitution, dosage, administration, or storage of medicines, that may have serious consequences; or, is there a risk of addiction? Describe what is known of the learning curve, intra- or inter-observer variation in interpretation of outcomes, errors or other user-dependent concerns in the quality of care.</p> <p><u><a href="http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Safety.pdf">For further information see Endpoint used in REA of pharmaceuticals – Safety.  http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Safety.pdf</a></u></p>
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## Appendix 1: Information sources

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3 **Important notice:** *This appendix represents auxiliary content of the HTA Core Model. It is under*  
4 *construction and not fully updated for the HTA Core Model version 2.0. It is not yet a*  
5 *comprehensive presentation of useful information sources for core HTA information producers. It*  
6 *will be updated and amended during Joint Action 2 by September 2015.*

## 7 Registers

8 Registers may act as an important information source for those involved in the conduct of HTA.  
9 Registers are usually managed by medical societies, scientific associations or government  
10 institutions; industry-managed registers also exist. Registers collect data for a defined geographical  
11 area, usually a single country. However, regional or even European registers also exist.

12 Registries commonly release periodic reports for disseminating findings and results. The reports are  
13 often open-access and downloadable free of charge from the homepage of the registry.  
14 Dissemination is also achieved by publishing specific studies or reports in specialised peer-  
15 reviewed journals. Registers include technology, procedure and disease registers.

### 16 **Technology and procedure registers**

17 Technology and procedure registers gather information on the use of specific technologies and  
18 procedures (e.g., knee arthroplasty register). A new case is registered in the database every time the  
19 technology is used (i.e. a procedure is undertaken, an intervention takes place). In some countries,  
20 there is an obligation to report the indications and consequences of using a technology before it is  
21 approved, for example when there is no high quality evidence to establish effectiveness and, or the  
22 safety of the technology.

### 23 **Disease registers**

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

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

34 [http://www.kvalitetsregister.se/web/Quality\\_Registries.aspx?pageID=8d07dd0a-4079-4ad7-b47b-](http://www.kvalitetsregister.se/web/Quality_Registries.aspx?pageID=8d07dd0a-4079-4ad7-b47b-58759d7055cb)  
35 [58759d7055cb](http://www.kvalitetsregister.se/web/Quality_Registries.aspx?pageID=8d07dd0a-4079-4ad7-b47b-58759d7055cb)

### 36 **Quality registers in Sweden**

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

1 British Heart Foundation's statistics website is an up-to-date source of statistics on the burden,  
2 prevention, treatment and causes of heart disease in the UK <http://www.heartstats.org/homepage.asp>

### 3 ***Technology registers***

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

### 10 ***Pharmaceutical registries***

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

### 14 ***Utilisation registers***

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

### 18 ***ATC INDEX with DDDs***

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

21

## 22 **Regulatory institutions**

### 23 ***EMA***

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

- 27 • Once a medicine has been granted a Community marketing authorisation by the European  
28 Commission, the EMA publishes a full scientific assessment report called a European Public  
29 Assessment Report (EPAR)  
30 [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar\\_search.jsp&menu=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125&jsearch=true](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&menu=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125&jsearch=true)  
31
- 32 • All medicines for human and animal use derived from biotechnology and other high-tech  
33 processes must be approved via the centralised procedure. The same applies to all advanced-  
34 therapy medicines and human medicines intended for the treatment of HIV/AIDS, cancer,  
35 diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and  
36 viral diseases, as well as to all designated orphan medicines intended for the treatment of  
37 rare diseases.

- EMA becomes involved in the assessment of medicines that do not require centralised procedure, in cases where they have been referred to the Agency due to a disagreement in authorisation or use of the medicine between two or more Member States, or due to some other issue that requires resolution in the interest of protecting public health.
- EMA constantly monitors the safety of medicines through a pharmacovigilance network, and takes appropriate actions if adverse pharmaceutical reaction reports suggest that the benefit-risk balance of a medicine has changed since it was authorised.
- EMA can be considered as the 'hub' of a European medicines network comprising over 40 national competent authorities in 30 EU and EEA-EFTA countries, the European Commission, the European Parliament and a number of other decentralised EU agencies.
- The EMA monitors the safety of authorised medicines through a pharmacovigilance network, and takes appropriate actions if adverse drug reaction reports suggest that the benefit-risk balance of a medicine has changed since it was authorised.

## **FDA**

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

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

## **Standardisation and regulatory concerns of medical devices**

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

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

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

The ISO standards for medical devices are covered by

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

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

## Packaging standards

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

## Medical Device Directive

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

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

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

1 **Other sources**

2

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

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

1  
2  
3  
4  
5

1 **National or international safety monitoring systems (databases)**  
2 **(which may be managed by a national statutory body or by a supra-national body)**

- 3 IAEA: Safety standards for diagnostic radiology [http://www-](http://www-pub.iaea.org/MTCD/publications/PDF/Pub1206_web.pdf)  
4 [pub.iaea.org/MTCD/publications/PDF/Pub1206\\_web.pdf](http://www-pub.iaea.org/MTCD/publications/PDF/Pub1206_web.pdf)
- 5 IAEA: Radiological protection of patients <http://rpop.iaea.org/RPoP/RPoP/Content/index.htm>
- 6 ICRP: Publications of International Commission of Radiological Protection <http://www.icrp.org/>
- 7 TGA (Therapeutic Goods Administration), <http://www.tga.gov.au/index.htm>
- 8 US Food and Drug Administration, MedWatch safety alert system  
9 <http://www.fda.gov/medwatch/safety.htm>
- 10 The Medical Devices section of the UK Medicines and Healthcare Products Regulatory Agency  
11 (<http://devices.mhra.gov.uk/>)
- 12 National Prescription Database for pharmaceuticals.
- 13

14 **A0021 List of websites of national agencies with information on reimbursement**

- 15 AIFA: <http://www.aifa.gov.it/>
- 16 Australia:  
17 [http://www.health.gov.au/internet/main/publishing.nsf/Content/Pharmaceutical+Benefits+Scheme+](http://www.health.gov.au/internet/main/publishing.nsf/Content/Pharmaceutical+Benefits+Scheme+%28PBS%29-1)  
18 [%28PBS%29-1](http://www.health.gov.au/internet/main/publishing.nsf/Content/Pharmaceutical+Benefits+Scheme+%28PBS%29-1)
- 19 Belgium: [http://www.riziv.fgov.be/inami\\_prd/ssp/cns2/pages/SpecialityCns.asp](http://www.riziv.fgov.be/inami_prd/ssp/cns2/pages/SpecialityCns.asp)
- 20 Canada: <http://www.cadth.ca/en/products/cdr> or <http://www.pcodr.ca>
- 21 Czech Republic: <http://www.sukl.eu>
- 22 Finland: <http://www.kela.fi/in/internet/english.nsf>
- 23 France: [http://www.has-sante.fr/portail/jcms/j\\_5/accueil](http://www.has-sante.fr/portail/jcms/j_5/accueil) and  
24 <http://www.codage.ext.cnamts.fr>
- 25 The Netherlands: <http://www.medicijnkosten.nl/>
- 26 Norway: <http://www.legemiddelverket.no/>
- 27 Poland: <http://www.aotm.gov.pl/>
- 28 Portugal: <http://www.infarmed.pt/portal/page/portal/INFARMED>
- 29 Scotland: <http://www.scottishmedicines.org.uk/>
- 30 Spain: <http://www.msc.es/profesionales/farmacia/>

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

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

3

## Appendix 3. Shared methodologies

**Important notice:** This appendix represents auxiliary content of the HTA Core Model. It is under construction and not fully updated for the HTA Core Model version 2.0. It is not yet a comprehensive presentation of useful methodologies for core HTA information producers. It will be updated and amended during Joint Action 2 by September 2015.

### Diffusion and translation models

The relation between technology and organisation can be tackled in different ways. At least two different and incompatible views on causality and transferability can be differentiated with respect to the organisational issues: the diffusion model and the translation model (Kristensen 2001, Latour 1987). Parallel viewpoint is seen in the social domain.

#### *Diffusion model*

- bases on a linear, unidirectional conception of causality
- considers technology as an exogenous and independent entity
- seen as a given object which stands outside or above the society, its organisations and actors
- supposes that technology stays constant
- sees technology be diffused and transferred from the innovator to different users

(Leavitt 1965)

#### *Translation model (Leavitt 1965):*

- sees technology as endogenous, as a part of the organisational and use process
- technology can't be separated from the organisation and its users
- technology does not stay constant during the implementation process
- human activity is a part of the technology in question
- asks "how many and what kind of resources (material entities, time, money, people, etc.) must be mobilised and organized in order to produce satisfactory results from a health technology."
- technology does not causally affect the organisation and change its social structures
- organisation and its work processes and social structures have to be organized so that good results can be produced from the technology.

(Leavitt 1965)

#### **References:**

- Kristensen FB, Horder M, Poulsen PB (eds). Health Technology Assessment Handbook 1<sup>st</sup> edition. Danish Institute for Health Technology Assessment (DIHTA). 2001
- Latour B. Science in Action. How to follow scientists and engineers through the society. Harvard University Press, Cambridge, MA, 1987
- Leavitt HJ. Applying Organisational Change in Industry: Structural, Technological and Humanistic Approaches. In Handbook of Organisations, edited by James G March. Chicago: Rand McNally. 1965.

## **General guidance to critical appraisal of published studies and other information**

### ***Critical appraisal of HTAs***

[to be added]

### ***Critical appraisal of systematic reviews***

AMSTAR

### ***Critical assessment of indirect comparisons***

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

<http://www.ispor.org/workpaper/conducting-Indirect-treatment-comparison-and-network-meta-analysis-studies.pdf>

### ***Critical appraisal of guidelines***

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

### ***Critical appraisal of trials***

[to be added]

### ***Critical appraisal of observational studies***

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

- Newcastle Ottawa Scale <http://www.cochrane.org/training/cochrane-handbook>
- AHRQ: Systems to Rate the Strength Of Scientific Evidence <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=erta47>
- Checklist of items that should be included in reports of observational studies (actually not meant for assessing quality): STROBE <http://www.strobe-statement.org>

### ***Critical appraisal of diagnostic accuracy studies***

QUADAS-2

### ***Critical appraisal of modelling studies***

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

1 References:

2 Weinstein et al. Principles of Good Practice for Decision Analytic Modeling in Health-Care Evaluation: Report  
3 of the ISPOR Task Force on Good Research Practices - Modeling Studies. Value in Health 2003;6:9-17.  
4 <http://www.ispor.org/workpaper/healthscience/TFModeling.asp>

5 ***Critical appraisal of economic evaluation***

6 There are several methodological characteristics to consider, when assessing the quality of an  
7 economic evaluation. Several checklists have been published for reporting an economic evaluation,  
8 but also to help in identifying the strengths and weaknesses of different studies (e.g. Drummond  
9 1996, Drummond 2005). An example of a checklist (by Drummond 2005) is:

10

- 11 1. Was a well-defined question posed in answerable form?
- 12 2. Was a comprehensive description of the competing alternatives given?
- 13 3. Was the effectiveness of the programmes or services established?
- 14 4. Were all the important and relevant costs and consequences for each alternative identified?
- 15 5. Were costs and consequences measured accurately in appropriate physical units?
- 16 6. Were costs and consequences valued credibly?
- 17 7. Were costs and consequences adjusted for differential timing?
- 18 8. Was an incremental analysis of costs and consequences of alternatives performed?
- 19 9. Was allowance made for uncertainty in the estimates of costs and consequences?
- 20 10. Did the presentation and discussion of study results include all issues of concern to users?

21

22 References:

23 Drummond M, Manca A, Sculpher M. Increasing the generalizability of economic evaluations:  
24 Recommendations for the design, analysis, and reporting of studies. International Journal of Technology  
25 Assessment in Health Care 2005;21: 165-71.

26 Drummond MF, Jefferson TO, on behalf of the British Medical Journal Economic Evaluation Working Party.  
27 Guidelines for authors and peer reviewers of economic submissions to the BMJ. British Medical Journal  
28 1996;313:275-283

29

30 ***Critical appraisal of qualitative studies***

31 Examples of quality assessment instruments:

- 32 • Critical Appraisal Skills Programme – CASP  
33 [www.phru.nhs.uk/Doc\\_links/Qualitative%20Appraisal%20Tool.pdf](http://www.phru.nhs.uk/Doc_links/Qualitative%20Appraisal%20Tool.pdf)
- 34 • QARI software by Joanna Briggs Institute. [www.joannabriggs.edu.au/services/sumari.php](http://www.joannabriggs.edu.au/services/sumari.php)
- 35 • EPPI-review by the EPPI Centre. <http://eppi.ioe.ac.uk/eppireviewer/login.aspx>
- 36 • Quality Framework UK Cabinet Office  
37 [http://www.gsr.gov.uk/downloads/evaluating\\_policy/a\\_quality\\_framework.pdf](http://www.gsr.gov.uk/downloads/evaluating_policy/a_quality_framework.pdf)
- 38 • Checklist of items that should be included in reports of qualitative studies (not checklist for  
39 assessing quality) COREQ [http://www.aaz.hr/dokumenti/odjel-raz-ist-i-zdra-teh/edukativni-](http://www.aaz.hr/dokumenti/odjel-raz-ist-i-zdra-teh/edukativni-materijali/smjernice/7.%20Guidelines%20for%20qualitative%20research.pdf)  
40 [materijali/smjernice/7.%20Guidelines%20for%20qualitative%20research.pdf](http://www.aaz.hr/dokumenti/odjel-raz-ist-i-zdra-teh/edukativni-materijali/smjernice/7.%20Guidelines%20for%20qualitative%20research.pdf)
- 41 • Popay et al (1998)
- 42 • The Mays & Pope criteria (2000)

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### ***Quality assessment of routine collected statistics and administrative data***

Routine collected administrative data (e.g. DRG, discharge databases, reimbursement claims databases) can be useful too, when available. For example sickness funds collect great amounts of information which could be used to analyse utilisation of technology etc. However, analysis of this kind of data might be very time consuming, since data need to be “prepared” before analysis. By definition, these data has been collected for other purposes than research and they cannot be used to answer scientific questions without previous processing. This might not be feasible in the context of an HTA project, due to resource constraints.

The use of routine collected statistics has several limitations. The reliability of the diagnosis varies and usually it is not possible to differentiate between different stages of the disease. Even the validity of the coding of causes of death may be variable, and in some countries it is known to be very limited.

Own analysis of administrative data often requires authorization from the data owner, which in some countries might be difficult to obtain due to issues of privacy protection and confidentiality.

### ***Critical appraisal of register data***

ISPOR is developing guidelines for patient registry data:

[http://www.ispor.org/sigs/PR\\_analysis\\_data\\_mgt.asp](http://www.ispor.org/sigs/PR_analysis_data_mgt.asp)

## **General guidance to conducting own research**

### ***Guidance for modelling***

International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has published an article describing the basic guidelines for conducting and reporting modelling studies. ISPOR is also developing more specific guidelines on different modelling methods.

#### **References**

Weinstein et al. Principles of Good Practice for Decision Analytic Modeling in Health-Care Evaluation: Report of the ISPOR Task Force on Good Research Practices - Modeling Studies. Value in Health 2003;6:9-17.  
<http://www.ispor.org/workpaper/healthscience/TFModeling.asp>

### ***Guidance for conducting a register study***

[to be added]

### ***Guidance for conducting survey (questionnaire, interview)***

[to be added]

## **General guidance for synthesis**

### ***Meta analyses of accuracy studies***

#### **No heterogeneity**

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. Forest plot illustrates

the range of results, enables the reader to assess heterogeneity, and possible trade-off between sensitivity and specificity, and may show the 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, simple summary measures for sensitivity, specificity, or likelihood are adequate.

When pooling pairs of sensitivity and specificity, the statistical model used depends on the studies selected. Fixed effect model 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 weights individual studies based on the inverse variance of the accuracy or the number of participants. Random effects model 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.

### **Heterogeneity present**

When forest plot and heterogeneity testing shows that there is significant heterogeneity in sensitivities and specificities across studies, it is not appropriate to report the pooled values of sensitivity and specificity as a summary estimate. Instead, further analysis of the heterogeneity detected is needed, and it starts with examining of threshold effect. Threshold effect can be seen in 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 to examine the threshold effect further.

Paired estimates of sensitivity and 1 - specificity in original studies are plotted in a ROC plane. Regression model is used to fit the SROC curve (Moses 1993). 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 in the model the slope  $b$  (estimated regression coefficient) is not statistically significant and approaches zero, The SROC will be symmetrical.

Spearman's test for a nonparametric distribution has also been used to test for a threshold effect. Using this method, the correlation between sensitivity and 1-specificity for each study is measured and a Spearman rank correlation coefficient  $> 0.6$  is used to confirm variation across studies due to a threshold effect (Moses 1993). If the correlation is poor (Spearman rank correlation coefficient  $< 0.6$ ) the variation between studies is attributed to other differences. This is a crude measure and is not generally recommended.

### **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 allows assessment of their interdependence. Summary DOR (SDOR) of the test and a comparator test can be presented with 95 % CIs to compare differences in diagnostic performance. The area under SROC curve and its 95% confidence interval provides a global summary of overall test accuracy. The point on the curve where sensitivity equals specificity, the  $Q^*$  statistics, can also be used as a summary measure of the accuracy of the test. These summary measures can also be used to



compare the accuracy of two test strategies. Software for diagnostic meta-analysis include Meta-Test, Meta-Disc, Stata and SAS.

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

If the slope  $b$  in the SROC model is statistically significant, the SROC will be asymmetrical and the DOR changes along the threshold. In such cases advanced methods for fitting the SROC is used. Advanced methods to pool are indicated if heterogeneity in the results can be attributed to known sources of variation (see above Chapter Assessing heterogeneity). Otherwise the interpretation of the summary estimate is not possible (Lijmer 2002).

Possible sources of variation include

1. Chance
2. Different threshold
3. Different study designs, methods, biases: 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 can not be attributed to these known sources of heterogeneity, then pooling of the results to one summary estimate should not be attempted, because its interpretation will be impossible (Lijmer 2002).

Methods to test for heterogeneity (Medical Services Advisory Committee 2005):

1. Plot the sensitivity and specificity from each study with their 96% confidence interval in a table and/or forest plot to illustrate the range of estimates and identify outliers.
2. If sufficient data are available, plot the paired sensitivity and 1-specificity results for each study on the ROC plane to detect heterogeneity and identify outliers. A small number of studies will limit the power of regression to detect 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.

Advanced models enable incorporation of covariates, e.g. population subtype in the meta-regression analysis. Poor reporting of primary studies may though lead to biased estimates. The two main advanced models are hierarchical SROC and bivariate meta-regression, and they are mathematically identical (Harbord 2007). Syntax to run these models in SAS, STATA, WINBUGS, S-PLUS and R are or will be available. Hierarchical SROC (HSROC) produces informative summary measures with confidence ellipses (Reitsma 2005). Model is infrequently used, probably due to complex fitting.

*More reading: (Deeks 2001, Deville 2002, Kester 2000, Irwig 1995)*

## References:

- Harbord RM, Deeks JJ, Egger M, Whiting P, Sterne JAC. A unification of models for meta-analysis of diagnostic accuracy studies. *Biostat* 2007 April 1;8(2):239-251.
- Lijmer JG, Bossuyt PM, Heisterkamp SH. Exploring sources of heterogeneity in systematic reviews of diagnostic tests. *Stat.Med.* 2002 Jun 15;21(11):1525-1537.
- Medical Services Advisory Committee. Guidelines for the assessment of diagnostic technologies. August 2005.
- Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. *Stat.Med.* 1993 Jul 30;12(14):1293-1316.
- Reitsma JB, Glas AS, Rutjes AWS, Scholten RJPM, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *Journal of Clinical Epidemiology*, 2005 10;58(10):982-990.

## General guidance for interpretation

### *Guidance for assessing applicability*

Atkins et al. (2011):

- Step 1. Determine the most important factors that may affect applicability
- Step 2. Systematically abstract and report key characteristics that may affect applicability in evidence tables (highlight studies with a pragmatic approach and data on effect size of effect modification).
- Step 3. Make and report judgements about major limitations to applicability of individual studies.
- Step 4. Consider and summarize the applicability of a body of evidence