

	
<b>EUnetHTA</b>	
<b>HTA CORE MODEL FOR DIAGNOSTIC TECHNOLOGIES 1.0R</b>	
WORK PACKAGE 4	
DECEMBER 2008	
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## **HTA Core Model for Diagnostic Technologies v 1.0r**

was developed by

**Work Package 4**

**The HTA Core Model**

**Work Package 4 Lead Partner: FinOHTA, Finnish Office for HTA, Finland**



**December 2008**

## **General information on the European network for Health Technology Assessment, EUnetHTA**

### **Background**

Health Technology Assessment (HTA) is increasingly used in European countries to inform decision- and policy-making in the health care sector. Several countries have integrated HTA into policy, governance, reimbursement or regulatory processes. Therefore, the EU and Member States in 2004 expressed the need for a sustainable European network for HTA.

EUnetHTA was established to respond to this need. The European Commission and Member States co-funded the three year project (2006–2008) with the aim to develop a sustainable network and information resources to inform health policy making (1, 2, 3). The project, which was based on three prior projects, connected national HTA agencies, research institutions and health ministries and enabled an effective exchange of information and support to policy decisions (4).

### **What is health technology assessment?**

EUnetHTA used the definition of *health technology* offered by the *International Network of Agencies for Health Technology Assessment (INAHTA)*: “Any intervention that may be used to promote health, prevent, diagnose or treat disease, or for rehabilitation or long-term care. This includes pharmaceuticals, devices, procedures and organisational systems used in health care” (5).

EUnetHTA defined *health technology assessment* (HTA) as “a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe effective, health policies that are patient focused and seek to achieve best value”.

### **EUnetHTA aims and strategic objectives**

The EUnetHTA project was established to create an effective and sustainable network for HTA across Europe that could develop and implement practical tools to provide reliable, timely, transparent and transferable information to contribute to HTAs in Member States.

The strategic objectives of the EUnetHTA project were to:

- reduce duplication of effort in order to promote more effective use of resources
- increase HTA input to decision making in Member States and the EU in order to increase the impact of HTA
- strengthen the link between HTA and health care policy making in the EU and its member states
- support countries with limited experience of HTA.

### **Structure of EUnetHTA**

The EUnetHTA Partnership involved 64 organisations: 1 Main Partner, 33 Associated Partners, and 30 Collaborating Partners. In total, 33 countries (Europe: 25 EU and 2 EEA countries (Norway, Iceland), Switzerland and Serbia; outside Europe: Australia, Canada, Israel, USA) participated in the project. The list of partners is accessible at: [www.eunethta.net](http://www.eunethta.net)

## **Management and leadership**

EUnetHTA governance structure consisted of

- the Steering Committee which comprised the heads of each of the Associated Partners or representatives appointed by the head. The head of the Main Partner chaired the Steering Committee. The Steering committee mandated the the management of the network to:
- the Executive Committee representing the Main Partner and Work Package Lead Partners,
- the Secretariat under the leadership of the Main Partner which provided managerial support to the overall project and ensured ongoing contact to the DG SANCO.

Collaborating Partners participated in the work packages and received internal communication on a regular basis.

The modes of operation of the network were described in a standard operating procedures (SOP) manual, a communication strategy, and supported by virtual and face-to-face meetings, website (with the Members Only work area), regular e-newsletter and other types of communication tools. The Associated Partners agreed on 3-year work plan during the first Steering Committee meeting and project results were presented at the EUnetHTA Conference “HTA’s Future in Europe”, in journal articles and conference presentations.

## **Work Packages and major results**

The scientific work in the EUnetHTA project took place in separately managed **Work Packages** (WPs), each led by a Lead Partner. The following major results were achieved:

- A well functioning network of partners and colleagues from HTA agencies, research institutions and health ministries (WP1 - DACEHTA/National Board of Health, Denmark)
- A well functioning Information platform and website ([www.eunethta.net](http://www.eunethta.net)) (WP2 - SBU, Sweden and Co-Lead Partner – DIMDI, Germany)
- Internal evaluations that helped to adjust work plans (WP3 – NOKC, Norway)
- A comprehensive, evidence-based and validated common framework for HTA information (HTA Core Model) applied to two types of technology to produce generic Core HTAs a) on medical and surgical interventions (Drug Eluting Stents) and b) on diagnostic technology (Multislice CT coronary angiography) (WP4 - FinOHTA, Finland)
- A handbook instructing in the use of the Core HTA Model (WP4 - FinOHTA, Finland)
- An Adaptation Toolkit (and a guidance document) composed of a series of checklists and resources which address the relevance, reliability and transferability of data and information from existing reports (WP5 - NCCHTA, UK)
- A book ”Health technology assessment and health policy-making in Europe” (WP6 - DACEHTA/National Board of Health, Denmark)
- A web-based Stakeholder Open Forum, a Draft Stakeholder Policy and Discussion Topic Catalogue; (WP6 - DACEHTA/National Board of Health, Denmark)
- Web-based tools for information sharing on the monitoring of new promising technologies and information service on emerging technologies (WP7 – HAS, France, and Co-Lead Partner- LBI/HTA, Austria)
- A handbook on HTA capacity building (WP8 - CAHTA, Spain)

- A proposal for a permanent EUnetHTA Collaboration after two rounds of public consultation (WP1 - DACEHTA/National Board of Health, Denmark)

Based on best practice each Work Package developed the methods suitable for their purpose, which is described in WP-specific products. The Lead Partners were responsible for coordination within the WP, for bringing work forward, producing and reporting results, for sending management information reports to the Main Partner and for responding to internal evaluation questionnaires.

### **The next phase**

Through a series of internal and public consultation rounds, the network developed a Proposal for the EUnetHTA Collaboration (published June 16, 2008) detailing the approaches for the future development of the network. A group of founding partners was established after this to implement the proposal for EUnetHTA Collaboration.

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4. Kristensen FB. EUnetHTA and health policy-making in Europe. Eurohealth, 2006; 12:1, 36-38.
5. INAHTA: <http://www.inahta.org/GO-DIRECT-TO/Members/> (downloaded 20 October 2008)

## **HTA Core Model for Diagnostic Technologies**

This document is a revised version of the final project deliverable on the 31<sup>st</sup> of December 2008.

The HTA Core Model will be developed further within the EUnetHTA Collaboration. The most recent version of the Model should be used when conducting assessments.

The HTA Core Model is subject to Terms of Use.

For the most recent version of the Model and the Terms of Use, please visit <http://www.eunetha.net>.

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## *Editors' Notes*

This is the final version of this document. It represents a considerable amount of work by many people across Europe. The document is divided into chapters, most of which present one domain of work within HTA. In the beginning of each chapter the main authors have been listed. Several others, however, have contributed to the work. Their names can be found in the chapter "Teams" of this report.

Each chapter describing domains of the HTA Core Model contains the following sections:

- Domain description: what this domain is about?
- Methodology: what kind of research methodology is typically used (or should be used) within this domain?
- Assessment elements: what is being studied within this domain (in more detail), what are the topics and issues within this domain?
- References

A validation of the draft version of this document, published in July 2007, has been performed. Results of the validation as well as feedback acquired through a public consultation have been considered when finalizing this document.

The HTA Core Model represents a novel method of performing and reporting HTA and hence the current version requires further testing and refinement. Future development will take place within the EUnetHTA Collaboration. Users of the HTA Core Model should always utilize the most recent version, available through [www.eunetha.net](http://www.eunetha.net).

An online tool to support easier utilization of the Model is under construction. It will be available in 2009.

The HTA Core Model is subject to Terms of Use, available through [www.eunetha.net](http://www.eunetha.net).

## WP4 Teams

The work on different domains has been done as a collaborative effort of WP4 teams. Each team consists of investigators that are responsible for writing the sections of the report and reviewers whose task is to provide support and feedback to investigators in their team. Each team has also a coordinator on behalf of FinOHTA.

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# Introduction

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The organization of health technology assessment (HTA) and the settings in which HTA agencies operate vary considerably across countries.<sup>3</sup>

According to a recent study there are also significant differences in the practical application of HTA.<sup>4</sup> HTA is usually defined as a multidisciplinary field of research, but the extent of analysis varies. Whereas in some countries HTA merely studies the clinical effectiveness and perhaps safety and cost-effectiveness of technologies, agencies in other countries apply a broader perspective and consider also other issues, such as ethics, or organisational, social or legal aspects of technology.

Differences in health care systems and in the organization of HTA probably explain a large part of the variance in international HTA. On the other hand, differences in how HTA is *perceived, understood or used* in various parts of the world may have an important impact on the way it is performed and used. Hence different applications of HTA may exist even in settings where there are no substantial differences in the health care system or in the organization of HTA.

The varying implementation of HTA internationally and even within Europe makes sharing of information difficult and reduces the applicability of foreign HTA results for one's own purposes. This applies even in cases where use of assessment produced elsewhere would be feasible because of low context-dependency of their results.

Another problem in importing assessment results of HTAs is the non-standardized information structure of reports. An HTA report can be seen as a collection of information which represents the result of an assessment process. Information in the reports is typically organized in a specific – though very rough – structure that follows the traditional headings of a scientific publication (abstract, background, methods, results, conclusions and references). This structure varies somewhat depending on the local characteristics of HTA (i.e. inclusion of recommendations section or appendices which document stakeholders' positions, etc.).

## **Definitions of HTA**

*Technology assessment in health care is a multidisciplinary field of policy analysis. It studies the medical, social, ethical, and economic implications of development, diffusion, and use of health technology.*  
*INAHTA 2007<sup>1</sup>*

*Health technology assessment (HTA) is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value.*

*Despite its policy goals, HTA must always be firmly rooted in research and the scientific method.*  
*EUnetHTA 2007<sup>2</sup>*

Besides variation in the number of sections, the internal structure of chapters also varies. Currently, most - if not all - reports represent a mixture of plain text and evidence tables, lacking an in-depth structure that would enable easy access to various pieces of information - either by humans or computers. Different sections contain pieces of information that are quite difficult to extract or analyze without reading the whole report and using substantial human effort in merely identifying those parts of the data that are of greater interest for one's own purpose.

The need for clear structure, transparency, and rigorous handling of information in any HTA leads to a need for standardisation. Steps towards definition of some standards at the international level have been done by INAHTA (checklist) and the previous European Projects (EUR-ASSESS, ECHTA/ECAHI).

The exchange of HTA reports across borders is an important means to enable each national HTA agency to work more efficiently. There are examples of HTA reports being successfully adopted across agencies, but also of duplication. Developing a core model for HTA will aim to increase the use of HTA-reports across agencies.

Practical advice on how to conduct HTA is available in earlier European projects and relevant national guidelines. In the European context we refer particularly to the Working Group 4 - "Best practice in undertaking and reporting HTA" - of the ECHTA/ECAHI project. The core model developed within the EUnetHTA project builds on earlier work and aims at being more specific when a) operationalising the questions that should be asked and answered within an HTA and b) defining and standardising the fine structure of the final product - the HTA report. This is explained in more detail in the next chapter "General design".

## **Research methods in HTA**

HTA applies a number of research methods, many of which draw from the general development in evidence-base healthcare. Often information is collected through production of a systematic literature review that brings together and summarises the available evidence in the scientific literature. Further joint estimates of the effects of technology can be produced through meta-analyses of available studies. Whenever adequate information is not available, primary research may be warranted. Currently randomised controlled trials represent the state-of-the-art method in providing reliable data particularly on questions regarding effectiveness. Also many other research methods can be and are used in HTA, e.g. register studies, surveys and focus group interviews. Preferred or most suitable methodology varies between HTA agencies and the aspects and contexts of assessment.

Various research methods have been well documented in scientific literature. The core model for HTA does not redefine these basic scientific methods, but it employs all available research methods whenever feasible. Detailed descriptions of the methods can be found in relevant literature and standards.

Sometimes the scientific paradigm that the researchers base their work on may strongly affect the design and results of HTA. An important example can be seen in innovation research, where two models have different starting points. The (linear) diffusion model perceives new technology as an external stable entity that is brought to a (health care) system and induces changes. A competing paradigm, the translation model, presumes that technology undergoes changes in the environment it is brought into (such as a health care setting). Hence the final

impact will not depend on the original technology only. Application of these two paradigms is discussed further in the chapters on social and organisational aspects of HTA.

## Ethics of HTA

The HTA Core Model assumes that ethical aspects of health technologies should be considered in HTAs. Ethics, however, has also a broader application within 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 emphasise 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).

These issues are discussed in further detail in the appendix below.

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## Appendix: Ethical considerations within HTA process

Every HTA process should be performed considering the following ethical issues:

- The driving forces (and valued interests) to perform the assessment at this stage should be identified, including the stakeholders and the whole HTA organisation.  
*Are there particular interests that make this technology subject to assessment (pressure from producers, patient groups or professionals, costs)?*
- The morally relevant reasons for performing / not performing a HTA on this topic should be identified.  
*Is the topic a significant public health issue? Is the technology likely to benefit public health? Are HTA resources wisely spent on this topic? Is the topic a priori morally contentious? Is there fear of presenting unpopular results? Has the technology already been implemented without proper, objective evaluation? Is the technology being used beyond its actual target group? Have the costs exceeded the resources?*
- The interests of the producers of the technology should be identified.  
*Developers and producers are interested in promoting their technology which influences the distribution and use of technologies. What are the financial interest in respect to "well doing".*
- It should be identified whether there are related technologies that are morally contentious, or if the technology is a novel, innovative mode of care.  
*It is important to identify, from the beginning, whether there are ethically relevantly similar technologies in use. They may provide useful casuistic background for the ethical analysis. On the other hand, novel, innovative technologies may pose unexpected ethical problems and value conflicts, which may justify extra emphasis placed on ethical analysis.*
- The interests of the content expert group should be discussed openly so that the work can be conducted in an objective and independent way.  
*It is morally important to evaluate the relationship between professionals and the industry with respect to the development and use of the technology in question. What are their final interests? Is the technology of relevance for the professional identity and development?*
- The choice of end points in the assessment has to be carefully considered.  
*The choice of end points lead to questions that of moral relevance. What is the aim of technology - to reduce mortality, increase functional status, improve quality of life, lengthen disease-free time, save money? Are there other stakeholders with possible gains or loses that should be evaluated? The decision on endpoints has also an impact on the inclusion criteria of original studies and thus may not reflect the entire existing literature on the technology in question.*
- The morally relevant issues related to the selection of meta-analysis and studies to be included in the HTA have to be identified  
*The choice of endpoint affects the inclusion criteria for original studies to be accepted. What to do when the quality criteria are not filled by any existing studies or when no RCT studies exist - especially when the technologies are*

*already being used? When is it necessary to continue with the HTA even if no RCTs are available?*

- The scope of the HTA and choice of research methods (e.g. inclusion of other aspects of assessment than effectiveness in the literature searches).  
*The literature searches focused only on the effectiveness of the technology in question seldom give access to articles relevant to other domains of assessment (e.g. the ethical, social or organizational analysis). Ethically relevant issues may be identified during the entire HTA process and the literature searches are thus possible first after their identification. The literature search should cover other related technologies with similar ethical challenges. The detailed presentation of questions and experiences related to a (ethically relevantly) similar technology are important, as they may help decision makers identify relevant issues and adopt coherent policies.*

# *General design*

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## **The HTA Core Model**

The HTA Core Model is an attempt to define and standardise elements of an HTA. The model tackles particularly the two problems of HTA reports presented in the introduction: variation in the contents and lack of a refined (detailed and standardised) structure.

First the HTA Core Model facilitates a shared understanding of what belongs to HTA. In other words, it suggests what kinds of information one could find in an HTA report - and perhaps should find in an ideal comprehensive assessment. As a consequence, it can contribute to reducing the differences in content across local (national, regional, etc.) reports. This process, however, should not be understood as an attempt to completely standardise either HTA reports or their production process. There may be valid reasons for differences in the contents of local assessments because of eg. context-dependent situations. The aim of EUnetHTA is to provide the HTA community with a Model that makes it easier for researchers to take into account important aspects of assessment and address them in a cohesive manner.

Secondly, the Model enables future international, systematic and even automated use of HTAs through a shared and more detailed structure. The Model can also be used for educational purposes within HTA.

Different types of technology - such as drugs, devices or procedures - may require different kinds of assessment. The current model is an application or a "subset" of the HTA Core Model and limited to diagnostic technologies. Another model for medical and surgical interventions has also been produced within the project.

The HTA Core Model builds on earlier work of projects EUR-ASSESS<sup>1</sup>, HTA Europe<sup>2</sup> and ECHTA/ECAHI<sup>3</sup> as well as on other theoretical guidance<sup>4-6</sup>. It is loyal to the definitions of HTA that emphasize the multidisciplinary nature of assessments. The current first version employs the nine domains that were originally identified in the EUR-ASSESS project and applied in the model for medical and surgical interventions, adding accuracy as a new domain:

1. Current use of the technology (implementation level)
2. Description and technical characteristics of technology
3. Safety
4. Accuracy
5. Effectiveness
6. Costs, economic evaluation
7. Ethical aspects
8. Organisational aspects

## 9. Social aspects

## 10. Legal aspects

Features of technology that are relevant to its accuracy (ie. sensitivity and specificity of diagnostic tests) could have been positioned into at least two of the nine domains used in the model for medical and surgical interventions. Placing of such elements depends largely on how one chooses to view accuracy. On the one hand accuracy can be viewed primarily as an inherent property of technology and hence such elements could have been included in the domain "Description and technical characteristics of technology". On the other hand the accuracy of any given diagnostic test is rarely standard, but rather highly dependent on the population, disease and other features of the setting in which it is used. Therefore it can be seen also as related to clinical effectiveness, and this would have been placed in that domain. In this version of the model we decided to create a new domain for "accuracy" in order to acknowledge the fact that it lies between the two aforementioned domains. It is neither about pure technical characteristics nor about direct health outcomes that the clinical effectiveness domain mainly considers. This view is in accordance to the well accepted hierarchical model for the evaluation of diagnostic technologies proposed by Fryback and Thornbury<sup>7</sup>. On the other hand, further discussions and validation results suggest that accuracy most likely will be merged with clinical effectiveness domain in subsequent versions. This change, however, requires some technical considerations that were not possible to complete during the project period and is left for further refinement.

The current approach draws also from recent developments in information science. It goes a step beyond earlier methodological guidance that has strongly relied on the classical structure of a scientific paper and constructs an *ontology* for HTA. The aim is to facilitate extraction and usability of information.

## *Ontology of HTA*

In philosophy, an ontology has traditionally been a theory of *being* or *existence*, i.e. a description of what types of things exist. In recent times, the term has been increasingly used slightly differently in the context of information management - the semantic web in particular.<sup>8</sup> In such contexts, one of the key aims has been to assign meanings to pieces of information and to describe the relations between concepts. Hence an ontology of postal addresses may define that "*zip code*" and "*postal code*" essentially describe the same data, although the heading is different. A range of postal codes may in turn describe a range of codes within one *city*.

Ontologies typically make it easier for both humans and computers to understand information and its context. They also promote the usefulness of information beyond the system or setting in which they were produced or originally used. Such application is particularly relevant for European HTA, since the use of foreign HTAs essentially requires extraction of data from foreign reports and appraisal of its usability in local settings. When data extraction is made easier through well-defined structure and when meanings of each piece of information are clear, the application of foreign data is likely to be less complicated than before.

Increased standardisation of the way of searching, handling, and presenting of information may lead to better use of informatics within HTA in the future and promote a clearer systematic approach that is more easily reproducible. Similar problems related to presentation and use of information have been well noted within many other medical settings, e.g. in the development of electronic patient records. Structuring information is a key field of research

and development in knowledge representation and artificial intelligence. Due to the difficulties in utilizing non-structured data, modern information applications tend to go towards well-defined information structures that enable transparent, verifiable and standardized extraction, analysis and other use of data - with or without the help of computers.

### *Assessment elements*

The basic unit of the model is an *element*. It defines a piece of information that describes the technology or the consequences or implications of its use, or the patients and the disease for which it is applied. In the context of clinical research, an element may describe a clinical outcome (e.g. reduction of symptoms), whereas in social science an element may describe the impact of technology on patient's life (e.g. ability to work). The nature of elements may vary across domains, since the consequences and implications are understood and studied differently in each domain. The common denominator for all elements is that they *provide information* that may be useful when deciding on the use or non-use of any given technology.

As the number of possible elements of HTA is very large, perhaps infinite, the model focuses particularly on

- a) elements that deal with context-independent information and
- b) elements that are particularly significant from the viewpoint of HTA (even if these would not be easily transferable).

These two features of elements are not mutually exclusive. An element may be both context-independent and very important. In this model context independent information is such information on any given technology that is transferable to another context (e.g. another geographical area, health care system or policy setting). Transferability and importance are discussed further below (see "Element cards" and "Inclusion in the core").

It would also be possible - and perhaps useful - to perceive any piece of information contained in an HTA report as an assessment element (such as details on original policy question, literature search, or conclusions). At this phase, however, the ontology excludes such elements.

The globalisation of health care interventions challenges HTA institutions to develop methods to share the assessment work and results.<sup>9</sup> It is expected that future HTAs which are conducted using the core model can be more easily utilized in another region or country. This assertion builds on a key hypothesis of the EUnetHTA project, which is that by reaching clarity on and describing what the core of HTA consists of, this will lead to much better opportunities to share what can be shared in the production of HTA – be it a completely new HTA with a prospectively produced core or sharing of existing HTA from other settings.

## *Basic concepts*

The ontology of HTA is structured according to the following basic concepts:

### **Domain**

A wide framework within which the technology is considered. An angle of viewing the use, consequences and implications of any technology. A standard set of domains is agreed on within the project.

Currently the following domains (headings slightly modified from EUR-ASSESS) are considered:

- 1) Health problem and current use of technology,
- 2) Description and technical characteristic of technology,
- 3) Safety,
- 4) Accuracy,
- 5) Clinical effectiveness,
- 6) Costs and economic evaluation,
- 7) Ethical analysis,
- 8) Organisational aspects,
- 9) Social aspects,
- 10) Legal aspects.

### **Topic**

A more specific area of consideration within any of the domains. One domain is divided into several topics. Similar topics may be addressed within more than one domain.

*Examples:*

Clinical effectiveness / Life expectancy;  
Current use of technology / Regulatory status;  
Societal aspects / Ability to work;  
Societal aspects / Economic self-sufficiency

### **Issue**

An even more specific area of consideration within any of the topics. One topic typically consists of several issues, but it may also contain only one issue. An issue is expressed as a question. Such questions may be similar to research questions within scientific studies.

*Examples:*

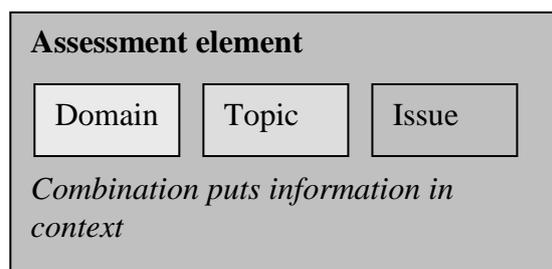
Clinical effectiveness / Mortality / What is the effect of the intervention on the mortality caused by the target disease?;  
Clinical effectiveness / Mortality / What is the effect of the intervention on the mortality due to other causes than the target disease?;;  
Current use of technology / Regulatory status / Has the technology been approved by relevant authorities in the EU?

The combination of a domain, a topic and an issue defines a single *assessment element*. The model structure is based on such domain-topic-issue combinations. Each element is described in more detail in an element card (see below).

Similar issues may exist within different domains, perhaps even within different topics of one domain. Such overlaps do not constitute a problem in this model, since the combination of domain-topic-issue reveals the context of an issue.

If two issues that look similar at the first glance are genuinely different, i.e. they would be analyzed differently from the viewpoint of two different domains (or topics), they constitute two separate elements. If on the other hand the issue is largely perceived and analyzed similarly within both domains (or topics), it constitutes only one assessment element that is common to both domains.

The current version of the model contains a total of 153 assessment elements. The number of topics within each domain ranges from 3 to 9 and the number of issues from 6 to 31. On average each topic is divided into approximately 3 issues. Details are available in the following table.



**Figure 1. An assessment element**

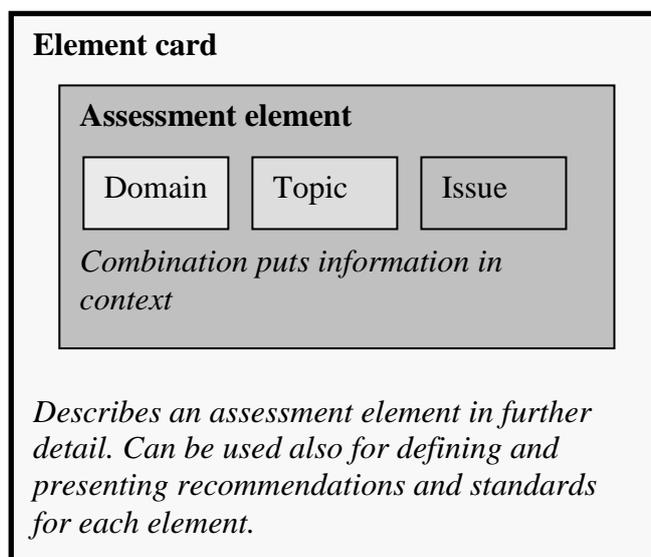
**Table 1. Number of topics and issues in the domains.**

	<b>Topics</b>	<b>Issues</b>	Issues per Topic
Health problem and current use	6	19	<b>3,2</b>
Description and technical characteristics	3	18	<b>6,0</b>
Safety	6	16	<b>2,7</b>
Accuracy	3	8	<b>2,7</b>
Effectiveness	5	18	<b>3,6</b>
Costs, economic evaluation	5	6	<b>1,2</b>
Ethical analysis	9	17	<b>1,9</b>
Organisational aspects	4	11	<b>2,8</b>
Social aspects	3	9	<b>3,0</b>
Legal aspects	8	31	<b>3,9</b>
<b>TOTAL</b>	<b>52</b>	<b>153</b>	<b>2,9</b>

## Element cards

Each assessment element is described in further detail in *element cards*. These descriptions are generic in nature, i.e. they are not specific to any technology. The basic set of cards and their content in the model is constant. Hence the cards do not change depending on technology. Any changes to the cards alter the whole model. It should be emphasised, however, that the model at hand applies only to medical and surgical interventions - not to any type of health technologies.

The practical application of the cards, i.e. how to use the model, is explained in detail below.



**Figure 2. Relationship between assessment elements and element cards**

Examples of element cards are included at the end of the general design section. The following information is available in each card:

Information	Explanation	Format	Defined by
Element ID:	An individual code for each element.		
Domain:	The domain within which the element belongs to.	Standard list	General design team
Topic:	The topic within which the element belongs to.	Standard list	Each team within their domain. In collaboration with the general design team.
Issue:	The specific question within the aspect and topic. Should be in the form of a question.	Standard list	Each team within their domain.
Clarification:	A brief clarification that explains what the issue is about. Clarification is not necessarily needed if the issue is self-explanatory.	Free text.	Each team within their domain.
Importance:	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. This is not always the same as "relevance" in a particular policy context.	3 categories: <i>Critical</i> <i>Important</i> <i>Optional</i>  Further requirements may be indicated, such as " <i>Critical if the technology is</i>	Initially within each team.  Wider consensus sought from all project participants.

		<i>a device."</i>	
Information sources(s):	An explanation of how to find answers to this particular issue.  What methodology to use? If there are several possible methodologies, which are preferred? Where to find relevant information?	Free text	Each team within their domain.
Transferability:	An estimate about the transferability of data or other findings from one context to another.	3 Categories: <i>Complete</i> <i>Partially</i> <i>Not</i>	Initially within each team in collaboration with WP5.  Wider consensus sought from all project participants.
Reference:	Indicates the reference of the issue. Serves (among other things) the following purposes:  - Credit to earlier work - Sources for more information on the topic  Particular attention to earlier European HTA projects, as well as to international standards, such as the ICF (International Classification of Functioning, Disability and Health).	Free text.	Each team within their domain.
Relations:	Some (perhaps most) of the elements are in some related to other elements in the whole model. For instance issues within the topic "quality of life" may be discussed both in the context of "effectiveness" as well as in the context of "economic evaluation". This field provides a means to express such relations.  In the current version relations are expressed in free text. In an electronic version of the model, relations may be expressed through direct links between elements.	Primarily a list of Element IDs  Free (explanatory) text allowed as well.	All teams, including the general design team.
Status:	Indicates whether the element belongs to the HTA core or a wider HTA framework. See chapter "Inclusion in the core"  Elements that clearly do not belong to the core are not described in their respective cards in such a detailed manner as all the other elements.	3 categories: <i>Core</i> <i>Borderline</i> <i>Not core</i>	Initially within each team in collaboration with WP5.  Wider consensus sought from all project participants.

Displaying the assessment elements as cards fits better electronic formats and resources. To prevent an excessively large paper report, key information regarding each card has been collected into a table format within each domain. These tables are available in respective chapters (see "Assessment elements" within each domain).

## *Inclusion in the core*

The model defines a common core for HTA that can be used in multiple countries or regions. Not all elements defined in the ontology belong to the core. In this model, the inclusion of an element in the core is a function of two basic characteristics of the element: its importance and transferability.

Transferability is an obvious factor in such consideration, as any information that is very specific to a particular context (e.g. region, country, health care system) is most likely not useful in other settings. On the other hand, if the information is fully or partly transferable, it may provide valuable input beyond its original production location.

Importance is included in the consideration 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 important from the viewpoint of HTA are often useful when making decisions on health care policy.

Importance and transferability are not necessarily dependent on each other. There may be issues that are very important to consider from the viewpoint of HTA, but that contain data that is only partly transferable to other settings. Likewise, there may be data on other issues that are very easy to transfer from one setting to another, but that are not so significant from the viewpoint of HTA.

The inclusion in the core is defined according to the following core matrix:

CORE MATRIX		Importance		
		<i>Optional</i>	<i>Important</i>	<i>Critical</i>
Transferability	<i>Complete</i>	Borderline -> Not Core	Core	Core
	<i>Partially</i>	Not core	Borderline -> Core	Core
	<i>Not</i>	Not core	Not core	Borderline -> Core

Category "borderline" was included in the matrix during the project period, but it was to be removed from the final version of the Model. The table above indicates our proposed final version at this stage, but further testing will be required to confirm the selections.

It should be emphasized that the inclusion or exclusion of an element into or from the Core is driven by usability of the information across national borders or 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 assessment elements (that are not transferable) are excluded from the Core by definition (see Core matrix above). Such elements are likely to provide useful or even critical information to guide decision-making and need to be addressed locally by individual HTA agencies.

In the current version of this document the importance and transferability of each element - and hence their status regarding the Core - has not always been considered enough. Therefore any judgements should be regarded as tentative. Further testing, that will take place after the project period, will provide more accurate values.

## Working method

The HTA Core Model was built by several working groups (called "teams") within WP4. Each team focused on one domain. The teams were first requested to agree on a definition of the domain they work on. This definition focused the efforts and provided some indications of possible overlaps with other domains. After this, the teams were requested to define lists of topics and issues within the topics. Hence various teams had created a number of assessment elements. Finally, the importance and transferability for each element was considered and other data on the element were included in an element card. The results of this process are presented in a table within each domain chapter (under heading "Assessment elements"). For practical reasons individual cards are not included in this report.

It is important to acknowledge at this phase of the core model development that the two key characteristics assigned to elements, i.e. their importance and transferability, are a result of a consensus process. Various teams aimed at finding a consensus on the category assigned to each element. Hence the category suggested here does not necessarily reflect a unanimous rating of importance and transferability of each element by the team members. Neither should the ratings suggested here for each element's importance and transferability be seen as final judgements. Further testing may affect the status of each element.

## From HTA Core Model to Structured HTA information and Core HTAs

The HTA Core Model can be utilized in two ways for conducting HTA.

*Core HTAs* are comprehensive assessments that take into account the multidisciplinary nature of health technology assessment. When producing a Core HTA, one should consider all the domains of the Core Model (see the process in more detail below). A Core HTA also contains a summary of the findings of each domain, drawing together evidence gathered in the multidisciplinary process. It should be emphasized that the Core HTA - including its summary - refrains from giving recommendations of the use or non-use of technology.

The second type of use is a more "liberal" selection and use of various assessment elements, perhaps from only one or few of the domains.

Both the Core HTAs and other type of information created through the process explained below constitute a collection of *Structured HTA Information* that can be utilized in multiple ways when performing local HTAs.

### *Process*

The detailed characteristics and breadth of an HTA depends on the technology to be assessed. These differences are taken into account when applying the core model to a single HTA. In that process topic-specific judgements and adjustments need to be made on two levels.

First one needs to consider whether a particular element is relevant for the technology to be assessed. If it is relevant, an answer to the issue question should be found within the core

HTA. If the model suggests an issue that is not relevant, finding an answer may be omitted. This exclusion, however, should be recorded in the report, as it may provide useful information for report users who are not necessarily able to make such judgements themselves. For instance issues related to mortality are most likely quite relevant in the context of technologies such as drug eluting stents or gamma knife, but not equally relevant in the context of e.g. mild cortisone creams.

The second adjustment converts the issues into actual research questions. Many of the issues defined in the model are too general to be used as research questions without modifications. The issue within the model only presents the problem on a general level; each research group needs to translate the issue into a research question or several of them. The core HTA should find answers to these questions.

The model guides researchers in selecting which aspect of technology or its use they could (or should) study. Research tradition and guidelines within each scientific domain guide the process in which questions are formulated. In clinical research it is often useful to apply the PICO principle (patients/population, intervention, comparison, outcomes) at this phase.

The element cards provide guidance on how to conduct research, i.e. how to answer the actual research questions. Particularly the field "Information sources" in the cards may contain useful hints, recommended research methodologies or even common research standards (if so desired).

**Table 2. Examples of hints, recommendations and standards in element cards**

<b>Content of field "Information sources"</b>	<b>Nature of recommendation</b>
Database X can be used	Hint
Use of Database X is recommended.	Recommendation
Database X shall be used to check Y.	Standard
A systematic literature review may be useful	Hint
A systematic literature review is recommended	Recommendation
A systematic literature review shall be conducted	Standard
A systematic literature review shall be conducted using the methodology described in the Cochrane Handbook for Systematic Reviews of Interventions	Standard with detailed requirements regarding methodology

Notice that the information intended to be used in the cards is available in the chapter "Assessment Elements" within each domain (see particularly the tables). Actual cards are not included in this version, as those are more suitable for databases in online environment.

## *Reporting*

The model also provides the assessment with a common structure for presenting the findings. Various domains, topics and issues can be used as headings for the report when writing a

"traditional" paper report. In the structure of the core HTA, issues can also be replaced with research questions - as we will do in the first core HTA on drug eluting stents. The structure also enables the storage of the assessment in electronic databases and other applications where the results of assessments can be combined and analysed.

**Table 3. Examples of how issues defined in the core model are translated into research questions.**

<b>CORE MODEL</b>	<b>CORE HTA</b>
<b>Issue</b>	<b>Research question (in different settings)</b>
Does the technology reduce the severity of symptoms of disease?	Do drug eluting stents reduce chest pain in patients with angina pectoris?
Can informed consent be received?	Are stroke patients able to provide informed consent for anticoagulation treatment?
Does the technology challenge cultural values?	Is screening for fetal malformations accepted by all subgroups in the population?

## Examples of element cards

### Example 1: Empty element card

<b>Element ID:</b>		
<b>Domain:</b>	<input type="checkbox"/> Health problem and current use of technology	
	<input type="checkbox"/> Description and technical characteristics	
	<input type="checkbox"/> Safety	
	<input type="checkbox"/> Accuracy	
	<input type="checkbox"/> Clinical effectiveness	
	<input type="checkbox"/> Economic evaluation	
	<input type="checkbox"/> Ethical analysis	
	<input type="checkbox"/> Organisational aspects	
	<input type="checkbox"/> Social aspects	
	<input type="checkbox"/> Legal aspects	
<b>Topic:</b>		
<b>Issue:</b>		
<b>Clarification:</b>		
<b>Importance:</b>		<b>Explanation:</b>
	<input type="checkbox"/> Critical	<i>Should always be considered in an HTA</i>
	<input type="checkbox"/> Important	<i>Should be considered in most HTAs</i>
	<input type="checkbox"/> Optional	<i>May provide useful information</i>
<b>Specific requirements for importance:</b>		
<b>Information source(s):</b>		
<b>Transferability:</b>		<b>Explanation:</b>
	<input type="checkbox"/> Complete	<i>Data/findings are context independent</i>
	<input type="checkbox"/> Partially	<i>Data/findings are not directly transferable from one setting to another. Adjustments are needed.</i>
	<input type="checkbox"/> Not	<i>Data/findings are not transferable from one setting to another without serious difficulties.</i>
<b>Reference:</b>		
<b>Relations:</b>		
<b>Status:</b>		<b>Explanation:</b>
	<input type="checkbox"/> Core	<i>Belongs to core.</i>
	<input type="checkbox"/> Borderline	<i>May belong to core. (Comment: need to discuss whether this category is needed).</i>
	<input type="checkbox"/> Not Core	<i>Does not belong to core. Part of wider HTA framework.</i>

## Example 2: Element card on Mortality

<b>Element ID:</b>	00001	
<b>Domain:</b>	<input type="checkbox"/>	Health problem and current use of technology
	<input type="checkbox"/>	Description and technical characteristics
	<input checked="" type="checkbox"/>	Safety
	<input type="checkbox"/>	Accuracy
	<input checked="" type="checkbox"/>	Clinical effectiveness
	<input type="checkbox"/>	Economic evaluation
	<input type="checkbox"/>	Ethical analysis
	<input type="checkbox"/>	Organisational aspects
	<input type="checkbox"/>	Social aspects
<input type="checkbox"/>	Legal aspects	
<b>Topic:</b>	Life expectancy	
<b>Issue:</b>	What is the direct effect of the technology on the mortality of patients?	
<b>Clarification:</b>	Use of technology may have a direct impact on patients' life expectancy. It is an important part of effectiveness.	
<b>Importance:</b>		<b>Explanation:</b>
	<input checked="" type="checkbox"/>	Critical <i>Should always be considered in an HTA</i>
	<input type="checkbox"/>	Important <i>Should be considered in most HTAs</i>
	<input type="checkbox"/>	Optional <i>May provide useful information</i>
	<b>Specific requirements for importance:</b> None	
<b>Information source(s):</b>	<p>Typically studied by conducting a systematic literature review.</p> <p>Preferred study type: randomised controlled trial.</p> <p>If adequate data is not found in the literature, conducting relevant primary research should be considered.</p> <p>Health care registers may provide useful data on mortality.</p>	
<b>Transferability:</b>		<b>Explanation:</b>
	<input type="checkbox"/>	Complete <i>Data/findings are context independent</i>
	<input checked="" type="checkbox"/>	Partially <i>Data/findings are not directly transferable from one setting to another. Adjustments are needed.</i>
	<input type="checkbox"/>	Not <i>Data/findings are not transferable from one setting to another without serious difficulties.</i>
	<p>In most cases data on mortality is transferable from one population or setting to another.</p> <p>The following factors should be considered when using information produced in other countries or settings:</p> <ul style="list-style-type: none"> <li>- patient characteristics (age, gender, race)</li> <li>- comorbidity</li> <li>- co-interventions</li> </ul>	
<b>Reference:</b>	Mortality is discussed in several sources.	
<b>Relations:</b>	Mortality is considered also in the context of quality of life.	
<b>Status:</b>		<b>Explanation:</b>
	<input checked="" type="checkbox"/>	Core <i>Belongs to core.</i>
	<input type="checkbox"/>	Borderline <i>May belong to core. (Comment: need to discuss whether this category is needed).</i>
	<input type="checkbox"/>	Not Core <i>Does not belong to core. Part of wider HTA framework.</i>

### Example 3: Element card on Approval

<b>Element ID:</b>	00002	
<b>Domain:</b>	<input type="checkbox"/> Health problem and current use of technology	
	<input type="checkbox"/> Description and technical characteristics	
	<input type="checkbox"/> Safety	
	<input type="checkbox"/> Accuracy	
	<input type="checkbox"/> Clinical effectiveness	
	<input type="checkbox"/> Economic evaluation	
	<input type="checkbox"/> Ethical analysis	
	<input type="checkbox"/> Organisational aspects	
	<input type="checkbox"/> Social aspects	
	<input checked="" type="checkbox"/> Legal aspects	
<b>Topic:</b>	Regulatory status	
<b>Issue:</b>	Has the technology been approved by relevant authorities in the EU?	
<b>Clarification:</b>	The use of many health technologies requires authorization by relevant bodies either on international or national level. Data on possible approval defines also the legal status of the technology and often provides information on safety.	
<b>Importance:</b>	<input checked="" type="checkbox"/> Critical	Explanation: <i>Should always be considered in an HTA</i>
	<input type="checkbox"/> Important	<i>Should be considered in most HTAs</i>
	<input type="checkbox"/> Optional	<i>May provide useful information</i>
	<b>Specific requirements for importance:</b> Critical if the technology requires approval by an authority (such as drugs and medical devices). Medical and surgical procedures do not always require authorisation.	
<b>Information source(s):</b>	EMEA, national authorities	
<b>Transferability:</b>	<input checked="" type="checkbox"/> Complete	Explanation: <i>Data/findings are context independent</i>
	<input type="checkbox"/> Partially	<i>Data/findings are not directly transferable from one setting to another. Adjustments are needed.</i>
	<input type="checkbox"/> Not	<i>Data/findings are not transferable from one setting to another without serious difficulties.</i>
<b>Reference:</b>	EUR-ASSESS [Int J Technol Assess Health Care 1997;13(2):198] ECHTA [ECHTA Report, page 413]	
<b>Relations:</b>	See also relevant elements within safety and legal aspects. ( <i>LIST OF THOSE ELEMENTS NEEDED HERE</i> )	
<b>Status:</b>	<input checked="" type="checkbox"/> Core	Explanation: <i>Belongs to core.</i>
	<input type="checkbox"/> Borderline	<i>May belong to core. (Comment: need to discuss whether this category is needed).</i>
	<input type="checkbox"/> Not Core	<i>Does not belong to core. Part of wider HTA framework.</i>

### Example 4: Element card on Working life

<b>Element ID:</b>	00003	
<b>Domain:</b>	<input type="checkbox"/>	Health problem and current use of technology
	<input type="checkbox"/>	Description and technical characteristics
	<input type="checkbox"/>	Safety
	<input type="checkbox"/>	Accuracy
	<input type="checkbox"/>	Clinical effectiveness
	<input type="checkbox"/>	Economic evaluation
	<input type="checkbox"/>	Ethical analysis
	<input type="checkbox"/>	Organisational aspects
	<input checked="" type="checkbox"/>	Social aspects
	<input type="checkbox"/>	Legal aspects
<b>Topic:</b>	Working life	
<b>Issue:</b>	What kind of changes can the implementation of the technology mean in the working capacity/life of a person?	
<b>Clarification:</b>		
<b>Importance:</b>		Explanation:
	<input checked="" type="checkbox"/>	Critical <i>Should always be considered in an HTA</i>
	<input type="checkbox"/>	Important <i>Should be considered in most HTAs</i>
	<input type="checkbox"/>	Optional <i>May provide useful information</i>
<b>Specific requirements for importance:</b>		
<b>Information source(s):</b>	Search 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.	
<b>Transferability:</b>		Explanation:
	<input type="checkbox"/>	Complete <i>Data/findings are context independent</i>
	<input checked="" type="checkbox"/>	Partially <i>Data/findings are not directly transferable from one setting to another. Adjustments are needed.</i>
	<input type="checkbox"/>	Not <i>Data/findings are not transferable from one setting to another without serious difficulties.</i>
Unemployment and social security benefits may vary across countries. Consider particularly the criteria for benefits and the amount of benefits.		
<b>Source:</b>	ICF, Activities and participation, Chapter 8 Major life areas, Work and employment: d840-859.	
<b>Relations:</b>	Effectiveness, organisational aspects.	
<b>Status:</b>		Explanation:
	<input type="checkbox"/>	Core <i>Belongs to core.</i>
	<input checked="" type="checkbox"/>	Borderline <i>May belong to core. (Comment: need to discuss whether this category is needed).</i>
<input type="checkbox"/>	Not Core <i>Does not belong to core. Part of wider HTA framework.</i>	

**Example 5A. Element card on utilisation (followed by the same card filled within an HTA)**

<b>Element ID:</b>	00030	
<b>Domain:</b>	<input checked="" type="checkbox"/> Health problem and current use of technology	
	<input type="checkbox"/> Description and technical characteristics	
	<input type="checkbox"/> Safety	
	<input type="checkbox"/> Accuracy	
	<input type="checkbox"/> Clinical effectiveness	
	<input type="checkbox"/> Economic evaluation	
	<input type="checkbox"/> Ethical analysis	
	<input type="checkbox"/> Organisational aspects	
	<input type="checkbox"/> Societal aspects	
	<input type="checkbox"/> Legal aspects	
<b>Topic:</b>	Utilisation	
<b>Issue:</b>	Are there variations in use across countries/regions/settings?	
<b>Clarification:</b>	Quantitative differences of the utilisation of the technology in question	
<b>Importance/relevance:</b>		Explanation:
	<input type="checkbox"/> Critical	<i>Should always be considered in an HTA</i>
	<input checked="" type="checkbox"/> Important	<i>Should be considered in most HTAs</i>
	<input type="checkbox"/> Optional	<i>May provide useful information</i>
<b>Specific requirements for importance:</b>		
<b>Information source(s):</b>	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>Transferability:</b>		Explanation:
	<input type="checkbox"/> Complete	<i>Data/findings are context independent</i>
	<input checked="" type="checkbox"/> Partially	<i>Data/findings are not directly transferable from one setting to another. Adjustments are needed.</i>
	<input type="checkbox"/> Not	<i>Data/findings are not transferable from one setting to another without serious difficulties.</i>
<b>Source:</b>		
<b>Relations:</b>	Related Topic "Life Cycle" of this domain and to domain "Organisational"	
<b>Status:</b>		Explanation:
	<input type="checkbox"/> Core	<i>Belongs to core.</i>
	<input checked="" type="checkbox"/> Borderline	<i>May belong to core. (Comment: need to discuss whether this category is needed).</i>
<input type="checkbox"/> Not Core	<i>Does not belong to core. Part of wider HTA framework.</i>	

**Example 5B. Filled element card on utilisation (all medical data included for example only). Illustrative example only. The future electronic version of the Model will use somewhat different structure.**

<b>Element ID:</b>	00030																												
<b>Domain:</b>	<input checked="" type="checkbox"/> Health problem and current use of technology																												
	<input type="checkbox"/> Description and technical characteristics																												
	<input type="checkbox"/> Safety																												
	<input type="checkbox"/> Clinical effectiveness																												
	<input type="checkbox"/> Economic evaluation																												
	<input type="checkbox"/> Ethical analysis																												
	<input type="checkbox"/> Organisational aspects																												
	<input type="checkbox"/> Societal aspects																												
<input type="checkbox"/> Legal aspects																													
<b>Topic:</b>	Utilisation																												
<b>Issue:</b>	Are there variations in use across countries/regions/settings?																												
<b>Research question(s):</b> <i>Translated from "issue"</i>	Are there variations in use of DES across European countries, and within single countries across regions?																												
<b>Result:</b> <i>Note that when filling the card in an assessment „Clarification“ converts in „Results“</i>	<p>The proportion of DES among the total number of implanted stents varies across European countries (see Table).</p> <table border="1"> <thead> <tr> <th rowspan="2">Year</th> <th colspan="3">Drug Eluting Stents % of all Stents</th> </tr> <tr> <th>Spain</th> <th>Germany</th> <th>Sweden*</th> </tr> </thead> <tbody> <tr> <td>2002</td> <td>4,1%</td> <td>-</td> <td>-</td> </tr> <tr> <td>2003</td> <td>20,2%</td> <td>-</td> <td>28%</td> </tr> <tr> <td>2004</td> <td>36,5%</td> <td>-</td> <td>44%</td> </tr> <tr> <td>2005</td> <td>-</td> <td>30%</td> <td>63%</td> </tr> <tr> <td>2006</td> <td>-</td> <td>-</td> <td>26%</td> </tr> </tbody> </table> <p>* End of Year</p> <p>Regional variations of the use of DES have been also described within the same country. In Spain the proportion of DES varied from 23,1% to 55,9% in 2004. Three regions used DES in more than 50% of stent implantations, whereas four regions used DES in less than 25% of stent implantations. In Sweden the use of DES varied from 12% to 92%.</p>		Year	Drug Eluting Stents % of all Stents			Spain	Germany	Sweden*	2002	4,1%	-	-	2003	20,2%	-	28%	2004	36,5%	-	44%	2005	-	30%	63%	2006	-	-	26%
Year	Drug Eluting Stents % of all Stents																												
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2004	36,5%	-	44%																										
2005	-	30%	63%																										
2006	-	-	26%																										
<b>Importance/relevance:</b>	<input type="checkbox"/> Critical	Explanation: <i>Should always be considered in an HTA</i>																											
	<input checked="" type="checkbox"/> Important	<i>Should be considered in most HTAs</i>																											
	<input type="checkbox"/> Optional	<i>May provide useful information</i>																											
	<b>Specific requirements for importance:</b>																												
<b>Information source(s):</b>	<p>Literature and internet search for publications reporting data from interventional cardiology registers.</p> <p>Register of the Spanish Society on Haemodynamics and Interventional Cardiology. It covers 96% of the Spanish centers and gathers aggregated data for each center (no individual data). López-Palop et al. Registro Español de Hemodinámica y Cardiología Intervencionista. XIV Informe oficial de la Sección de Hemodinámica y Cardiología Intervencionista de la Sociedad Española de Cardiología (1990-2004). <i>Rev Esp Cardiol</i> 2005; 58(11): 1318-34.</p> <p>Swedish Coronary Angiography and Angioplasty Register. Covers 100% of centers and procedures done in Sweden. It gathers individual data and is linked to other registries (mortality, medication use, hospitalization). Lagerqvist and Wallerstein. Long-term outcome of DES vs BMS Implanted in Sweden (2003 – 2004). Presentation at FDA hearing Dec 7, 2006 <a href="http://www.ucr.uu.se/scaar/arsrapporter/swedish_SCAAR_registry_FDA%20Dec_7_200602.pdf">http://www.ucr.uu.se/scaar/arsrapporter/swedish_SCAAR_registry_FDA%20Dec_7_200602.pdf</a></p>																												

	German Data from Expert Opinion Carlsson. Verwirrung und Ernüchterung in der invasiven Kardiologie. Dtsch Aertztebl 2007; 104(3): A96-A99.	
<b>Transferability:</b>		<b>Explanation:</b>
	<input type="checkbox"/> Complete	<i>Data/findings are context independent</i>
	<input checked="" type="checkbox"/> Partially	<i>Data/findings are not directly transferable from one setting to another. Adjustments are needed.</i>
	<input type="checkbox"/> Not	<i>Data/findings are not transferable from one setting to another without serious difficulties.</i>
The finding that there are national and regional variations can be transferred. The data (% of DES, range of DES use across regions) are not transferable to the own setting		
<b>Source:</b>		
<b>Relations:</b>		
<b>Status:</b>		<b>Explanation:</b>
	<input checked="" type="checkbox"/> Core	<i>Belongs to core.</i>
	<input type="checkbox"/> Borderline	<i>May belong to core. (Comment: need to discuss whether this category is needed).</i>
	<input type="checkbox"/> Not Core	<i>Does not belong to core. Part of wider HTA framework.</i>

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# *Health problem and current use of technology*

*Marcial Velasco Garrido, Sigurdur Helgason, Leonor Varela Lema et al<sup>i</sup>*

## **Domain description**

This domain of an assessment deals with the health problems for which the diagnostic technology under assessment is intended to be used (target conditions, target groups) and with the availability and patterns of use of the technology in question. Some of the topics considered relevant for this domain of the assessment have generally been called “Background Information” in previous European projects or recommendations for conducting assessments<sup>1,2,3</sup>.

Topics within this domain include the epidemiology of the target health problem, the burden – both on individuals and on the society – caused by the health problem, the alternatives to the technology in question and regulatory status of the technology. The requirements for its use are under the scope of the domain “Description of and technical characteristics of technology”.

The description of the current status of a health technology provides a baseline description of the situation of the technology which is useful to put the results of other parts of the assessment (e.g. clinical effectiveness) in the own geographical context or in the own setting. It also provides information relevant for the construction of economic and/or organisational models in order to assess the impact of, for example, the introduction of a technology (e.g. the addition of a new imaging procedure to an established diagnostic chain, or the substitution of a diagnostic test by another one), the promotion of its utilisation, etc. It is thus an important part of a health technology assessment report.

Dealing with the issues included in this domain at the early stages of an assessment is also needed in order to refine the research questions (e.g. choosing relevant outcome parameters) and to formulate the methodological approach to be taken in other domains of the assessment (i. e. identification of information sources, formulation of selection and appraisal criteria, etc.). Some elements of this domain will thus overlap to some extent with elements of the effectiveness domain and economic evaluation domain (e.g. issues of outcomes measured and alternative intervention), organizational domain (e.g. patterns of use) and legal domain (e.g. regulatory status). Thus, the elements described in this section of the core model are not to be understood as obligatory chapters of an assessment. They represent information pieces which are needed when conducting an assessment. How this information is presented in an HTA-report (i.e. whether it gets located in an specific chapter or whether it is spread among several

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<sup>i</sup> The Core Model for diagnostic technologies is based on the HTA Core Model for medical and surgical Interventions, to which the following persons also contributed: Marta Lopez de Argumedo, Alberto Ruano Ravina, Bo Freychuss and Monika Reesev.

chapters) will depend on the report structure of each agency. However the information can also be provided in the card form (as explained in the Chapter on “General Design of the Model”) in order to allow an easier exchange and sharing of information among HTA-agencies.

## Methodology

The elements included in this domain are heterogeneous. There is no one single methodological approach which can be applied to all elements. For some of the elements there may even be several possible approaches in order to give appropriate answers to their questions. The approaches can be divided into two groups: either analysis of published scientific literature or analysis of primary sources of information or data (including both own primary data collection or analysis of available data collected by third parties, i.e. for other purposes than the assessment). In principle both approaches can be used to study any issue. However the validity of the results for a single issue may differ considerably between the two approaches. For example, one might try to obtain information on the approval status of a technology by doing a literature review for this element. Even if there are scientific papers which have studied this issue (i.e. policy studies) they are likely to be rapidly outdated. The information obtained by directly inquiring the relevant approval agencies will be more reliable (e.g. via telephone interview) and practical.

The choice of the most appropriate source of information depends thus mainly on the element in question. However, the resources given in a specific assessment project also play a limiting role on the choice: It is not always possible to analyse primary sources of data or to collect and analyse primary data (even in a situation when these were the best approaches for a given issue) because of time and money constraints faced by nearly all institutions conducting HTA.

We present here the principal aspects of both methodological approaches. More detail referring to the types of sources to be used in each assessment element is given in the brief descriptions of the single issues.

Independently from which approach is chosen for each assessment element, these should be explained clearly and the findings referred to sources in order to enhance the transparency of this part of HTA reports.

### *Literature analysis*

Ideally, the analysis of literature should always follow the principles of systematic reviews as they have been stated elsewhere<sup>4</sup>:

- Formulation of an answerable question (i.e. the element question)
- Formulation of selection and appraisal criteria
- Searching the relevant literature databases using sensitive search strategies.

Theoretically it is possible to apply this approach to all issues of this domain. The issue itself is a question which can be considered to be the research question, i.e. the starting point, for

the systematic review. Each issue will require different criteria for the selection and quality appraisal of the relevant scientific literature. The most appropriate study design to be included varies according to each question too, thus a general recommendation of the best study design cannot be given here.

Practically, the conduction of a systematic review of primary studies is probably not feasible within an HTA project to assess each one of the issues for which this approach would be appropriate. In some cases – for example in the assessment of alternative interventions – it is more realistic to focus on existing systematic reviews. An acceptable approach for the identification of relevant literature can be to snowball references from papers identified in a first search or after contacting experts in the field.

Nevertheless any kind of literature (be it identified through a comprehensive literature search, through snowball references, from talks with experts, etc.) included in the assessment of any issue should be appraised. The appraisal criteria should reflect the widely accepted set of assessing the validity or quality of research (i.e. assessing risk of bias), assessing reporting, and assessing relevance/transferability<sup>5</sup>.

The choice of the databases to be used in the search for relevant scientific literature is also determined by the element itself. The combination of different databases enhances sensitivity of the literature search. Each database will provide different possibilities to build more or less elaborated systematic search strategies.

The kind of scientific literature object to this systematic approach can be both “primary” (experimental or observational studies) or “secondary” (i.e. systematic reviews, guidelines) literature.

### *Analysis of primary sources of information or data*

In general this approach is preferred when it can be expected that an analysis of published scientific literature will not deliver reliable results. Some of the issues included in this domain can be answered more straightforward when the HTA-researchers draw on information and/or data from primary sources as when they try to conduct a systematic literature review. There are several sources of information which we consider here as “primary”: registers, routine collected statistics, regulatory institutions, manufacturers, expert clinicians, own research.

### *Registers*

The information provided by registers can be useful to answer some of the issues in this domain. Mainly two types of registers relevant to this domain exist: technology registers and disease registers.

Technology registers gather information on the use of a single technology, for example a register on knee total endoprosthesis. A new case is registered in the database every time the technology is used (i.e. a procedure is done, an intervention takes place). Whereas registers of therapeutic technologies are increasingly widespread, this does not seem to be the case for diagnostic technologies. However, in some situations (i.e. in some countries) when there is no high quality evidence to establish effectiveness and/or safety, potentially relevant diagnostic

technologies might be subject to the obligation of reporting information on indications for and the clinical consequences of the use to a central institution before it is finally approved or a decision is made to provide it within the public health services. This has been the case for the use of PET-Scans in the diagnosis and/or staging of cancer in Spain, where this diagnostic technology was submitted to a limited, monitored use<sup>6</sup>.

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

- How representative is the register? (European, National, Regional, Local?) What are the inclusion/exclusion criteria?
- What is the quality of information?
- How complete is the coverage?
- What kind of information concerning the diagnostic procedures is coded?

Data access is an important aspect when working with registers. Own analysis of the data may require previous authorization. It might be impossible for institutions other than the ones managing the register to analyze the raw data, however some registers would conduct customized analyses (i. e. according to the needs of the HTA-researcher). However, relevant results might be available for the public in the form of grey literature or in the internet or results may even have been published in the scientific literature.

### *Routine collected statistics*

Several sources of routine collected statistics exist which can be used to assess the incidence, prevalence or the burden of disease (e.g. life-years lost). These statistics are usually available in aggregated form (increasingly available through the internet). National or regional statistics offices and international initiatives (like EUROSTAT or Health For All Database) are examples of sources of this kind. The use of these sources 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.

Routine collected administrative data 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 can not 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. As with data from registers, own analysis of administrative data often

requires authorization from the data owner, which in some countries might be difficult to be obtained due to issues of privacy protection and confidentiality.

### *Regulatory institutions*

Regulatory institutions can be approached to get information on the regulatory status of technologies. Some of these institutions have internet-based searchable databases which are regularly updated. Alternatively key officials/ civil servants can be contacted directly with specific questions.

### *Manufacturers*

Manufacturers can be used as primary sources of information too. The information provided by them might be limited by issues of confidentiality and marketing. This source can be useful in order to answer questions concerning the requirements for use of the technology, development status or forthcoming innovations of the technology. Manufacturers may also provide information on ongoing research and on scientific literature which has not been published yet. Potential bias in the information provided by manufacturers need to be carefully assessed.

### *Collecting own primary data*

For some questions it might be necessary that the HTA researchers conduct own primary research. This approach should be considered very carefully since it may be very time-consuming and costly. For many agencies it is not feasible to conduct primary data collection, even if this would provide very valuable information.

When performing primary research, investigators should minimize the risk of bias, maximize validity and relevance and use the most appropriate methods (i.e. cross-sectional survey, focus-groups, etc.) depending on the question to be answered.

## **Assessment elements**

When developing the Core Model for Interventions, the working group originally identified around 30 issues potentially belonging to this domain, which were reduced to a number of 20 (see Core Model First Public Draft<sup>7</sup>). However some of them were judged to be better placed in other domains (most of them in the organisational and in the description of the technology domain), thus coming to a final selection of 20 issues<sup>7</sup> or the Core Model on interventions<sup>ii</sup>.

Drawing on this previous work, we have identified 19 issues relevant for a Core Model on Diagnostic Technologies. Overall all issues have been judged to be “critical” or “important” There are issues which we have considered of critical importance, because they are very relevant for local decision makers. However, the transferability of the findings is not given (or at the best only partially, i.e. as an orientative indication). Although in the last column these

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<sup>ii</sup> The Core Model on Interventions is now under review in order to incorporate feedback from othe EUnetHTA members and from the public. The number of issues may change by the end version.

issues may score only as “borderline” and thus may fall out of the Core Model, we think they should be considered in any local HTA.

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference (was: "source")***	Relations	Status 3=core 2=borderline 1=not core
A0001	Health Problem and Current Use of the Technology	Target Condition	For which disease/health problem/potential health problem will the diagnostic intervention used?*	Definition (naming) of the condition, health problem, disease for which the technology is intended.	3	3	Medical Literature, at the best (Systematic) Reviews on mechanism of disease, risk factors, course and prognosis. Descriptions of the technology (e.g. provided by developers, manufacturers) on the potential targets and what they expect/claim from the technology	Burls et al. 2000 <sup>1</sup> , Busse et al. 2002 <sup>2</sup> , Liberati et al. 1997 <sup>3</sup> Imaz-Iglesia et al. 1999 <sup>8</sup> , Kristensen et al. 2001 <sup>9</sup>		3
A0002	Health Problem and Current Use of the Technology	Target Condition	What, if any, is the precise definition/ characterization of the target disease? Which diagnosis is given to the condition and according to which classification system (e.g. ICD-10)?*	Characteristics of the condition which allow a precise diagnostic and differentiation of the indication for the use of the technology.	3	3	Medical Literature, at the best (Systematic) Reviews on mechanism of disease, risk factors, course and prognosis.	Burls et al. 2000 <sup>1</sup> , Busse et al. 2002 <sup>2</sup> , Liberati et al. 1997 <sup>3</sup> Imaz-Iglesia et al. 1999 <sup>8</sup> , Kristensen et al. 2001 <sup>9</sup>	Choice of "Patient" component of the PICO for effectiveness assessment Subgroups or indications are also considered under Clinical Effectiveness	3
A0003	Health Problem and Current Use of the Technology	Target Condition	Which are the known risk factors for acquiring the condition?*	Self-explaining. The prevalence of different risk factors might be different in different geographic areas.	2	2	Medical Literature, at the best (Systematic) Reviews on mechanism of disease, risk factors, course and prognosis.	Burls et al. 2000 <sup>1</sup> , Busse et al. 2002 <sup>2</sup> , Liberati et al. 1997 <sup>3</sup> Imaz-Iglesia et al. 1999 <sup>8</sup> , Kristensen et al. 2001 <sup>9</sup>	Identification of alternative (i. e. preventive) approaches	2
A0004	Health Problem and Current Use of the Technology	Target Condition	What is the natural course of the condition?*	For example stages of the disease which can be object of different diagnostic interventions.	3	3	Medical Literature, at the best (Systematic) Reviews on mechanism of disease, risk factors, course and prognosis.	Burls et al. 2000 <sup>1</sup> , Busse et al. 2002 <sup>2</sup> , Liberati et al. 1997 <sup>3</sup> Imaz-Iglesia et al. 1999 <sup>8</sup> , Kristensen et al. 2001 <sup>9</sup>	Choice of outcome parameter for effectiveness assessment (PICO). Disease path can be used to construct economic models	3
A0005	Health Problem and Current Use of the Technology	Target Condition	What are the symptoms of the disease?*	Self-explaining	2	3	Medical Literature, at the best (Systematic) Reviews on mechanism of disease, risk factors, course and prognosis.	Burls et al. 2000 <sup>1</sup> , Busse et al. 2002 <sup>2</sup> , Liberati et al. 1997 <sup>3</sup> Imaz-Iglesia et al. 1999 <sup>8</sup> , Kristensen et al. 2001 <sup>9</sup>	Choice of outcome component of the PICO for effectiveness assessment.	3

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference (was: "source")***	Relations	Status 3=core 2=borderline 1=not core
A0006	Health Problem and Current Use of the Technology	Target Condition	What are the consequences of the condition?*	Qualitative description of the burden of disease for the individual (e.g. disability, pain)	3	2	Medical Literature, at the best (Systematic) Reviews on mechanism of disease, risk factors, course and prognosis.	Burls et al. 2000 <sup>1</sup> , Busse et al. 2002 <sup>2</sup> , Liberati et al. 1997 <sup>3</sup> Imaz-Iglesia et al. 1999 <sup>8</sup> , Kristensen et al. 2001 <sup>9</sup>	Choice of outcome parameter for effectiveness assessment (PICO). Disease path can be used to construct economic models	3
A0007	Health Problem and Current Use of the Technology	Target Condition	How many people belong at the moment (will belong) to the specific target group (describe according to sex, age)?	Incidence and/or prevalence of the target condition or the indication for use of the technology	3	1	Literature: Systematic reviews of epidemiological studies such as Cross-Sectional Studies (Prevalence), Cohort-Studies (Incidence) Routine Statistics Own analysis of: Disease Register, Administrative Databases (discharge databases, reimbursement claims databases)	Burls et al. 2000 <sup>1</sup> , Busse et al. 2002 <sup>2</sup> , Liberati et al. 1997 <sup>3</sup> Imaz-Iglesia et al. 1999 <sup>8</sup> , Kristensen et al. 2001 <sup>9</sup>	Data can be used when constructing models, however only if they are really generalisable/transferrable. It is also useful to calculate budget impact of the implementation	2
A0008	Health Problem and Current Use of the Technology	Target Condition	What is the burden of disease (mortality, disability, life years lost)?	Disease-specific mortality Prevalence of disability or disabling symptoms caused by the condition Prevalence/Incidence of early retirement due to the condition. This question provides information on which is the most important outcome (measure) for the specific disease?	3	2	Literature: Systematic reviews of epidemiological studies such as Cross-Sectional Studies (Prevalence), Cohort-Studies (Incidence) Routine Statistics Own analysis of: Disease Register, Administrative Databases (discharge databases, reimbursement claims databases)	Burls et al. 2000 <sup>1</sup> , Busse et al. 2002 <sup>2</sup> , Liberati et al. 1997 <sup>3</sup> Imaz-Iglesia et al. 1999 <sup>8</sup> , Kristensen et al. 2001 <sup>9</sup>	Data can be used when constructing models, however only if they are really generalisable/transferrable. It is also useful to identify relevant outcome measures.	3
A0009	Health Problem and Current Use of the Technology	Target Condition	What aspects of the burden of disease are targeted by the technology, i.e. are expected to be reduced by the technology?	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	3	3	Literature: Systematic reviews of epidemiological studies such as Cross-Sectional Studies (Prevalence), Cohort-Studies (Incidence) Routine Statistics Own analysis of: Disease Register, Administrative Databases (discharge databases, reimbursement claims databases)	Core model for therapeutic interventions		3

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference (was: "source")***	Relations	Status 3=core 2=borderline 1=not core
A0010	Health Problem and Current Use of the Technology	Target Condition	How long is the waiting time for diagnosis and/or treatment of the specific disease?	This refers to the time between presentation and final diagnosis and the time between presentation and initiation of therapy. These can be described as "provider delay". These times reflect mainly quality shortcomings but they may be also an indication of the lack of good diagnostic test.	2	1	Literature: Systematic reviews of epidemiological studies such as Cross-Sectional Studies, Cohort-Studies, etc.	Comments from Validation		2
A0011	Health Problem and Current Use of the Technology	Utilisation	How much is the technology being used?	Self-explaining	3	1	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)	Burls et al. 2000 <sup>1</sup> , Busse et al. 2002 <sup>2</sup> , Liberati et al. 1997 <sup>3</sup> Imaz-Iglesia et al. 1999 <sup>8</sup> , Kristensen et al. 2001 <sup>9</sup>	Important for modelling and budget impact analysis	2
A0012	Health Problem and Current Use of the Technology	Utilisation	Describe the variations in use across countries/regions/settings, if any?	Self-explaining	2	2	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)	Burls et al. 2000 <sup>1</sup> , Busse et al. 2002 <sup>2</sup> , Liberati et al. 1997 <sup>3</sup> Imaz-Iglesia et al. 1999 <sup>8</sup> , Kristensen et al. 2001 <sup>9</sup>		2

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference (was: "source")***	Relations	Status 3=core 2=borderline 1=not core
A0013	Health Problem and Current Use of the Technology	Current Management of the Condition	How is the disease/health condition currently being diagnosed?	Self-explaining.	3	1	Surveys, utilisation reviews, (How is it managed) If such information is lacking: Expert Surveys / Expert Interviews	Burls et al. 2000 <sup>1</sup> , Busse et al. 2002 <sup>2</sup> , Liberati et al. 1997 <sup>3</sup> Imaz-Iglesia et al. 1999 <sup>8</sup> , Kristensen et al. 2001 <sup>9</sup>	Findings can be used to assess whether technology could add anything in the management of the disease. Findings can be used when constructing CE-Models comparing to alternatives Different diagnostic techniques are applied by different professional groups, thus this item is also relevant for organisational domain.	2
A0014	Health Problem and Current Use of the Technology	Current Management of the Condition	According to published algorithms/guidelines (if any), how should the condition be diagnosed?	An assessment of this and the above element allow to draw conclusions on how far the current management is optimal	3	2	Review of Clinical Guidelines, Recommendations (How should it be managed), appraising their quality with for example AGREE Instrument. If such information is lacking: Expert Surveys / Expert Interviews, textbooks.	Burls et al. 2000 <sup>1</sup> , Busse et al. 2002 <sup>2</sup> , Liberati et al. 1997 <sup>3</sup> Imaz-Iglesia et al. 1999 <sup>8</sup> , Kristensen et al. 2001 <sup>9</sup>	Findings can be used to assess whether the technology could add anything in the management of the disease.	3
A0015	Health Problem and Current Use of the Technology	Current Management of the Condition	What are the other evidence-based alternative diagnostic procedures, if any?	Self-explaining	3	2	Clinical Guidelines, Recommendations (How should it be managed), Systematic Reviews	Burls et al. 2000 <sup>1</sup> , Busse et al. 2002 <sup>2</sup> , Liberati et al. 1997 <sup>3</sup> Imaz-Iglesia et al. 1999 <sup>8</sup> , Kristensen et al. 2001 <sup>9</sup>	Choice of comparator for effectiveness assessment (PICO) Choice of comparator for cost-effectiveness assessment	3

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference (was: "source")***	Relations	Status 3=core 2=borderline 1=not core
A0016	Health Problem and Current Use of the Technology	Life-Cycle	In which phase is the development of the technology (experimental, emerging, routine use, obsolete)?	This is related to the question whether there is enough evidence or experiences on the use of targeted technology on the condition.	3	2	Literature Horizon Scanning Databases, Ongoing research databases Information from Manufacturers	Burls et al. 2000 <sup>1</sup> , Busse et al. 2002 <sup>2</sup> , Liberati et al. 1997 <sup>3</sup> Imaz-Iglesia et al. 1999 <sup>8</sup> , Kristensen et al. 2001 <sup>9</sup>	Status determines the kind of information which can be expected on other domains (specially in long-term safety, effectiveness)→ Uncertainty grade	3
A0017	Health Problem and Current Use of the Technology	Regulatory Status	Which approval status has the technology in other countries, or international authorities?	Imaging devices may require approval. In addition, substances needed for the obtention of images may require additional approval (e.g. radiotracers)	3	3	e.g. CE-Approval, (EMA)National Authorities Manufacturer: Manufacturers should be contacted in order to identify which steps have they taken/ are they planning to take concerning Market-Approval	Burls et al. 2000 <sup>1</sup> , Busse et al. 2002 <sup>2</sup> , Liberati et al. 1997 <sup>3</sup> Imaz-Iglesia et al. 1999 <sup>8</sup> , Kristensen et al. 2001 <sup>9</sup>	Legal Domain	3
A0018	Health Problem and Current Use of the Technology	Regulatory Status	Has the technology been included in / excluded from the benefit basket of any country? How is the coverage of the technology across countries? (e.g. full-coverage, co-payments, coverage under special circumstances/conditional coverage?)	Are there co-payments, to what extent?	2	3**	Lists of benefits / services of the National Health Services / Sickness Funds, inquiry of technical officers from MoH Manufacturers Literature on Benefit Basket (Comparative policy studies)	Burls et al. 2000 <sup>1</sup> , Busse et al. 2002 <sup>2</sup> , Liberati et al. 1997 <sup>3</sup> Imaz-Iglesia et al. 1999 <sup>8</sup> , Kristensen et al. 2001 <sup>9</sup>	Legal Domain	3
A0019	Health Problem and Current Use of the Technology	Other	Who manufactures the technology?	Self-explaining	2	2		Burls et al. 2000 <sup>1</sup> , Busse et al. 2002 <sup>2</sup> , Liberati et al. 1997 <sup>3</sup> Imaz-Iglesia et al. 1999 <sup>8</sup> , Kristensen et al. 2001 <sup>9</sup>	Related to Organisational or Social domain	2

\* These issues are very closely related. Depending on the condition in question the separation proposed here might be more or less feasible and may be merged when writing the topic.

\*\* Per definitionem this is international comparative information. The transferability rating does not refer to the model of coverage itself (i.e. the decision on the inclusion in the benefit basket).

\*\*\* In all elements, group deliberations took a prominent role.

## *Target Condition*

A Core HTA should provide a brief description of the disease or health problem for which the technology has been designed/ is intended to be used. The characterization of the target health problem considers both qualitative and quantitative issues.

## *Qualitative Issues*

The qualitative description of the target condition refers to its underlying mechanism(s) (pathophysiology), its natural history (i.e. course of disease), its prognosis and its consequences, as well as risk factors for acquiring the disease. If necessary – i.e. when the technology does not target the whole condition- a description of subgroups or special indications within the disease should be included.

These issues are usually addressed at early stages of any assessment and are generally taken into account in the formulation of the research questions for the the domain of effectiveness. They are also likely to be important in other parts of the assessment (social domain, economic domain, etc).

Since research questions for effectiveness are basically formulated following the PICO model (see chapters on General Methodology and on Definitions) – which itself is the basis for establishing selection and appraisal criteria for the scientific literature – the information provided by the issues described here can be considered to be essential for the formulation of the criteria to be followed in other parts of the assessment (that is mainly for the “P” and the “O” of the PICO model).

Knowledge on the natural course and on the consequences of the health problem is essential for the construction of decision analytic models which reasonably fit the reality. In addition parts of the information can contribute to feed the economic model (e.g. transition probabilities from one stage to another, probabilities of different presentations). It is also important to know whether the health problem and the target population for which the technology is intended can be clearly defined. If this is not the case the appropriate use of the technology may be rightfully challenged.

The issues to be considered here can be assessed using the medical literature. An effective approach can be to use information from existing systematic reviews, (i.e. on risk factors, on prognosis) or to conduct one. Commonly, the types of studies which can be expected to provide this type of information are cohort and case control studies to identify risk factors.

## *Quantitative Issues*

As stated above this topic has several issues which can be considered quantitative in their nature. The importance of these issues is given by the fact that they quantify the burden of disease. They deal with the incidence and the prevalence of the target condition, as well as with the incidence and/or prevalence of the consequences of the condition (i.e. mortality, disability, sickness leave, retirement, etc.). In addition the burden of diseases for the society can be assessed by addressing the cost of illness, i.e. the economic burden of disease.

Besides systematic reviews of the literature (i.e. of cross-sectional surveys, cohort studies), primary data sources can be used (or even should be used) to assess these quantitative issues. Routinely collected statistics can be used to obtain information on incidence or prevalence of some conditions.

In addition, cause-specific mortality rates are also available from routine statistics. Depending on their scope, registers can also be helpful to estimate some measures of disease frequency or to estimate how many people belong to different subgroups.

The data gathered concerning these elements can be used in other parts of the assessment (e.g. for economic models), or provide a kind of baseline for the assessment of the potential impact of a technology.

Depending on the disease these issues may widely vary between different geographical contexts (e.g. infectious diseases). A Core HTA could however provide available information from different countries (or at least European estimates), which can be used by other assessors when adapting the Core HTA, especially when information from their own geographical context is not available.

### *Utilisation*

These issues refer to the evidence on how much the technology is being used in the country where the assessment is being conducted. In addition the issues address variations in utilisation at the national level (regional variations) or the international level (inter-country variations) which may be an indication for under- or overuse of the assessed technology. Studying these issues may allow an estimation of the effort necessary in order to increase or reduce its use, depending on the outcome of other domains of the assessment. These issues are quantitative and probably difficult to transfer although important for “local HTA”. Their relevancy for Core HTA seems not to be given (at the best borderline issues).

The sources of information for these issues might be the literature (e.g. utilisation surveys) or the analysis of data provided by registries (depending on their scope and completeness).

### *Current management of the condition*

The issues within this topic ask how the disease is being currently diagnosed and whether there is a consensus on the steps to be taken in order to establish the diagnosis of the condition in the form of evidence-based clinical practice guidelines. It is also important to assess whether (and if possible to what extent) current practice differs from these guidelines.

Here it can be very useful to draw a picture of the current diagnostic pathway(s) (if any exist) for the target condition and to graphically represent where the technology under assessment will fit in this pathway. Is it for example an add-on at the beginning of the diagnostic chain, intending to enhance the predictive value of the subsequent tests? Is it intended to completely replace another diagnostic procedure? Or should it be applied parallel to existing tests in order to enhance the accuracy of the diagnostic?

This information is useful to assess whether the current diagnostic approach is optimal or not. If the current diagnostic approach is not in accordance to evidence-based recommendations, the public may have the impression of the need for new technology – which might be costly and not more effective than older ones. In such a situation it would perhaps be more appropriate to improve guideline compliance than to add a newer technology of similar effectiveness or higher costs. In addition it is also useful to assess whether the technology in question will/should add to an existing

diagnostic path or might substitute other technologies. Both types of information can also be used when assessing the organisational domain.

Also under the scope of this topic is the issue of potential alternatives for the technology. It is useful to formulate PICO questions for comparative assessment of effectiveness and cost-effectiveness. The available options for approaching the diagnosis of the target condition should be described here. However these may vary from country or region to another. (i.e. not all options might be available everywhere). A presentation of available options worldwide in a Core HTA might, however, be helpful for assessors to identify technologies whose introduction could be alternatively considered.

Information sources for the issues in this topic might be studies on the current diagnostic procedures for the target condition(s) (i.e. cross-sectional surveys, audits, etc.). In addition an overview of guidelines should be given, synthesizing the main recommendations. Guidelines can be searched in both medical literature databases (i.e. Medline) since they are frequently published in indexed journals, or in special databases (i.e. GIN database). They might be also available via internet from the relevant professional associations.

### *Life Cycle*

This topic has only one issue concerning the position of the technology in its life cycle.

The overall information concerning most of the domains of an assessment can be expected to be very limited when the technology is at the beginning of its life cycle.

To assess whether a technology is to be considered as emerging (other experimental) or not Horizon Scanning initiatives (i.e. EUROSCAN) can be consulted. In addition contact to manufacturers can be initiated, since these stakeholders can have relevant information concerning the development status of the technology in question.

It is difficult to predict whether a technology has already reached the summit of its utilization, whether it is on the way of reaching it or whether it will be rapidly abandoned.

### *Regulatory status*

The issues of this topic aim at providing a comparison with health systems other than the own one.

For decision-makers it is probably useful to know whether the technology in question has been evaluated to some extent by other state bodies or international institutions - and what was the outcome of those evaluations. Since it is expected that no great variations between countries in the issue of approval are observed in Europe (i.e. CE-marking in Europe), the main interest lays probably on the issues concerning the reimbursement (i.e. coverage) status. However, in some cases it may be of interest to compare approval status with non-European countries (i.e. USA, Australia, New Zealand, etc.). This kind of information may have a great impact on the outcome of the decision-making process, since decision-makers often take into consideration what is being done in other systems or in other countries<sup>10</sup>. This may be particularly important when the estimation of the harm-benefit-costs equation is inconclusive.

To assess these issues the most appropriate approach is to consult primary sources of information, since the published literature may rapidly be outdated. The market approval status can be reviewed by contacting the institutions responsible for this. Alternatively key officials at the responsible ministers can be contacted directly with specific questions.

The assessment of the coverage status in other countries (i.e. inclusion in the benefit catalogue, levels of co-payment, etc.) is often difficult. This kind of information is not easy to retrieve and usually requires deep knowledge of the health-care system in order to identify adequate and usable information sources<sup>11</sup>. A comprehensive assessment of this issue may not be feasible during a given HTA project.

The Core HTA should attempt to elucidate the market approval status in supranational authorities and if necessary in European national authorities as well as the coverage status across Europe.

The need for assessment of the market approval status depends on the kind of technology since not all technologies require approval: this concerns mainly devices and the substances needed to obtain specific kinds of medical images. The need for assessment of the coverage status refers also to other types of technology such as diagnostic protocols and manoeuvres as well as to the use of any kind of diagnostic procedure linked to an specific condition or surgical procedures.

## *Other*

This topic refers to issues which cannot be placed under any of the other topics. Currently we have only an issue here, concerning the manufacturers of the technology. The group considered this issue as being borderline to the core. Knowing who manufactures the technology is relevant in order to identify potential sources of information (e.g. on ongoing developments, ongoing trials).

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## **Appendix**

Sigurour Helgason has proposed to create a list of certain institutions/agencies involved in each country in approval, regulation, registries. This list might be useful because researchers not involved in regulations and bureaucracy sometimes like to compare regulations/approval status between countries.

The list could include the following for diagnostic technologies:

- a. approval agencies - regulatory institutions
- b. registries either technological or disease that are in the public domain.
- c. good sources for the „grey literature" or internet based registries.

The list will be considered for future versions of the Model.

# *Description and technical characteristics of technology*

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## **Domain description**

Description of the diagnostic technology and its technical characteristics helps with translating policy questions into research questions. Different generations or versions of a single technology may have different indications, accuracy and applicability. The technology may be intended to replace another technology or it may be an amendment in the diagnostic chain. Good description of the technology is particularly important in a fast developing field where even minor changes or improvements in a technology can have variable effects on measures of diagnostic accuracy and utility. The information given in this domain should enable the user to quickly assess the relevance or applicability of the report for his own purposes. This includes the rationale behind the use of the technology and potential utility for patients.

Description and Technical Characteristics -chapter in a diagnostic Core-HTA-report needs to be detailed enough to separate the technology in question from related technologies, using terms/concepts that allows persons unfamiliar with the technology to get an overall understanding on its functioning and use. Important terms should be defined and a glossary or a list of product names could be useful. The section may include pictures, diagrams, videos, or other visual material, in order to facilitate understanding.

Assessment elements in the Description and Technical Characteristics domain of a diagnostic core-HTA-report should cover following question.

Features:

- What is the diagnostic technology and how does it work? What was the history and development of the technical characteristics and functioning? What is the phase of the technology: emerging, new, established? What are the technical characteristics important for the accuracy or effectiveness of the technology? What is the reference standard and does this technology add to, triage or replace other technologies? Are there other diagnostic tests and strategies that could be and are used in clinical practice instead or in addition to the technology in question? Are there important technical differences within generations or versions of the technology? Is there evidence for or expected important variation in use (or conflicting opinions on patient selection/indications)?

Investments:

- What are the material and immaterial requirements for its use? Premises, equipment, maintenance, updating, staff requirements (person time), changes it causes to diagnostic

pathway, level of health care? Are there special measures needed in implementation phase? Does it lead to increased need of resources or other change in the treatment? Do the users of the diagnostic technology need qualification? IT-requirements, records and registers to monitor the use of the technology?

Information needs:

- What kind of training and information is needed for users (those who apply and interpret the technology may be different groups), those who support and maintain the technology, patients, their family and public?

## Methodology

Previous work in the area has not covered this domain in much detail; some of the issues relevant for this part of the assessment have been discussed in “Background Information” in previous projects (1, 2).

Where to find information?

- Review articles and textbooks can be helpful when searching for information about the history and characteristics of the technology.
- Useful databases are MEDLINE (published by the United States National Library of Medicine), EMBASE (Excerpta Medica published by Elsevier) the Cochrane Library and possibly HTA and/or clinical practice guideline search engines and others.
- Grey literature: technical reports from government agencies or scientific research groups, working papers from research groups or committees, white papers, or preprints
- Further information sources may be manufacturers of the technology, clinicians, nurses, paramedics and patients. The manufacturers have their internet sites and single users/ stakeholders can be interviewed. Discussion forums in internet may be valuable.
- Gathering descriptive information does not necessarily imply systematic search. However, for the transparency of HTA the approaches and sources of information should be documented.

## Assessment elements

Element Identification Code (ID)	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status 3=core 2=borderline 1=not core
B0001	Description and technical characteristics of technology	Features of the technology	What is this technology?	Provide a short technical description: Type of device, questionnaire, imaging, etc. Rationale and mechanism of action of the technology. Minor modifications between manufacturers/products need to be accounted for as these may affect diagnostic performance and users need to know exactly that the HTA addresses one or many similar technologies	3	2	Manufacturers' sites, reviews, textbooks, introduction sections of research articles.			3
B0002	Description and technical characteristics of technology	Features of the technology	Why is this technology used?	Describe the aim of using the technology: How is it expected to be an improvement as compared to previous technologies used for the same health problem?	2	3	Research articles		Current Use	3
B0004	Description and technical characteristics of technology	Features of the technology	Who will apply this technology?	What types of professionals (nurses, doctors, other professionals).	3	2	Manufacturers' sites, reviews, textbooks, introduction sections of research articles, interviews, web.		Current Use	3
B0016	Description and technical characteristics of technology	Features of the technology	Who are the persons this technology will be used on?	Define as many narrow groups as possible. The technology might behave differently in different patient groups. Are there specific populations that should not be recipients of the technology because of technical difficulties, inaccuracy or certainty of inconclusive results or because of safety issues?	3	2	Manufacturers' sites, reviews, textbooks, introduction sections of research articles, interviews.		Current Use	3
B0005	Description and technical characteristics of technology	Features of the technology	Place and context for utilising the technology	Primary care, secondary care? Place in diagnostic pathway: replacement-add-on triage?	3	2	Research articles, specialist interviews.		Current Use	3
B0003	Description and technical	Features of the technology	Phase of the technology: When	Is it a truly novel one, or has it been used earlier for this or some other purpose? Is the	3	2	Manufacturers' sites, reviews,		Current Use Safety	3

Element Identification Code (ID)	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status 3=core 2=borderline 1=not core
	characteristics of technology		was it developed or introduced in health care?	technology fully developed or in its early stages? Most technologies will be introduced at approximately the same time in several countries. If an HTA has been done more than a few months before using it, the technology might have been studied in more detail and moved into another phase (with more published trials, for example).			textbooks, introduction sections of research articles.			
B0017	Description and technical characteristics of technology	Features of the technology	Is the technology rapidly changing / improving?	For end users it is useful to know if a new improved technology is expected in the near future.	2	3	Manufacturers' sites, reviews, textbooks, introduction sections of research articles.			3
B0018	Description and technical characteristics of technology	Features of the technology	Are the reference values or cut-of points clearly established?	Are conflicting /varying definitions of abnormal likely to affect the interpretation of the results?	2	2	Research articles, specialist interviews.			2
B0006	Description and technical characteristics of technology	Features of the technology	Are there any special features relevant to this technology?	Any points where this technology is different from its predecessors (other technologies used for similar purposes); new aspects that need to be considered when applying it.	2	2	Manufacturers' sites, reviews, textbooks, introduction sections of research articles, specialist interviews.			2
B0007	Description and technical characteristics of technology	Investments and tools required to use the technology	What material investments are needed to use the technology?	Devices, machinery, computer programs, etc. Those parts of the technology that need to be purchased (and often installed) by an organization in order to use the technology. Includes need for back-up investment to cover for breakdowns in use.	2	2	Manufacturers' sites, reviews, textbooks, introduction sections of research articles, specialist interviews.		Costs, economic evaluation domain	2
B0008	Description and technical characteristics of technology	Investments and tools required to use the technology	What kind of special premises are needed to use the technology?	Many technologies require purpose-built premises within organizations, such as radiation-secured areas, Faraday cages, etc. Typical premises in primary or secondary care may differ markedly from country to country. A clear description of necessary facilities is needed instead of lump statement (e.g. to be used in hospitals only)	2	2	Manufacturers' sites, approving authority, reviews, textbooks, introduction sections of research articles, specialist		Safety domain, Organisational domain	2

Element Identification Code (ID)	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status 3=core 2=borderline 1=not core
							interviews.			
B0009	Description and technical characteristics of technology	Investments and tools required to use the technology	What equipment and supplies are needed to use the technology?	Syringes, needles, medicines, fluids, bandages etc. All disposable items necessary for using the technology	2	2	Manufacturers' sites, reviews, textbooks, introduction sections of research articles, interviews.		Costs, economic evaluation domain	2
B0010	Description and technical characteristics of technology	Investments and tools required to use the technology	What kind of data and records are needed to monitor the use the technology?	What kind of data needs to be collected about the use of this technology regarding care processes, professionals involved, patients and their health outcomes? How is this collected?	2	2	HTA-reports, local authorities			2
B0011	Description and technical characteristics of technology	Investments and tools required to use the technology	What kind of registers is needed to monitor the use the technology?	Are there existing registries that should be used, or should a registry be established, to collect the necessary data?	2	1	HTA-reports, local authorities		Organisational domain	1
B0012	Description and technical characteristics of technology	Training and information needed for utilizing the technology	What kind of qualification, training and quality assurance are needed for the use or maintenance of the technology?	We need to differentiate between the users who are 1. applying the technology (could be different from those interpreting results) 2. interpret the results and make treatment decisions 3. take care of service and maintenance. Training materials: writing and/or translation, other adaptation? Personal training: individual and/or group sessions, number and length of sessions, number and qualifications of trainers. Are regular/ frequent standardisation or quality checks required? E.g. CME points.	3	2	Manufacturers' sites, reviews, textbooks, HTA-reports, interviews.		Organisational domain	3
B0020	Description and technical characteristics of technology	Training and information needed for utilizing the technology	How does training and quality assurance affect the management or effectiveness?		2	2			Effectiveness Safety	2
B0014	Description and technical characteristics	Training and information needed for utilizing the	What kind of training or information about	Training materials: writing and/or translation, other adaptation? Personal training: individual and/or group	2	2	HTA-reports, manufacturers' sites, interviews		Societal aspects domain	2

Element Identification Code (ID)	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status 3=core 2=borderline 1=not core
	of technology	technology	the technology is needed for the patients, their families and general public?	sessions, number and length of sessions, number and qualifications of trainers						
B0015	Description and technical characteristics of technology	Training and information needed for utilizing the technology	What information do patients and their families and general public need on the technology?	Information materials: writing and/or translation, other adaptation? Informed consent for participating?	3	2	HTA-reports, manufacturers' sites, interviews, discussion forums in web		Societal aspects domain	3

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# Safety

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## Domain description

Safety information, balanced with the effectiveness data, forms the basis for further assessments of the technology on e.g. costs and organisational aspects. Assessment of safety issues is especially needed when

- the diagnostic technology has major risk of harm
- the margin between benefit and harm is narrow; diagnostic technology has some risk of harm and at the same time test accuracy is poor or beneficial treatment effect is modest or uncertain.
- several diagnostic technologies with similar accuracy profiles can be used for diagnosing a single condition, and they have different safety profiles
- the rate of false positive is big and patients may end up with unnecessary harmful investigations or treatments
- adverse effects or poor tolerability threatens the acceptability and use of the diagnostic technology (modified from YK Loke 2007) (1).

The definitions and the terminology of safety used in HTA have not been standardised. A Core HTA preparer can use any set of terms but be explicit with them when presenting the results. We talk about side-effects, adverse events or adverse effects, complications, harms, risks and hazards, safety, tolerability and toxicity. It has been suggested that the term ‘harms’ should replace the use of the word safety in randomized trials (2). The Cochrane Handbook proposes some definitions for safety related terms (3). A number of initiatives aim to harmonise safety terms. Examples include the National Cancer Institute severity grading system <http://ctep.cancer.gov/reporting/CTC-3.html> and the WHO system-organ class categories <http://www.unc-products.com/graphics/3149.pdf>. Some researchers have found that the standard ‘preferred terms’ can distort descriptions in the original reports of adverse events and blur distinctions between them (4).

A diagnostic technology may have many potential safety problems. Systematic assessment of each of them can be time consuming. The authors of a diagnostic Core-HTA-report should select those safety issues that are significant for patients or most likely to be important in guiding the decision of health care providers and policy makers. Following harm categories may help identifying and classifying assessment elements for the Safety domain.

- A diagnostic technology may have **direct** harm; mortality, morbidity or disability due to e.g. radiation, toxic contrast media or invasiveness; or it can **indirectly** cause harm due to sub-optimal patient selection or incorrect diagnosis.
- There are harms that are **operator or setting dependent** and they can be modified by changing practices or affecting users’ knowledge, skills and behaviour. Or the harms can be **patient dependent**, which means that there are vulnerable patient groups that should be especially protected against harms.

- Harms can be of **different intensity, seriousness and severity**, and the result may be different if the informant is the clinician or the patient. Intensity is typically graded into four classes: mild, moderate and serious/ severe (3). ‘Serious’ refers to adverse effects that have significant medical consequences, e.g. lead to death, permanent disability or prolonged hospitalisation. In contrast, ‘severe’ refers to the intensity of a particular adverse effect. For example, a non-serious adverse effect, such as headache, may be severe in intensity (as opposed to mild or moderate). Severe and life threatening harms should always be reported. Mild harms should be considered if they are of importance for patients (serious for the patient), particularly when the benefit or diagnostic accuracy is limited.

The harms can be **intended or unintended**

- Another way to classify harms is to assess their **dose relatedness or time relatedness**.
- Besides the patients, the use of a diagnostic technology may cause harm to their **family** and close ones, health care **professionals, public**, and the **environment**.

## Methodology

The methodology of systematically reviewing experimental and observational data on harms is not well developed. The aim is not necessarily to cover all known and previously unrecognised harms of a technology. Rather, Core HTA preparers should focus their review and predefine the safety issues they wish to work in their assessment.

Reviewers, who are not aware of any specific safety problem, could 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 (1).

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
- 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 (3).

## *Study types*

Randomised controlled trials, observational studies and case reports provide evidence on the 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, 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, nested case-control, and cross-sectional studies).

Estimates of the frequencies of harm may differ greatly in different study types. A study comparing harms reported in randomised and observational studies found that observational studies yield lower estimates of absolute risk of harm (5). Also case-reports of harms of a technology may be useful.

Individual measurements of late onset harms (e.g number of radiation induced cancers) can usually not be seen in research publications. Frequency of such stochastic harms is always an estimate, and based on analogies and presumptions from epidemiological risk research.

Besides published research, routinely collected data can be used. Often these databases are generic and may not contain enough information. However, their advantages are bigger size or coverage over long periods of time (6). The value of including data from these additional sources is uncertain (1).

## *Sources of diagnostic safety information*

The sources of information to be examined should be clearly stated. Potential sources of information include:

Medical reference databases: CLIB, MEDLINE; EMBASE

Manufacturers' product data sheets or applications for a product license

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.

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

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

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

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

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

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

WHO Uppsala Monitoring Centre spontaneous reporting database (UMC; <http://www.who-umc.org>)

Disease or technology registries of patients subjected to tests 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

Internet discussion forums may provide valuable patient experiences especially in emerging technologies.

Specific enquiries to manufacturers, regulators or professional bodies may help identify additional sources of information.

### *Search strategies for diagnostic safety information*

Searching for information about harms can be problematic. Inadequate reporting and inconsistent terminology and indexing of harms data make their identification difficult in medical reference databases. Harm specific search terms, like nausea or lymphoedema, should be used to improve the yield. New, previously unrecognised harms remain therefore easily undetected (7). Several study types should be considered for inclusion in the search.

Combination of different approaches in MEDLINE and EMBASE is needed (8). Searches do not detect all relevant studies while 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 (9). To improve the sensitivity of the search, terms for specified adverse effects have to be defined and looked up in each database thesaurus to identify the relevant subject headings to be added in the search strategy (8).

There is no optimal search strategy for specifically identifying reports of adverse effects (5). Following approaches can be used to complement the search strategy with key elements derived from study population and the technology in question:

- Index terms (thesaurus terms, e.g. MeSH in Medline)
  - for specified adverse effects: e.g. Gastrointestinal Hemorrhage, Lymphedema, Pain, Nausea, Lethargy, Fatigue
  - for harm in general: e.g. Adverse Effects (sub-heading), Safety, Toxicity, Drug Toxicity, Complications
- Text words (terms used by the original authors in title and abstract), also taking into account different conventions in spelling and variations in the endings of the terms.
  - for specified adverse effects: nausea, pain, anxiety, tiredness, lethargy, malaise, fatigue
  - for harm in general: side-effect, adverse effect/event/reaction and complications.
- Search terms to capture certain study design, such as cohort studies or case reports.

Different approaches used in identifying literature on harms will lead to different estimates of harm (10). Therefore, the search strategies for electronic reference databases and study inclusion criteria should be clearly reported. This applies also for information retrieved elsewhere

## *Extracting evidence*

A table of included evidence might be a helpful way to make overall assessment for each assessment element. The table contains following information for each included piece of evidence.

- Reference: article/ book/report/ web/ database reference
- Source: name of reference database, agency, discussion forum, other, e.g. Medline, IAEA.
- Study/information type: e.g. prospective cohort study, systematic review, HTA report, manufacturer report, register data, consensus
- Which harm?
- Severity: 1=mild, 2=moderate, 3=severe, and 4= life threatening
- Other classification: self reported/objective measure, immediate/delayed etc.
- Number of harm events per study arm
- Quality of information (see below): how was data collected etc
- Comments on generalisability of the evidence

The definition of a particular harm may vary between studies, as can definitions of severity. They can be measured in different ways and different thresholds can be used. Many trials are too small for reliable estimates and they are usually not designed to collect information of adverse events, at least not as their primary outcomes. This may lead to partial or inadequate reporting of harms: lumping adverse effects of varying severity into one number, or giving only generic statements like "few patients had adverse effects". Note, that no mention of harms in an original study does not necessarily mean that no harms occurred. Authors must choose whether to exclude the study from the harms analysis or, exceptionally, to include it on the assumption that the incidence was zero (5).

Withdrawal and drop-outs can be used as surrogate measures for safety and tolerability, but caution is needed when interpreting such data because of the potential for bias. Reasons for discontinuation may be due to mild but irritating side effects, serious toxicity, lack of efficacy, non medical reasons and a combination of causes (2).

## *Quality Assessment*

There is often a trade-off between the comprehensiveness and quality of the harms data to be included in an assessment. Including evidence that is likely to be biased, even if no better evidence exists, may lead to biased conclusion. All included data should be critically appraised (5).

Adverse events are sometimes poorly reported in randomised trials. Basic requirements for the data are: it should be presented in numbers; the severity of adverse effects should be stated (at minimum the frequency of severe events should be provided per study arm); and the data should be given separately for each type of adverse effect (11). The analysis of zero events ("no serious adverse effects were seen") needs careful consideration. Before concluding that no adverse effect occur, reviewers should ask themselves how thorough were the methods used to detect adverse effects in the original studies and how many patient were studied and for how long (1)? An extension of the CONSORT Statement (Consolidated Standards for reporting Trials) is made for better reporting of harms in randomised trials (2).

Caution is needed when interpreting withdrawal or drop-out data as surrogate measures for safety or tolerability. The reason of withdrawal can be anything from mild side effects to serious toxicity or

lack of efficacy or non-medical reason. Patients in trials and investigators may be more (or less) willing than generally to continue in trial although there are some side effects (1).

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 harm. Nested case control studies (12,13), full cohort analysis survival analysis methodologies are the study designs frequently used for harms assessment. Major sources of bias in observational studies are confounding by factors associated with both treatment and outcome, bias due to differential recall of exposure, and bias due to differential detection of outcomes (14). A brief summary of the strengths and weaknesses of different study designs that may be included in a systematic review of harms is given by Jefferson and Demicheli (15). Newcastle Ottawa scale is a tool to assess observational studies, available at [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.htm](http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm) . STROBE-Statement provides a checklist of items that should be addressed in reports of observational studies (16).

Case reports of suspected adverse events are widely published in scientific journals and few of these reports have been subsequently investigated or confirmed to be valid (17). Some spontaneous reporting systems are inevitably erroneous (1).

Different methods of monitoring harms yield different results, which make comparisons between studies meaningless (18). Active surveillance and use of checklists yield higher harm frequencies than passive or less-focused methods (1). Authors in the original studies may report only some outcome categories although they measured several, or the intervention groups may be combined (e.g. X participants withdrew from the study), or the statements are unclear or too generic (e.g. no unexpected adverse effects were seen).

The authors of a diagnostic Core-HTA-report should consider at least some important aspects:

- How rigorous were the methods used to detect adverse effects? Were the methods used for monitoring reported?
- Was follow up sufficiently long to assess the risk for serious longer term safety issues?
- How complete is the reporting? Did the investigators report all important or serious harms? Did the report give numerical data by group?
- How were data collected: prospective/routine monitoring, spontaneous reporting, patient checklist/questionnaire/diary; systematic survey of patients
- Were any patients excluded from the harms analysis

There is a lack of a relevant quality assessment tool to harms analysis (1). Any available tool should be used cautiously. Comparing evidence from randomised trials and observational studies is useful.

### *Synthesizing and analysing evidence*

At this stage authors of a diagnostic Core-HTA-report should check, that the data extracted is relevant to the research questions, and that analysing and synthesizing the data is still answering the question. Often the evidence available is not quite as useful as hoped, and in that case it should be made explicit how well it answers the original research question.

Standard approaches to data synthesis and analysis can be used when necessary. It is recommended that whenever possible the overall effect of the harms needs to be quantified, as a QALY or DALY

as well as information on the frequency of occurrence, relative risk or number needed to harm (NNH) (6).

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 harms can be reported congruently, whereas unanticipated harms, that are detected during a trial, might be reported in a markedly different ways by different investigators (19).

There is no consensus on how to synthesise information about quality from a range of study designs within a systematic review. Special techniques have been tried (15,20).

### *Reporting and interpreting evidence*

The interpretation of evidence should clearly state qualitative and quantitative limitations of the sources, searches, data and methods used for the analysis. Presentation through tables is transparent and may be helpful in summarising different data (6).

When discussing the safety of a technology, the way harms were caused should be described. Harm may be device dependent or related to the application of the technology. Occurrence of adverse effects may be also operator or setting dependent (e.g. learning curve). Timing and severity of adverse effects should be considered too and the differences in risk among different groups of patients.

A small absolute risk is still clinically important if an adverse event is serious or severe, or if the absolute benefit of the intervention is also small (19). Comment should be made about the generalisability of the findings to the population for whom the HTA may be used.

## Assessment elements

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status 3=core 2=borderline 1=not core
C0008	Safety	Technology dependent safety risks	What is the spectrum of technology dependent harms: their incidence, severity and duration?		3	3	Observational research, safety monitoring databases, registers, statistics	1,2,3,5,6,8,11,14,17		3
C0010	Safety	Technology dependent safety risks	What is the timing of onset of harms: immediate, early or late?		3	3	Research articles, manufacturers' product data sheets, safety monitoring databases	21		3
C0033	Safety	Technology dependent safety risks	What is the dose relatedness of the harms?	Here one should consider also the accumulated harm due to repeated testing	3	3	Research articles, manufacturers' product data sheets, safety monitoring databases	21		3
C0039	Safety	Technology dependent safety risks	What kind of psychological harms can the technology cause to the patient?		2	2	Patient interviews, questionnaires, research articles		Social	2
C0027	Safety	Technology dependent safety risks	Which are the means to reduce the risk of harms?		3	3	Research articles, manufacturers' product data sheets, safety monitoring databases			3
C0026	Safety	Technology dependent safety risks	How does the safety profile of the technology vary between different devices or generations of devices?		3	3	Research articles, manufacturers' product data sheets, safety monitoring databases		Description and Technical Characteristics	3
C0022	Safety	Technology dependent safety risks	What is the safety of the technology in comparison to alternative diagnostic technologies?		3	2	Research articles, manufacturers' product data sheets, safety monitoring databases		Current use	3
C0040	Safety	Accuracy problems and incidental findings	Consequences of false positive, false negative and incidental findings		3	2	Research articles		Accuracy	3
C0041	Safety	Use or user dependent	What are the special features in using	Is there evidence for operator dependent harms? Is there a	2	2	Research articles, manufacturers' product data		Description	2

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status 3=core 2=borderline 1=not core
		safety risks	(applying/interpreting/maintaining) the technology that may increase the risk of patient safety?	learning curve and what is its consequence? Is there is a big intra- or inter-observer variation in the reading of test results, what is its consequence?			sheets, safety monitoring databases			
C0042	Safety	Use or user dependent safety risks	Which are the means to reduce the user dependent safety risks?	What kind of training and certification is needed for the operator or reader?	2	2	Research articles, consensus statements, manufacturers' product data sheets, safety monitoring databases		Description	2
C0028	Safety	Patient dependent safety risks	Are there patient related (individual or disease specific) factors that modify the safety of the diagnostic technology?	Susceptible patient groups	2	3	Research articles, manufacturers' product data sheets, safety monitoring databases	21		3
C0043	Safety	Patient dependent safety risks	Which are the means to reduce the patient dependent safety risks?	What can be done to the management of susceptible patient groups to reduce their risk of harms?	2	3	Research articles, manufacturers' product data sheets, safety monitoring databases			3
C0035	Safety	Occupational safety	Is there evidence of occupational harms?		2	3	Research articles, manufacturers' product data sheets, safety monitoring databases			3
C0036	Safety	Occupational safety	What kind of employee protection is needed?		2	2	Research in occupational health and safety			2
C0037	Safety	Environmental safety	Is there evidence of environmental harms?		1	2	Research articles, manufacturers' product data sheets, safety monitoring databases			1
C0038	Safety	Environmental safety	What kind of environment protection is needed?		2	2	Research articles, manufacturers' product data sheets.			2

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# Accuracy

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## Domain description

Accuracy describes the potential of the diagnostic technology to correctly distinguish those with the target condition from those without (diseased from non-diseased), or to reduce the uncertainty about the presence or absence of the target condition in subjects investigated. For simplicity, we use in this document the word 'disease' for 'target condition', although the term 'target condition' is broader and covers disease and surrogate markers of a disease as well. Similarly we use the word 'test' for diagnostic technology. Sufficient accuracy is a basic requirement for a diagnostic technology that can improve management or patient outcomes (see more details in Effectiveness Domain).

Most diagnostic research is done on diagnostic test accuracy. Evidence of accuracy does not automatically refer to evidence of effectiveness or efficiency. In certain situations, however, accuracy information alone may be sufficient to determine comparative effectiveness, e.g. when the new test is cheaper and/or safer than the existing test.

Basic question of diagnostic accuracy is: how correctly does the diagnostic technology (test) distinguish diseased from non diseased in different populations and at different thresholds (cut-off values)? In occasions when there is a proper reference test (reference standard or gold standard), the accuracy of the new test can be described in terms of test sensitivity and specificity, or in clinically more informative measures of likelihood ratios and predictive values. When there is no acceptable gold standard for diagnosis, the diagnostic test accuracy paradigm is abandoned, and the test results are related to other clinical characteristics (1). See further details in the effectiveness domain of this Model.

Further questions in accuracy domain would be: What is the most optimal threshold value for positive test result? Should different thresholds be identified for different settings, i.e. should we aim to rule in or rule out the disease depending on pre-test probability of the disease? What is the intra- or inter-rater agreement when reading the test results? Does the test perform better in certain patient subgroups or settings? What is the amount of false positive and false negative test results and what are their consequences? Are we interested in the accuracy of a technology as such (compared to reference standard) or compared to another technology that is in frequent use?

Diagnostic technologies can have three roles in the diagnostic pathway: replacement, triage and add-on (see more details below in the chapter Study types). In each of these three situations different requirements for study accuracy exist. Finding out whether a technology can serve its role is not exclusively based on its sensitivity and specificity, but on how the accuracy of the existing diagnostic pathway is influenced by the replacement, triage or add-on technology (2).

### Definitions

- Accuracy: The proportion of subjects that the test correctly identifies as positive or negative.

- Sensitivity: The probability of a positive test result in individuals with the disease.
- Specificity: The probability of a negative test result in individuals without the disease.
- False positive: A type of misclassification in which the disease is absent but the test result positive.
- False negative: A type of misclassification in which the disease is present but the test result is negative.
- Likelihood ratio: The odds that the test result comes from a person who has the disease for which the test was ordered.
- Predictive value: Proportion of people with positive/negative test result who have/have not the disease.
- Diagnostic odds ratio: The odds of a positive test in those with the disease compared to those without the disease.
- Receiver operating characteristics curve (ROC): a plot of paired estimates of sensitivity (on the vertical axis) versus false positive rate (1-specificity on the horizontal axis) of a single test at each possible cut-off point (threshold) for a positive test result (2).
- Index test: the test under study
- Reference standard: The best available comparator or gold standard for diagnosis. It is either a single test or a group of tests or combination of clinical findings and follow up information.
- Target condition: the disease and surrogate markers of a disease that the test aims to detect

## Methodology

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

### *Study types*

A basic diagnostic accuracy study consists of a group of patients in whom the target disease is suspected. All of them undergo the test under consideration (index test) and the best possible test to verify the diagnosis (reference standard, gold standard). Positive and negative results from both tests are shown in a 2x2 table or a variation thereof, depending on the number of cut-off points chosen.

If there is no appropriate reference test it is possible to construct a reference diagnosis by using a predefined rule for a set of other tests, consensus among experts, or a statistical model based on actual data (1). Another possibility is to investigate the probability of disease presence as a function of all diagnostic variables simultaneously with multivariable modelling (3). Problems may arise from the spectrum (patient characteristics, patient selection and setting), the non-optimal reference standard, partial verification (not all patients receive the reference test) or differential verification (patients receive different reference tests).

If a new technology can **replace** an existing one, the accuracy of the technologies has to be compared in comparable groups or preferably in the same patients (4). This can be done indirectly by looking at studies where test A has been compared with a reference standard, and other studies where test B has been compared with the same reference standard. Studies that do both tests and the

reference test to all patients are preferred (paired study). If not all patients had verification with the reference standard test, then the sensitivity and specificity of the two technologies cannot be calculated, but relative true and false positive rates can still be estimated, which allows the accuracy of the two tests to be compared against a common reference standard.

Another option is randomised controlled trial where patients are randomly allocated to receive either new or existing test, after which all patients undergo the reference standard testing. Randomised trials are preferred if the new test is too invasive to be done to all patients or if the tests interfere with each other (2).

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

Several designs can be used to compare the accuracy of the triage pathway to the existing pathway. In a paired study design all patient undergo the triage technology, the existing technology and the reference standard. Limited verification can be used here as well (2).

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

Fully paired or randomised methods are preferred but not always needed in researching add-on tests. Limited designs can be more efficient. E.g. limiting the study to patients who are negative after existing diagnostic pathway, with verification by reference standard only those who test positive on new technology, allows still us to calculate the number of extra true positives and false positives from using the new add-on technology (2).

## *Outcome measures*

Diagnostic test results are often reported as a numeric quantity on a continuous scale which is then divided by a threshold value above which the test is positive and below which it is negative. Results may then be summarized in a 2x2 table to reflect the agreement between the "true" disease state and the test result.

Figure 2x2 table

	Diseased	No disease
Test positive	<b>TP</b>	<b>FP</b>
Test negative	<b>FN</b>	<b>TN</b>

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

#### Measures of test performance (5)

Metric	Definition	Advantages	Disadvantages
Accuracy	$(TP+TN)/N$	Intuitive	Depends on prevalence
Sensitivity	$TP/TP+FN$	Does not depend on prevalence	
Specificity	$TN/TN+FP$	Does not depend on prevalence	
Positive predictive value	$TP/TP+FP$	Clinical relevance	Depends on prevalence
Negative predictive value	$TN/TN+FN$	Clinical relevance	Depends on prevalence
Positive likelihood ratio	$(TP/TP+FN) / (FP/TN+FP)$	Does not depend on prevalence	Applies only to positive test
Negative likelihood ratio	$(FN/TP+FN) / (TN/TN+FP)$	Does not depend on prevalence	Applies only to negative test
Diagnostic Odds ratio	$TP \times TN / FN \times FP$ $=Lr+/Lr-$	Does not depend on prevalence; combines sensitivity and specificity. Invariant to test positivity threshold.	Values FP and FN errors equally; not intuitive
Area under curve	Area under ROC curve	Does not depend on prevalence; combines sensitivity and specificity	Lack of clinical interpretation

TP = true-positive, TN = true-negative, FP = false-positive, FN = false-negative, N = sample size, ROC = receiver-operating-characteristic

Primary measures of diagnostic accuracy are sensitivity and specificity. They are always considered together as a combined measure of accuracy. They are not directly influenced by the prevalence of the disease and thus the results from one study may be applicable to different populations. Paired data with 95 % confidence intervals can be graphically presented and pooled.

Sensitivity and specificity depend highly on the test threshold. Increasing the threshold increases the specificity but decreases sensitivity. The inverse relationship between sensitivity and specificity is often best illustrated using a graph (ROC curve) where pairs of sensitivity and specificity are plotted for different thresholds.

There are explicit thresholds like laboratory test values, although different laboratory kits provide numbers that are not necessarily comparable. Then there are implicit differences in threshold caused by case-mix and factors affecting test reading. Especially in imaging tests it is the eye of the reader that determines test positivity, and different readers may result in different conclusions on test positivity.

Likelihood ratio (LR) describes how many times a person with a disease is more likely to receive a particular test result than a person without disease. It can be calculated for all different levels of the test result. It is therefore useful measure of test accuracy when test results can be reported in more than two categories. It can be combined with the estimated prevalence of the disease to calculate the post test probability of the disease. It can be treated as a risk ratio for data pooling and presented graphically with 95% confidence intervals (CI) in systematic reviews. Data can be pooled only if there is no variability in the test threshold used (6).

Diagnostic odds ratio ( $DOR=Lr+/Lr-$ ) provides a single summary estimate of test accuracy that combines sensitivity and specificity. It does not usually vary by the test threshold and is not dependent on the prevalence of the disorder (although it may vary with disease severity). It can be used for indirect comparisons between two tests. It can be calculated with 95% CI and presented in a forest plot. DOR from different studies can be pooled to calculate a summary DOR using standard meta-analytic methods, if no heterogeneity is present. Every single point in a symmetric (symmetry around the diagonal where sensitivity = specificity) ROC curve has the same DOR. An important disadvantage is that DOR as a single number leaves out information on sensitivity and specificity (the same DOR could result from tests with very different sensitivities or specificities). Furthermore, it cannot be used to summarise multi-level test results.

ROC curve demonstrates the trade-offs between the sensitivity and specificity of the test. A horizontal line would mean constant sensitivity, vertical line constant specificity. Constant likelihood ratio is seen as linear relationship of sensitivity and specificity. A diagonal line from lower left to upper right corner would mean that the test is not informative at all. Usually there is a curvilinear relationship with the plots. The point in the curve that is closest to the upper left corner gives the test threshold with best accuracy.

If the distribution of possible test values in healthy and sick is different, e.g. the distribution of PSA-measures in healthy is quite narrow and in prostate cancer patients broad, then the ROC curve becomes asymmetric and there is high and low DORs in different parts of the curve.

The area under ROC curve (AUC) provides a measure of the overall accuracy of the test. AUC can be interpreted as the probability of correctly identifying the disease on a pair of subjects, when one of them has the disease and the other has not. Values for AUC can range from 0 to 1. If the sensitivity and specificity of the test is 100% at each threshold, then AUC is 1.0 and the test is perfect. If AUC is 0.5, the test does not discriminate between the presence and absence of the disease.

### *Sources and search strategies for diagnostic accuracy information*

Inadequate and inconsistent reporting of diagnostic accuracy studies and their indexing in medical reference databases make their identification particularly challenging. Unpublished and ongoing studies of diagnostic accuracy would be valuable but not as easily detected as trials. Reviewers are likely to retrieve thousands of records to scan for potentially relevant studies.

Over 20% of studies included in previous diagnostic accuracy reviews were not found in MEDLINE and 6 % were not found by the electronic searches (Whiting et al 2007 in press). Majority of the studies that were not found in databases were identified by scanning reference lists of included articles.

Routine use of methodological search terms are not generally recommended while relevant records may be lost for no significant reduction in the number needed to read (7,8).

Look for more information on diagnostic search filters and information on their performance 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>

### *Extracting evidence*

Two authors should screen the records received from the electronic search to increase the sensitivity.

Included studies table columns

- Participants, prevalence of target condition
- Prior tests
- Index test, cut-off point
- Reference test
- Test results (2x2 data)
- Sensitivity/specificity + 95% CI
- Other accuracy metrics
- Study quality

## *Quality assessment of diagnostic accuracy studies*

Quality assessment of diagnostic accuracy studies is not as straightforward as it is for interventions. It is subjective and hampered by poor reporting. Statistical incorporation of quality in overall assessment is difficult due to limited studies. Relation between quality items and bias are not as straightforward as it is for interventions.

There are many different tools to assess the quality of diagnostic accuracy studies. Cochrane handbook recommends QUADAS tool with its 11 mandatory and more than 10 facultative items.

### QUADAS quality assessment tool (9)

#### Mandatory items (as in Cochrane handbook)

1. Was the spectrum of patients representative of the patients who will receive the test in practice?
2. Is the reference test likely to correctly classify the target condition?
3. Is the time period between reference test and index test short enough to be reasonably sure that the target condition did not change between the two tests?
4. Did the whole sample, or random selection of the sample, receive verification using a reference standard of diagnosis (reference test)?
5. Did patients receive the same reference test regardless of the index test result?
6. Was the reference test independent of the index test i.e. the index test did not form part of the reference test?
7. Were the index test results interpreted without knowledge of the results of the reference test?
8. Were the reference test results interpreted without knowledge of the results of the index test?
9. Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice?
10. Were uninterpretable / intermediate test results reported?
11. Were withdrawals from the study explained?

#### Additional items

12. If a cut-off value has been used, was it established before the study was started (pre-specified cut-off value)?
13. Is the technology of the index test likely to have changed since the study was carried out?
14. Did the study provide a clear definition of what was considered to be a "positive" test result?
15. Was treatment started after the index test was carried out but before the reference test was performed?
16. Was treatment started after the reference test was carried out but before the index test was performed?
17. Were data on observer variation reported?
18. Were data on instrument variation reported?
19. Were data presented for appropriate patient sub-groups?
20. Was an appropriate sample size included?
21. Were objectives pre-specified?

HTA-authors should create an own quality assessment tool, selecting relevant items from QUADAS. Two assessors are recommended. Background of assessors should be reported, and the way they resolved disagreements. Results of the quality assessment of the original studies should be presented in a table or graphically. Individual quality items should be investigated as a potential source of heterogeneity.

## *Adjustments or corrections of missing or imperfect reference standard*

If there is an acceptable reference standard test but for various reasons not all patients in the study received it, the researchers either impute or adjust for the missing data (1). 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 (1). The adjustment is based on previous research about the . 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 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-report. Simple methods of pooling sensitivities and specificities are contraindicated if heterogeneity exists.

Sources of heterogeneity are

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 (10).

Methods to test for heterogeneity (6):

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.

## *Assessing threshold effect*

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 (11). 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 (11). 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.

## *Synthesizing and analysing evidence*

### *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 (see above Chapter Assessing Heterogeneity ) 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 data further (see above Chapter Assessing Threshold Effect).

### *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 (10).

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 (12). 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 (13). Model is infrequently used, probably due to complex fitting.

More reading: (14-17)

### *Interpreting and reporting evidence*

If the study uses healthy controls the specificity goes up. If the reference test was not done for all, an over-estimation of test accuracy may result (incorporation bias, partial verification). Poor reference standard, on the other hand, may lead to underestimating of test accuracy.

Contrary to trials, in diagnostic research you have to divide the studies to clinically relevant subgroups.

Pair of sensitivity and specificity is a general measure of test performance. The numbers (0.0–1.0) per se are not very informative in determining whether the test performs well. The intended use of the technology determines the requirements for the test accuracy. If sensitivity is sufficiently high, a negative test result rules out the disease. High sensitivity is particularly important if the penalty for missing a disease is high. Sufficiently high specificity rules in the disease. High specificity is particularly important if a false positive result can harm the patient. Positive and negative predictive values are the most clinically informative measures of the accuracy of a diagnostic test, but less useful for systematic reviews of diagnostic accuracy studies.

Summary likelihood ratios can be estimated from the pooled estimates of sensitivity and specificity. Likelihood ratio tells how many times more likely the disease is in patients with that test result compared to those without the disease. A likelihood ratio 1 indicates that the test does not provide

any useful diagnostic information. Positive likelihood ratios more than 10 and negative likelihood ratios less than 0.1 can provide convincing diagnostic information. Some guidelines suggest that positive likelihood ratios more than 5, and negative likelihood ratios less than 0.2 can provide strong diagnostic evidence. However, the interpretation depends on the context and prevalence of the condition. Likelihood ratios usually have to be more than 10 for a test to be useful (6).

Diagnostic odds ratio shows the association between a dichotomous test result and the diagnosis. If the diagnostic odds ratio (DOR) is 1 then the test does not provide any useful information. The size of the DOR greater than 1 reflects the strength of the test to discriminate between the presence and absence of disease. A DOR of 100 provides convincing evidence of the presence or absence of disease and correspond 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 it should be over 80 in a good test. A DOR less than 1 indicates that the test identifies more positives among the non diseased than the diseased.

Diagnostic odds ratio is useful summary measure for meta-analysis but it does not provide information that can be directly applied to clinical decisions. Information about trade-offs between sensitivity and specificity will be lost, therefore comparing DORs of two tests is not useful. DOR cannot be used to judge a test's error rate at a particular prevalence (6).

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

Alternative methods of expressing test accuracy beyond sensitivity and specificity, e.g. likelihood ratios or diagnostic odds ratios, are preferred. Explaining how many patients will be missed (false negative rate) and how many treated unnecessarily (false positive rate) using certain cut-off point in a population with certain disease prevalence, may be illustrative.

Evidence table can be interpreted safely together with graphical display of included study results on ROC space. A pre-test — post-test graph could be drawn to show how much pre-test probability (the prevalence of the condition in the population who are investigated with the technology) will change if a positive or negative test result is obtained.

## Assessment Elements

Element Identification Code (ID)	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status 3=core 2=borderline 1=not core
J0001	Accuracy	Accuracy measures	What is the accuracy of the test against reference standard?	Accuracy in terms of sensitivity and specificity, likelihood ratios, pre-test probabilities, SDORs, AUC or Q*?	3	3				3
J0002	Accuracy	Accuracy measures	How does the technology compare to other optional diagnostic technologies in terms of accuracy measures?	Or, how does the technology compare to other development stages of the same technology?	3	3				3
J0003	Accuracy	Accuracy measures	What is the reference standard and how likely does it classify the target condition correctly?		2	2				2
J0004	Accuracy	Context related requirements for accuracy	What are the requirements for accuracy in the context the technology will be used?	Acceptable number of false negative and false positive test results is different e.g. in replacement/ triage/ add-on situations, and in life threatening / harmless conditions.	3	2			Ethics domain	3
J0005	Accuracy	Context related requirements for accuracy	What is the optimal threshold value in this context?		3	2				3
J0006	Accuracy	Context related requirements for accuracy	Does the technology have the potential to reliably rule in or rule out the target condition?		3	2			Safety, societal, ethical domains	3
J0007	Accuracy	Reliability and transferability of reported accuracy	How does test accuracy vary in different settings?	How do patient spectrum, disease prevalence, disease severity, and properties of the technology itself affect the accuracy of the test?	2	2				2
J0008	Accuracy	Reliability and transferability of reported accuracy	What is known about the intra- and inter-observer variation in test interpretation?		2	2				2

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# *Clinical effectiveness*

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## **Domain description**

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, may be insufficient (1).

There is a variety of reasons why the information provided by a diagnostic technology, even an accurate one, does not necessarily change therapy or patient outcomes. These reasons include following: Clinicians may be unaware of available treatment or fail to fully appreciate the diagnostic information provided. The information may be also insufficient to alter the treatment plan. Sometimes the same diagnostic information is obtained with the use of a combination of other diagnostic tests already available. There may be no effective treatment available, or the best possible treatment is already in use, irrespective of the test results (2).

Diagnostic technologies are used not only to confirm or exclude a disease to guide treatment. They are also used to classify a disease or risk factors for a disease. Classification of disease is done in order to grade its severity, size, shape and location. This may be important to guide timing or dosing of treatment, indicate prognosis, monitor the disease progression or evaluate response to current treatment (3,4). In such cases diagnostic technology may have other benefits, such as physician and patient reassurance. Test results may improve patient's quality of life that is not directly related to treatment.

The effectiveness of a diagnostic technology is determined by a combination of factors: the improved accuracy of the diagnostic pathway where the technology is used; the impact of the use of the technology on therapeutic decisions; and the effectiveness of the therapies selected on the basis of the use of the technology (2,5). Direct test-treatment trial evidence is scarce. However, a variety of pragmatic study designs illuminate the interdependence of the factors that determine effectiveness and inferences should be made out of the linked evidence they build (see more about linked evidence below).

The following questions can be asked when determining test effectiveness: What is the purpose of the test in question: is it an add-on test, or new test that replaces a current test, or a triage test? Do the clinicians use the test result in their decision making, and does the decision make any difference, or is the best possible treatment already in use? Is there an effective treatment for the condition that is detected by the technology? What is the sequence of further testing and alternative and delayed treatments in patients with false positive and false negative test results? What is the overall balance between benefits and harms between correctly and falsely diagnosed patients? Does the new test

perform as consistently, and is the treatment of the detected condition equally effective in different populations?

Sometimes, accuracy information alone may be sufficient to infer effectiveness of the new diagnostic technology. Consider a situation where we already have test-treatment RCTs or linked evidence from test accuracy studies and treatment RCTs with patients in whom the same test was applied. Then a new diagnostic technology with similar sensitivity but greater safety or specificity may be seen as improved effectiveness (6). If the new test is more sensitive than the old one, it will detect extra cases of disease, and then the effectiveness information from treatment trials that enrolled patients using the old test is not directly applicable to these extra cases.

Often we need to consider situations where the evidence is incomplete. Accuracy studies and treatment trials are usually done by different investigators at different times and in different settings. Clear understanding of the proposed use of the test in the diagnostic pathway is essential in assessing incomplete evidence.

Effectiveness of a diagnostic technology may depend on the person's ability to interpret or make appropriate management decisions based on the results of the test. Training and experience of the health professionals involved in studies of diagnostic effectiveness, the setting in which the study is conducted, and even their reimbursement schedule should therefore all be specified (2).

If there is no direct evidence and not enough evidence to be linked, accuracy and safety issues can be dealt with in their own domains and effectiveness issues (change-in-management and treatment) in this domain.

## Methodology

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?).

### *Optimal study types*

#### **Direct trial evidence**

Diagnostic RCT that randomises patients into a new or the existing diagnostic pathway is the most reliable study design. 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 pathway and in subsequent treatment decisions. Other comparative study designs like cohort and case-control studies have greater potential for bias.

## Linked evidence

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

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

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

Change-in-management, or therapeutic-impact, or diagnostic before-after-studies measure the amount of starting, stopping or modifying treatment before and after the incorporation of the new diagnostic technology in the management pathway (7). Physicians in change-in-management studies are provided with test results from a new diagnostic technology and the researchers then compare their pre-test management plan to post-test management plan. The study type is usually applied to add-on type technologies.

In replacement-type new technologies we usually assume that the behavioural pattern from test result to management decisions remains unchanged. Especially if there is a well established standard treatment for the condition detected. In other cases, change-in-management studies may be required to demonstrate that the test results are sufficient to alter the clinician's threshold for changing management (8).

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

When there is a trade-off between benefits and harms, e.g. when the better safety of a less invasive but less specific new test needs to be assessed against the harms arising from additional false-positive results, decision analytic model can be used. Decision analysis allows also comparison of the test effectiveness in those with a different prevalence of the disease. Decision analysis is appropriate when the evidence of test accuracy can be linked to the evidence of treatment effect. If this linkage is uncertain, we need randomised trials. In these situations, trials investigating the effect of treatment in patients who have positive results on the new test and negative results on the old test may be more efficient and more clinically relevant than trials conducted in all patients who are new-test-positive (9).

## *Search strategies for diagnostic effectiveness information*

See text in first Core Model effectiveness domain and this Core Model Accuracy domain

## *Quality Assessment*

### **Direct trial evidence**

Sources of bias in studies designed to evaluate the effectiveness of an intervention, or diagnostic test and subsequent interventions, relate to differences in patients assigned to intervention and control group, including differences in the selection process (selection bias); the unbalanced provision of care (performance bias; the methods of measuring or interpreting the outcomes (detection bias); or imbalances in patient drop-out (attrition bias) (10,11).

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

See more in the Core Model for medical and surgical interventions, Effectiveness domain.

### **Linked evidence**

Quality assessment of safety and diagnostic accuracy research are described in respective domains in this Core Model. Quality assessment items on treatment effectiveness are described in the Core Model for medical and surgical interventions.

The strengths and limitations of other study types than RCT need to be considered. There is quality check lists for studies of effectiveness in MSAC page 69 (8).

Change-in-patient-management studies can be appraised using the same criteria as case series (see list of criteria MSAC page 70) (8). Potential bias is common and it is related to the selection of patients, the objective execution of the diagnostic test, and measurement of the results in all eligible patients. One of their limitations is that stated plans may differ in the study setting compared to the real life situations where the technology is not available. Physicians' subconscious bias may also occur. Their results are applicable only when change in management benefits patient.

## *Synthesizing and analysing evidence*

Evidence from diagnostic RCTs can be pooled according to the same principles as treatment RCTs (see first Core Model).

Evidence about benefits and harms can be combined using decision analysis methods.

For accuracy and safety research see respective domains in this Core Model.

## Assessment elements

Element Identification Code (ID)	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status 3=core 2=borderline 1=not core
D0019	Effectiveness	Comparative accuracy of a replacement technology	Is there evidence that the replacing technology is more specific or safer than the old one?	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.	2	2			Accuracy and safety domain	2
D0001	Effectiveness	Safety	What is the mortality related to the diagnostic technology?		2	3			Safety domain	3
D0008	Effectiveness	Safety	What is the morbidity related to the diagnostic technology?		3	3			Safety domain	3
D0020	Effectiveness	Change-in management	Does the use of the technology lead to improved detection of the disease?	Physicians' ability to make correct diagnosis may depend on knowledge and ability to interpret the results.	2	2				2
D0021	Effectiveness	Change-in management	Does the use of the technology lead to a change in the physicians' management decisions?	There may be technology related or non-related factors that might influence the physicians ability and attitude to decision making.	2	2				2
D0022	Effectiveness	Change-in management	Does the use of technology detect other health conditions which have impact on the treatment decisions concerning the target condition?		2	2				2
D0023	Effectiveness	Change-in management	How does the technology modify the need for other tests and use of resources?		2	2			Economic & Organisation domains	2
D0010	Effectiveness	Change-in management	How does the technology modify the need for hospitalization?	Even at different levels of care e.g. ward instead of intensive care.	2	2			Economic & Organisation domains	2
D0024	Effectiveness	Health outcomes	Is there an effective treatment for the condition the technology is detecting?		3	2				3

D0025	Effectiveness	Health outcomes	What is the effect of the test-treatment intervention on mortality?		3	2				3
D0005	Effectiveness	Health outcomes	How does the test-treatment intervention modify the magnitude and frequency of morbidity?	A more accurate replacement test could improve treatment and effectiveness. A satisfactory triage test may decrease the number of adverse outcomes from another test. An add-on test may increase sensitivity so that more patients receive proper treatment and thus improved outcomes.	3	2				3
D0026	Effectiveness	Health outcomes	How does the technology modify the effectiveness of subsequent interventions?	Different tests may detect slightly different subpopulations of true positive. Effectiveness of intervention can be different in test A positive than in test B positive.	2	2				2
D0013	Effectiveness	Health outcomes	What is the effect of the technology on health-related quality of life?		3	2				3
D0027	Effectiveness	Health outcomes	What are the negative consequences of further testing and delayed treatment in patients with false negative test result?		2	2				2
D0028	Effectiveness	Health outcomes	What are the negative consequences of further testing and treatments in patients with false positive test result?		3	2			Safety domain	3
D0029	Effectiveness	Health outcomes	What are the overall benefits and harms in health outcomes considering the amount of false positive and false negative.		3	2				3
D0030	Effectiveness	Patient satisfaction	Does the knowledge of the test result improve the patient's quality of life?		2	2				2
D0018	Effectiveness	Patient satisfaction	Would the patient be willing to use the technology again?		2	2				2

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# *Costs and Economic evaluation*

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## **Domain description**

Rising health-care costs and limited resources have become issues of paramount importance over the past two decades. A rapid technological development also implies a conflict between technological possibilities and economic possibilities. Clinical investigators have begun to recognize the importance of performing economic evaluations alongside RCTs. It is not enough to get information just about efficacy and effectiveness when evaluating new technologies, information about costs and outcomes are also needed. Economic evaluation is an important part of health technology assessment.

The main aim of the costs and economic evaluation domain is to provide information to improve decision-making in the health care sector with respect to priority-setting between different health technologies, both emerging, new and existing ones (Kristensen 2007). An economic evaluation identifies, measures, values and compares the costs and outcomes of a technology with its relevant comparator. Its aim is to inform value for money judgements about an intervention (Guidelines for the Economic Evaluation of Health Technologies: Canada, 3rd edition, 2006).

Central to this area of economics are the concepts of opportunity cost and incremental change. In publicly funded health care systems limited resources mean that every available intervention cannot be provided in every situation for all who need or want it. Choices must be made among effective health care interventions, and the decision to fund one means that others cannot be funded. (Guidelines for the Economic Evaluation of Health Technologies: Canada, 3<sup>rd</sup> edition, 2006)

An economic evaluation should provide decision makers with information that is useful, relevant, and timely. The economic evaluation component of a HTA should be conducted within a common methodological framework that consists of a well-defined research question depicting a specific health policy problem or question, a perspective and scope of analysis, and a set of alternatives to be assessed comparatively (Liberati 1997). It is important to describe the alternatives in detail so that study users can assess the relevance to their own setting. Current practice may vary over time and from country to country. Other elements that are important for the economic evaluation may vary from country to country as well. Therefore, transparency in reporting of economic evaluations is of utmost importance to allow an assessment of the applicability and relevance of an economic evaluation performed in the context of a HTA for its own setting.

### Study frame and scoping of the economic evaluations<sup>3</sup>

A coherent and manageable economic analysis needs a framing or scoping of the analysis that defines the following aspects of the analysis:

Target population	The population or patient group that the intervention is aimed at
Intervention	The technology being studied
Comparators	The alternative technologies that the technologies is being compared to (often including, but not limited to, current practice or “no intervention”)
Outcomes	The positive or negative health outcomes that are included in the analysis
Time frame	The time frame during which cost and outcomes are assessed
Perspective	The perspective from which costs and outcomes are assessed

Some of these aspects are further discussed in the methodology section.

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<sup>3</sup> This section of framing and scoping of the economic analysis is placed in the economics chapter in the current version of the model because it is definitely needed here. Testing of the core model may show that the framing and scoping of the analysis needs to be defined as a separate domain or otherwise rewritten.

## Methodology

In the following condensed Table 1 (Modification from Drummond) we will review the four main types of economic evaluation which can be part of HTA. The difference between them is based on how health outcomes are measured and valued. The choice between the different types of economic evaluations for answering a specific question depends on the purpose of the evaluation, the availability of specific data and potentially the guidelines for economic evaluations that are to be followed in a specific context.

Table 1. Types of full economic evaluation.

Type of economic evaluation	Appropriate if ...	Valuation of costs	Valuation of outcomes	The question to be answered
Cost-minimisation analysis (CMA)	the compared technologies are equally effective; data on costs suffice.	Monetary units	None	Which intervention is the least costly?
Cost-effectiveness analysis (CEA)	the effectiveness of the compared technologies is different (e.g. the difference in costs have to be weighted against the difference in effectiveness);  activities with the same aim and measure of effectiveness are compared.	Monetary units	Natural units (e.g. life years gained, disability-days saved, points of blood pressure reduction, etc.)	What is the intervention's incremental cost per additional unit of outcome as compared to its best alternative?
Cost-utility analysis (CUA)	HRQoL is an important health outcome; <i>and/or</i> activities across specialities or departments in the health care sector are compared.	Monetary units	QALYs, HYEs	What is the intervention's incremental cost per additional unit of outcome as compared to its best alternative?
Cost-benefit analysis (CBA)	non-health effects are also of importance (e.g. the treatment process itself, utility of information); <i>or</i> only one technology is assessed (net benefit); <i>or</i> there is a wish that individual life's are valued in monetary units; <i>or</i> activities across different sectors in society have to be compared.	Monetary units	Monetary units	What is the economic trade-off between different activities that matter for society?

The basic idea behind economic evaluation is to improve allocative efficiency in health care, i.e. given the resources available optimize the health of the population.

### Perspective

The perspective of the economic evaluation is a key element in defining which costs and outcomes should be included in the analysis. For instance short stay at hospital may be cost-effective from the

perspective of the hospital but it may be more costly to society if the cost of home care is taken into account.

In the ideal situation the economic evaluation is conducted from the broadest possible perspective. The most comprehensive perspective is societal and then all relevant costs and outcomes of the technologies have to be identified, measured and valued, no matter whom these costs and outcomes fall on (Drummond 2005). Other possible perspectives are the health care sector's perspective, third party payer's perspective, hospital perspective or patients' perspective. The perspective chosen ultimately depends on the purpose of the economic evaluation. If the purpose is to inform societal resource allocation, the societal perspective should be taken. For hospital HTA, the hospital perspective may be more appropriate.

### Costs

The costing procedure can be divided into three phases: identification, measurement and valuation of resource use. First of all the relevant resources used have to be identified, then the volume or number of units of the resources uses has to be measured and finally these volumes have to be valuated.

Direct costs are all costs directly related to a disease or technology. They include costs borne inside the health care sector (e.g. materials, equipment, personnel, tests – direct health care costs) as well as outside the health care sector (e.g. patients' travel time – direct non-health care costs).

Indirect costs include the patient's temporary absence from work due to illness, reduced working capacity due to illness and disablement, or lost production due to an early death.

The lost production can be measured either by means of the human capital method or the friction cost method. Lost production is most often reported separately and not integrated in the cost estimate used for the calculation of the incremental cost-effectiveness or cost-utility ratio. Its valuation is made only in situations where it is judged to be relevant. The concept of lost production should not be confused with a transfer payment like sickness benefit.

Physical units or volumes of resources used should be reported separately from the unit costs of resources to allow decision makers to assess the applicability of resource use estimates to their own setting. In addition it is recommended to report direct costs separately from indirect costs.

### Outcomes

Health outcomes of interventions can be measured by natural units of health (e.g. deaths, life years gained (LYG)), valuations of health states or utilities, or in monetary terms (Table 1).

If the intervention affects both the length and the quality of life, a composite outcome measure, such as Quality-Adjusted Life Years (QALYs) or Healthy Years Equivalent (HYES) should be used. The QALY-approach and similar approaches are useful in policy analysis and program decision-making because they are generic and consequently allow broad comparisons between interventions and across diseases. They can in principle be estimated for any population, any disease, any intervention, and can be used to compare across diverse programs, assuming that studies use the same methodology. Health-related quality of life (HRQoL) refers to aspects of quality of life that are related to health. There are different tools to measure HRQoL and there is no single measure which has been accepted as the gold standard. Patient outcome measures that extend beyond

traditional measures of mortality and morbidity, to include physical, social, and emotional aspects that are relevant and important to an individual's wellbeing can be assessed using a disease-specific, generic, or a preference-based instrument. However, for economic evaluation an index measure is at least needed. To be able to compare outcomes in different disease areas, a generic measure should moreover be used.

### Incremental cost-effectiveness ratio (ICER)

To be able to conclude which health technology is cost-effective, both the total costs and the effectiveness of at least two interventions have to be compared. The comparison may lead to nine different situations, as described in the decision matrix below.

Table 2. The cost-effectiveness decision matrix (Kristensen 2007)

<b>A new technology compared with an old one</b>	<b>Less effective</b>	<b>Same effectiveness</b>	<b>More effective</b>
<b>Less costly</b>	1.No clear decision <i>non-dominance =&gt;</i> <i>Incremental analysis needed</i>	4.Adopt the new technology <i>the new dominates the old</i> <i>(weak dominance)</i>	7.Adopt the new technology <i>the new dominates the old</i> <i>(strong dominance)</i>
<b>Same costs</b>	2.Keep the old technology the old dominates the new <i>(weak dominance)</i>	5.The technologies are equal	8.Adopt the new technology the new dominates the old <i>(weak dominance)</i>
<b>More costly</b>	3.Keep the old technology <i>the old dominates the new</i> <i>(strong dominance)</i>	6.Keep the old technology <i>the old dominates the new</i> <i>(weak dominance)</i>	9.No clear decision <i>non-dominance =&gt;</i> <i>incremental analysis needed</i>

In situations described in cells 1 and 9 incremental analysis is needed to decide, which technology is preferable. For that purpose an incremental cost-effectiveness ratio (ICER) has to be calculated. It is a ratio of the difference in costs of interventions to the difference in outcomes. The ICER indicates the costs of achieving one extra unit of health benefit when switching from one alternative to another. The new intervention is cost-effective if the society is willing to pay for the additional benefits (cell 9) or if the society considers that the cost savings compensate for the lower effectiveness (cell 1).

### Threshold cost-effectiveness and net benefit approach

Whether an intervention is cost-effective depends on its relation to the maximum willingness-to-pay for a unit of outcome, or the so-called ICER threshold. If the ICER of the intervention is lower than the threshold, the intervention is considered cost-effective (i.e. improving efficiency in health care). If it is higher than the ICER threshold, the intervention is not considered cost-effective and resource allocation to this intervention would not increase efficiency in health care.

The ICER seems to be most popular method but the ratio gives no idea of the size or scale of the interventions being considered. The net benefit approach is an alternative summary measure of the value for money. Net monetary benefit (NMB) and net health benefit (NHB)) will be used to

overcome problems with cost-effectiveness ratios. Both NMB and NHB are functions of the threshold cost-effectiveness ratio (Drummond 2005).

### Modelling

There are several reasons for carrying out an economic evaluation with modelling, for example in a situation where economic and clinical data are missing or when there is a need for extrapolation of short-term clinical data to the long run. Decision trees and Markov models are the most frequently used types of models.

### Sensitivity analysis

Economic evaluation is often based upon estimates of variables that are characterised by a specific distribution. Besides parameter uncertainty, economic evaluations –and more specifically economic models- are often based on assumptions about the relationship between parameters which are also uncertain. It is important to take this uncertainty into account in the evaluation, either parameter or model uncertainty. Sensitivity analysis will show the decision maker, how robust (trustworthy) the results and conclusions of the economic analysis are. Deterministic and/or probabilistic sensitivity analyses should always be a part of an economic analysis (Guidelines for the Economic Evaluation of Health Technologies: Canada, 3rd edition, 2006; Guidelines for pharmacoeconomic evaluations in Belgium: Brussels, 2008). Especially in economic models it is very important to conduct a complete sensitivity analysis for all uncertain model inputs to determine the impact on the results. Omission of any model input from the sensitivity analysis should be justified. Different methods to handle uncertainty are presented by Briggs et al 1994 and Briggs et al 2006.

### Discounting

Cost and outcomes in the economic analysis that occur in the future should be discounted. Discounting, or calculating the present values of future costs and consequences, makes it possible to compare health technologies in an economic analysis whose costs and outcomes do not occur at the same time. Discounting should not be confused with inflation.

### *Transferability of resource utilization and unit cost elements*

Costs of technologies are generally not transferable from one country to another. However, transferability of individual elements of data differs. Table 3 contains our assessment of transferability for each element. Although the resource utilization and unit cost elements are only partially transferable or not transferable at all, they are all essential parts of an economic assessment. The relevance of economic evaluations cannot be judged without information on these elements. Moreover, data on types and amounts of resources used in one country are often valuable information for researchers performing a HTA in another country.

Table 3 Transferability of resource utilization and unit cost elements

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

## Assessment elements

The costs and economic evaluation domain consists of five topics: resource utilization, unit costs, indirect costs, outcomes, and is the technology cost-effective when compared to the most cost-effective alternative procedure(s). In each topic there are one to two issues, together six issues.

The following is a listing of elements that are specific to economic evaluation. In addition to these elements most economic evaluations will employ one or more outcome elements from the effectiveness and safety domains in order to specify positive and negative health outcomes in the economic analysis. The only exception to this is the case where all effectiveness and safety outcomes are equal for the technology and all comparators, in which case a cost-minimization analysis is relevant.

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference (was: "source")	Relations	Status 3=core 2=borderline 1=not core
E0001	Costs and economic evaluation	Resource utilization	What types of resources are used when delivering the assessed technology and its comparators (resource use identification)?	In order to do an economic evaluation all types of resource utilization must be identified. The study perspective determines what kinds of resource utilization must be identified. A societal perspective implies identifying all kinds of resource utilization irrespective of who pays for the resources. If a health care provider perspective is applied, then resource utilization paid for by the patient is not relevant	3	2	Health care registers, RCT's with resource utilization data, reimbursement databases, micro-level costing studies/ABC-costing studies	Guidelines for economic evaluation of Health Technologies: Canada, 3 <sup>rd</sup> edition, 2006, Guidelines for Pharmacoeconomic Evaluations in Belgium, 2008		3
E0002	Costs and economic evaluation		What amounts of resources are used when delivering the assessed technology and its comparators (resource use measurement)?	For all types of resource utilization the amounts of resources used when delivering the assessed technology as well as when delivering the comparator technologies must be measured	3	2	Health care registers, RCT's with resource utilization data, reimbursement databases, micro-level costing studies/ABC-costing studies	Guidelines for economic evaluation of Health Technologies: Canada, 3 <sup>rd</sup> edition, 2006, Guidelines for Pharmacoeconomic Evaluations in Belgium, 2008		3
E0003	Costs and economic evaluation	Unit costs	What are the unit costs of the resources used when delivering the assessed technology and its comparators?	Ideally unit cost estimates should be (proxies for) opportunity costs. By the opportunity cost is understood the (lost) health gains that could have been achieved from an alternative technology, which, however, cannot be introduced or retained, because the resources e.g. manpower, are used on the new technology. Market prices are often used as proxies for opportunity costs.	3	1	Market prices, companies, hospital accounting systems, reimbursement databases, micro level costing studies/ABC-costing studies	Guidelines for economic evaluation of Health Technologies: Canada, 3 <sup>rd</sup> edition, 2006, Guidelines for Pharmacoeconomic Evaluations in Belgium, 2008.		2
E0004	Costs and economic evaluation	Indirect Costs	What is the impact of the technology on indirect costs?	Indirect costs include costs to society of lost production. This can be due to patient's temporary absence from work due to illness, reduced working capacity due to illness and disablement, or lost production due to an early death	2	2	The data are available from different registers e.g. register on sick leave, sickness allowance, patient administration systems/ clinical databases, earlier studies, cost diaries.	Kristensen 2007	Overlap with societal domain.	2
E0005	Costs and economic evaluation	Outcomes	What are the incremental effects of the technology	The calculation of an incremental cost-effectiveness ratio requires the estimation of the incremental	3	2	Estimation of the incremental effects can be based on		Overlap with effectiveness domain	3

			relative to its comparator(s)?	effectiveness/utility/benefit of a technology relative to its comparator(s).			information provided in the 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 (amongst others)			
E0006	Costs and economic evaluation	Cost-effectiveness	What is the incremental cost-effectiveness ratio?	<p>The result of the economic analysis will most often be an incremental cost-effectiveness ratio eg. costs/QALY if quality-adjusted life years is used as the main outcome indicator. The incremental cost-effectiveness ratio does not in itself determine that a technology is desirable. Decision makers need – implicitly or explicitly – to weigh the benefits of a technology against the costs. The concept of a cost-effectiveness threshold is one way of expressing decision-makers willingness-to-pay for health benefits.</p> <p>If other types of economic evaluation is chosen, eg. cost benefit analysis, other types of measures are used to express results of the analysis, but most current economic analysis within HTA's are done within the cost-effectiveness/cost-utility framework</p>	3	1	Sources of data used are specified under relevant issues under domains safety, effectiveness and costs. The ICER estimate might result from the economic model, using inputs from the safety and effectiveness domain.		In addition to the resource utilization and unit costs specified below the economic evaluation uses information from all types of outcomes specified under the domains safety and effectiveness (mortality, morbidity, HRQoL etc.)	2

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# *Ethical analysis*

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## **Domain description**

### *Definition*

Prevalent morals, values and behavioural models of the society relevant for health technology assessment are considered in ethical analysis. These values, moral principles and social rules (norms) form the basis of social life as well as national laws and consequently it is important to understand them. These factors play a key role in shaping the context in which health technologies are used. The moral rules of the society reflect the values of the society and the values may be weighted differently in various societies. Evident cultural (e.g. religion) and economic (e.g. gross national product) differences have also a major impact on the moral value of the consequences that the implementation of a technology can have. In the context of HTA, ethical analysis is useful in examining the context for technology use, but also in highlighting that HTA is a value-laden process, and should not be considered as a purely technical tool for maximising the health-economic benefits of technology.

### *Place and significance of ethical analysis*

Within an HTA project the ethical analysis appraises the ethical questions raised by the technology itself and by the consequences of implementing / not implementing a health technology as well as the moral and ethical issues that are inherent in the HTA process. Although ethical analysis may be practically approached as a separate domain of the HTA process, moral issues are relevant to all HTA domains and the methods of ethical analysis should take this into account. The ethical analysis should be performed as an integral part during the entire HTA process. It is not a "one session" task. Instead, the various topics and issues described in the assessment element have to be dealt with in different phases of the assessment process. The analysis starts by identifying the technology specific ethical questions and ends in the formation of an HTA report that integrates the results of ethical analysis in such a way that the report can be used for its ultimate purpose: to assist decision making.

Appraising evidence and making decisions on the use of health care resources is never a straightforward, value-free technical process. Moral and social values and various consequences of implementing a new technology play an important role throughout the process and influence the final decision. For example, the choice of certain evaluation criteria and their weighing reflect the underlying values. An ethical analysis aims to provide thorough understanding of value-related aspects that need to be taken into account during the HTA and in the decision making process. Values are inseparable from HTA, so the question is whether to address them explicitly or implicitly. The relative weight placed on the ethical analysis and the selection of methods depends heavily on the technology being evaluated. In general, the more "extraordinary" the technology appears the more emphasis should be placed on the ethical analysis. Such situations arise e.g. when

the technology presents new, severe or fundamental value conflicts, or challenges everyday norms or beliefs. Methods and significance of integrating ethical analysis in HTA have been developed and actively advocated in recent years by the INAHTA ethics working group, whose work has greatly benefited this paper (Andersen et al 2005).

HTA organisations differ in their resources and mandate for decision-making: while some only provide synthesis of evidence, others conduct appraisal of evidence and formulate recommendations or produce clinical practice guidelines. Hence the available methods, weight and ways of reporting an ethical analysis might vary accordingly. For example, the more guiding authority the HTA organisation has, the more weight should be devoted to a balanced explication of the normative valuations underlying the recommendations. If the HTA organisation is clearly separated from decision-makers, it may be enough to describe the different values, attitudes and arguments that should be considered by the decision-makers. The “first” ethical question – which topics to conduct a HTA on – might also be outside the scope of some HTA organisations. Furthermore, a successful integration of ethical analysis into the HTA process depends on recognising its importance within the entire HTA organization: analysing ethical aspects should be conducted and developed through the entire HTA organization, and not as an add-on to selected HTA projects (ten Have 2004).

The ethical analysis is a natural place to go beyond the limits of the PICO approach (patients, intervention, comparison, outcomes, see chapter "Effectiveness"). Strictly applying the PICO model to ethics implies that the comparison technology is ethically problem-free and that, if there are no ethically relevant differences between the technologies, applying the new technology is equally ethically problem-free. As it is unlikely that a thorough ethical analysis has been conducted on the comparison technology, it is important to consider also this issue – in order not to overlook essential moral issues only because they also affect the comparison technology.

Integration of ethical analysis may take various forms in HTA organizations. Some methods align well with the more traditional approach to conducting HTA, e.g.: hiring a bioethicist to conduct a separate chapter on ethical analysis, or conducting meetings for HTA researchers to reflect on the issues raised by their HTA project. Other initiatives are more challenging to the traditional HTA culture, e.g. developing “interactive” or “constructive” HTA processes that involve stakeholders’ participation.

## *Ethical analysis of diagnostic technologies*

This chapter discusses the differences between ethical analysis of diagnostic technologies and of medical and surgical interventions. The assessment elements that have been reformulated to suit diagnostic technologies, but otherwise this ethical analysis chapter is identical to the intervention model.

The ethical analysis acknowledges the value-ladenness of the whole HTA enterprise (in addition to analysing the ethical aspects of the technology itself and its implementation). Thus HTA of diagnostic technologies is morally acceptable so far if these technologies have practical consequences which are in accordance with the general values of HTA (most importantly, improving health). Ethical analysis, like social and organisational domains, emphasises the context in which the technologies function. Ideally, therefore, diagnostic technologies are approached and analysed similarly to therapeutic interventions.

In practice, assessing diagnostic technologies only as interventions is rarely possible. Direct trials of diagnostic technologies are rare, as they are costly, time-consuming, not required for licensing

purposes and arguably not even always necessary for establishing the clinical effectiveness of a new diagnostic technology (Lord et al., 2006). This makes acquiring sufficient knowledge of all implications (clinical, social, organisational, and ethical) of diagnostic technologies even more challenging than for therapeutical interventions. Thus diagnostic technologies can be assessed at several levels of the care process that link the technical test to the desired health care outcome. For example: the technical quality of test information; information on diagnostic accuracy; effects on the physician's diagnostic thinking; effects on patient management plans; change in patient outcomes; and finally societal costs and benefits (Fryback and Thornbury, 1991). When the final outcome can not be (feasibly) directly assessed, key questions in assessing diagnostic tests become a) which of the surrogate endpoints can be assessed and b) how reliably this surrogate point can be linked with the final, desired outcomes ("linked evidence") (Lord et al., 2006, MSAC 2005). This is analogous to analysing interventions with surrogate endpoints, like blood pressure instead of mortality, with the exception that diagnostic knowledge as such may have value to people, and may lead also to different kinds of implications to many stakeholders.

The value and consequences of the information, which may be generated by the same test and consist of identical results may be very different depending on the context the diagnostic test is applied in and the purpose of its application. The same diagnostic technology can be applied to healthy people in search for a yet asymptomatic target condition or for a risk factor increasing for developing a target condition, which is referred to as "screening". On the other hand, it can be applied to symptomatic patients for the verification of a suspected target disease, for grading its severity or for ruling out other conditions, which is in a narrower sense referred to as "diagnostic testing". Also, the boundary between screening and diagnostic tests is sometimes blurred, for example in the case of opportunistic screening where the population taking the test may become selected on different grounds.

Diagnostic tests are increasingly being marketed to asymptomatic people for ruling out diseases, evaluating risks or investigating genetic predispositions. This increases the likelihood of inappropriate uses of tests and of their unintended consequences. The information provided by some tests (like genetic tests) may also affect other people (who have not consented) than the one tested.

The need and weight placed on the ethical analysis thus differs greatly between diagnostic technologies, and for the same technology depending on the purpose and context of its use. A (new) test that targets for the same biomarker than the one it intends to replace but does so with better specificity, sensitivity, safety and lower costs is more likely to be unproblematic than a new, risky technology for a previously undiagnosable disorder.

All the argumentation above also serves to emphasise the importance of conducting ethical analysis of diagnostic technologies together with the other domains of assessment and content experts.

## **Specific questions to consider when analysing diagnostic technologies**

### **1) What is the aim of the diagnostic test?**

This may have moral implications. Different aims can be, for example:

- Guiding further (invasive) diagnostic strategies
- Guiding treatment by confirming or excluding disease
- Grading severity in order to adjust or time intervention

- Patient (or relative) reassurance by lowering the probability of or excluding a disease
- Physician reassurance
- Predicting risk, susceptibility for some disease or condition (in patients or in relatives, or in occupational medicine setting)
- Medicolegal purposes
- 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 which expect a better management of their condition as a consequence of the test.

## **2) What kind of roles the diagnostic technology will have, with respect to other diagnostic tests?**

Within established diagnostic pathways a new diagnostic test theoretically can have three different roles: replacement, triage or add-on (see accuracy domain for definitions). The intended and actual roles of technologies may, however, differ. Thus, it is essential to try to predict whether the new test will contribute in a relevant 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 befall on new populations? How likely it is, 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 safety domain). The direct harms of the test (mostly physical e.g. infection, injury, radiation) are easily grasped as risks, although for many diagnostic procedures direct risk is considered almost negligible (e.g. tests performed on fluid samples, ecography, etc.). Apart from direct risks, diagnostic tests are often perceived as harmless, “information only” issue. This perception ignores the consequences that the test results have, specially the consequences of false positive and false negative results. Positive test results may initiate a chain of further diagnostic measures and/or treatments which usually have higher direct risks than the initial test, exposing the healthy individual (e.g. the false positive) to additional unnecessary risks. On the other side, false negative results may cause delays or even withholding of an appropriate treatment, this unnecessarily prolonging suffering or reducing example survival chances. Thus, the starting point is that more diagnostic tests produce more risks, and it is the benefits that must be proven. In order to balance harms and benefits, not only the direct risks but also the consequences of all four possible tests results (FP,FN,TP,TN) should be known and understood. The central question is who will do this balancing, how and on what grounds? Respecting individual autonomy, for example, would require the discussion of all treatment possibilities already before taking a diagnostic test. This is especially problematic when investigating the “worried well” group of patients who may have little objective risk factors for the current condition but who want the test. There is a temptation to use a diagnostic technology “therapeutically”, to confirm health in order to decrease worrying (e.g. with a reassurance aim).

Second, diagnostic tests may change care on ways that are difficult to foresee. Diagnostic tests are crucial parts of care pathways and treatment processes. A diagnosis, or a positive triage test, often has moral and practical consequences in requiring further tests, treatments or other modes of care. The latter being of particular importance, if the condition diagnosed is untreatable (e. g. the genetic test for Huntington`s disease.) Thus increasing diagnostic tests alone may lead far-going changes in the requirements placed on health care systems, and also on individual patients and professionals. This creates also challenges for assessing the optimal regulation needed for diagnostic technologies.

Third, diagnostic tests may change the way we see diseases and illnesses. A diagnostic technology may not become a pure replacement of an existing test especially if the new test is substantially different from the old one (e.g. different biomarkers for the same disease, genetic test instead of biochemical markers, imagining instead of laboratory tests). However, even a “better but otherwise similar” version of an older test (i.e. one that detects the same diagnostic marker somehow better) may allow for totally new uses of the test by, for example, allowing earlier, cheaper or less risky diagnoses. This may shift the diagnosed population towards milder cases (increasing prevalence) but may change the diagnosed population in also other ways. This, in turn, may require different therapeutic approaches – and thus also new effectiveness studies. In the long run, new diagnostic possibilities may facilitate change of public health priorities, diagnostic criteria and even views of diseases and conditions. For example, a laboratory test for a psychiatric disorder might fundamentally change the way the disorder is perceived potentially challenging current therapeutic approaches. A further mechanism for this is that diagnostic technologies are often applied in a dichotomous way (a disease is present or not) even if the phenomena measured is continuous (for example, seeing hypercholesterolemia as a dichotomous disease). There are risks of medicalisation, lowered treatment thresholds and increased costs with diminishing returns. (Fischer & Welch).

Fourth, diagnostic technologies tend to obtain substantial symbolic value (for example, genetic tests and advanced imaging technologies like PET, MRI and ultrasound for prenatal screening). These tests may have profound consequences on individuals` self-image and behaviour. In addition, this symbolic value may also to influence the evaluation, demand and practical application of these tests in a manner that may challenge justice in their distribution (e.g. the tests are not used for those with largest expected health gains).

Fifth, diagnostic test information may be of different value to different stakeholder groups. Information on contagious diseases and other health conditions, and the results of predictive (genetic) tests are not only of interest and importance for the patient and the treating physician. Besides relatives of the tested person whose health and life planning might be influenced by test results, also insurance companies, employers and even public health officials can have an interest in diagnostic information. It is a moral issue to whom diagnostic test information must and may be communicated. Along with this issue goes the danger of “labelling” a healthy person as unhealthy by communicating predictive test results.

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

First, the proper end-points for assessment must be determined. Issues above will help on this. Endpoints may be, for example

- Technical accuracy
- Diagnostic accuracy
- Reduced risk / increased safety

- Diagnostic impact
- Therapeutic impact (health improvement)
- Other patient outcome (knowledge, increased autonomy, lifestyle modification, worry)
- Organisational and economic impact
- Social impact (contagious illnesses, justice)

Often the endpoints are not reducible to one single goal, and more than one endpoint may be legitimate and expected. For example, a new test may increase safety of testing but reduce patient outcome and influence costs and social justice. This may make trade-offs between end-points morally challenging and requires value-decisions at planning, analysing and reporting stages of a HTA. Transparency on how, on what grounds and by whom this balancing is done is needed.

As discussed above, 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 positive final outcomes from implementing the new diagnostic technology. For a test intended to replace an older test, results from the accuracy studies are important for establishing the importance and focus of ethical analysis. For example, if the test is more specific with similar sensitivity it is likely only to reduce false positives, whereas a test with similar specificity but better sensitivity may change the diagnosed population in a way that is difficult to predict (Lord et. al. 2006).

Second, for assessing clinical effectiveness of diagnostic technologies, several normative and context-relative questions must be answered that correspond to questions arising when assessing therapeutic or preventive interventions. Diagnostic technologies as such are only parts of care pathways, and often only parts of diagnostic processes. Many diagnostic technologies - e.g. imaging technologies - require interpretative skills and are in practise always applied with clinical, situational background knowledge. Transferring clinical effectiveness results from one context to another may thus be difficult.

Third, assessing accuracy raises some normative issues that are most specific to diagnostic technologies. How accuracy is best assessed depends on the role of the technology, and different methods may be required based on the answers to questions above.

-Are the accuracy measures chosen and presented neutral and suitable for the purpose of the HTA? Sensitivity and specificity are less dependent on the study population than predictive values, which on the other hand may be more clinically relevant if the populations are comparable (see accuracy domain).

-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 TP and TN and badness of FN and FP). 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 such that the point closest to the upper left corner equals “best accuracy” (see Accuracy domain), this may not be the most acceptable cut-off to use (see “context related requirements for accuracy” under the Accuracy 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. The key issue is, again, to be transparent on who will do (or has done) this balancing, how and on what grounds?

## Methodology

Although there is wide consensus, that ethical analysis should be a mandatory element of HTA, there is no generally accepted, structured method for performing ethical analysis. The methods must be tailored to suit the HTA organisation, the topic under study as well as the local culture and health care system. Local variation of methods and procedures is not necessarily problematic as long as transparent documentation is provided. The locally most suitable method must be chosen to suit the resources available, HTA topic, position of the HTA organization in the health care system of the country and the competencies of those performing the ethical analysis. The relative weight placed on the ethical analysis and the selection of methods depends also on the technology being evaluated.

Identifying and defining the various methodological approaches for integrating ethical analysis into HTA has been initiated and conducted by the INAHTA ethics working group. Short descriptions of the various methodological approaches used by HTA agencies that were identified by INAHTA ethics working group and complemented by the EUnetHTA ethics working group are included next. Presenting concrete examples of how to apply these methods is beyond the limits of this document. All these emphasise the need to consider issues extending past utilitarian maximisation of (cost) benefits of technology.

## *Casuistry*

Casuistry means solving morally challenging situations ("cases") by referring to relevantly similar "paradigmatic" cases for which an undisputed solution has been found (Jonsen 2001,2005, van Willigenburg 2005, Giacomini 2005).

The methodology of casuistry comprises three steps. First, the case at hand is sorted to a broad category of problems, "topics" (e. g. medical indications, patient preferences, quality of life, contextual features). Details should be described in a standardised way (who, what, where, when, why, how, by what means). Second, common sense moral rules, "maxims", related to the case are explored (e.g. "the wish of the patient has to be respected"). If the maxims are contentious, the moral principles that underlie them in the case at hand are explored. Third, the case at hand is compared with a set of paradigmatic cases on the same topic that have been solved in agreement previously. Comparing the details of the case at hand, including the underlying maxims and principles, with the details of the paradigmatic case then may suggest a solution for the current problem (Neitzke 2005).

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

In pure casuistry, cases are approached without referring to ethical principles, norms or theories. The process might resemble coherence analysis 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. (Grunwald 2004, Musschenga 2005).

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 can be conducted by one expert or by a group. It 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 these (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.

### *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. (van der Wilt 2000, Reuzel 2004, McGee 1999, Habermas 1981, Skorupinski 2000).

The iHTA process begins by asking what kind of values are at stake, whose values they are, who are the important stakeholders and what values of theirs are at stake. 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 can not, 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.

### *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. (Beauchamp and Childress 2001, Vieth 2002).

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 (Beauchamp & Childress 2001) 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 can not 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 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 (see below) or participatory methods can be useful.

### *Social shaping of technology*

The social shaping of technology (SST) approach (Rip 1995, Clausen 2004, Reuzel 2004) 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).

### *Wide reflective equilibrium (WRE)*

The WRE (Rawls 1971, 1993, Daniels 1979, 1996) is an ideal, perpetual goal of justification in modern philosophical inquiry. It is based on pragmatism and social constructivism, which claim that ethical truths can not be revealed or directly experienced, and that there are no static, fundamental a priori valid universal principles. On one hand, the normative framework of society may change over time. On the other hand, humans need stability, cognitive coherence and some degree of reconciliation of individual and social norms and values. WRE is a central methodological part of the ‘four principles’ approach, discussed above (Beauchamp & Childress 2001).

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

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

### *Examples of local approaches*

#### **AETMIS: Promoting context-specific, integrated approaches to analysing ethical issues in HTA**

At AETMIS the ultimate objective is to integrate a context-sensitive ethical inquiry right from the beginning of the HTA (Caron 2005, 2006). Several approaches were developed for different HTA needs that apply at different times in the process of HTA:

- “*Start-up*” meetings, which is an institutional process to promote context-based, ethically-informed HTA projects. These are conducted at the very beginning of selected HTA projects;
- The “*comprehensive*” ethical approach, where ethical inquiry is an integral part of the evaluative framework. This means that ethical inquiry is “active” throughout the entire HTA process. Such approach is only used for specific HTA reports (e.g. genetic testing); and

- The more traditional ethical analysis, which refers to the write up of a separate section on ethical issues in an HTA report. Such “*add-on*” *ethical inquiry* is usually performed by an ethical expert in collaboration with the assessors.

Integration of ethical analysis throughout the entire HTA process is achieved by teaming a bioethicist with the assessment team responsible for the project. The assessment team can also be advised by a technology-specific advisory committee (e.g. for genetic testing). An “*integrated*” ethical inquiry involves a reflection on value-laden choices at all levels of the HTA process, namely in: a) defining the scope of assessment, b) performing literature review and primary research to document the experience of patients and their families as well as the context of service delivery, c) establishing a framework for appraisal of technologies and modes of intervention, d) conducting the appraisal of those strategies, e) highlighting specific ethical and social issues, and f) formulating recommendations. In addition to literature review, primary research can be conducted to better document the situation in the local jurisdiction, and to explore the perspectives of different stakeholders on the various issues linked with technology use. Ethical and social considerations pertaining to technology use are also documented in a specific section of the HTA report.

### **The eclectic approach of FINOHTA**

In Finohta, each HTA report is produced in co-operation with the methodological experts from Finohta and clinical experts from health care organizations (Autti-Rämö and Mäkelä 2007). Professional ethicists are included either during the HTA or peer review process depending on the technology to be evaluated.

General and technology specific ethical issues and consequences for various stakeholders are identified during the HTA process by the content experts, through literature search and (when possible) by stakeholder hearing. For each stakeholder, a) possible consequences of proceeding with or b) refraining from the implementation of the technology (as compared with other options) are listed. Including patient representatives is an option in this process.

A repetitive exchange of opinions and weighing different values has been the core of a successful ethical discussion and when making a summary of the evaluation process. New moral issues often emerge during the HTA process and novel aspects have come up even at the final comment round. Ethical evaluation is written as a separate chapter in Finohta reports, but its main aspects are interwoven in the discussion chapter so that evidence is balanced against ethical consequences.

### **Value analysis of NKCHC**

This method is used at the Norwegian Knowledge Centre for Health Services (NKCHC) and it is based on value analysis (axiology) developed with regard to technology, according to which technology is a part of human activity that is related to values in different ways (Hofmann 2002, Hofmann 2006):

- Function (value-ladenness, e.g. visualizing extracorporeal structures by ultrasound for a diagnostic ultrasound machine)
- Purpose (primary value of technology use, e.g. knowledge gained by diagnostic ultrasound)

- Intention (secondary value of technology use, e.g. possible actions as a result of diagnostic ultrasound)
- Intention (social values attributed to technology, e.g. social and professional status of diagnostic ultrasound)

Values come to play in many ways with regard to the implementation and application of health technology, such as:

- general moral issues (consequences, autonomy, integrity, human rights, dignity),
- issues related to stakeholders (professionals, users, industry, patient organisations, assessors),
- issues related to methodological choices (end points, level of evidence)
- issues related to technology assessment (selection of technology to be assessed) (Hofmann 2005a)

A Socratic approach has been applied in this framework through a set of questions which are applied to highlight the value issues at stake in the different areas. (Hofmann 2005b) In the Norwegian context the method has been normatively open, i.e. the value analysis has not resulted in explicit normative advice, but only outlined the important normative issues. This restrictive use is due to the context and not due to the method.

The method has been applied to a series of HTA reports by the NKCHC, such as proton therapy, treatment of CFS/ME, intracytoplasmic sperm injection, palliation of cancer patients, transfusion versus other methods at blood loss, effects of snuff use, methods for age estimation in asylum seekers, methods for removing amalgam fillings, benzodiazepines treatment for drug-dependent subjects, palliative surgery for cancer patients, and use of hemopoietic stem cells from cord blood. As the technologies are different, so are the values involved. Accordingly, only a subset of the questions is applied in each HTA.

### *The “triangular model” for ethical analysis based on human person - centred approach*

The triangular model is centred on a substantial conception of human person. It considers the man as reference-value in the reality, around which all the ethical judgements are coordinated. Based on a cognitivist approach to the ethics, this model considers that it is possible to get some truths, concerning man and his/her praxis, recognizable by everyone through a rational activity. (Sgreccia 2007).

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

This model highlights a triangular connection between bio-medicine, anthropology and ethics, settled on two levels: the explanation of a certain topic (descriptive step), followed by a normative phase, in which we can get conclusions within a debate of the meta-empirical perspectives i.e. relating to the steps 2 and 3 described above. It is evident that such an ideal process needs all three theoretical steps in order to be possible.

This model presumes a normative framework for ethical analysis (Sacchini et al. 2005, Sacchini & Refolo 2007). It 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 (Sgreccia 2007).

### *The process of producing the core of ethical analysis*

For each HTA project *a person* within the HTA team needs to be defined to be *responsible for facilitating and reporting the ethical analysis*. For a successful ethical analysis, it is necessary that it is always done together with the content experts and is not seen as an add-on that can be conducted by separate ethicists alone. A purely philosophical approach may ignore the broader context in which the ethical and moral arise. Ethical analysis is an ongoing process that lasts throughout the HTA project. Ideally, many of the ethical and moral issues should be considered early on while analysing other aspects of the technology and, vice versa, the ethical analysis is dependant on the results and insights gathered for the other domains. However, if the only alternative is to do an "add-on" ethical analysis (for example, by asking an ethicist who is not involved in other domains to answer the questions alone) this is most likely better than no ethical analysis at all. For clarity, within HTA the reflection of ethical aspects relates to two broad areas:

- a) Questions related to the HTA process (selection of topic, outcomes, methods, evaluating the importance of ethical analysis and planning it)
- b) Questions related to implementing or not implementing the technology

The choice of methods to conduct a formal analysis of ethical aspects depends on a number of interacting factors:

- a) The type of technology being assessed. Technologies with strong "prima facie" moral implications (like genetic testing or aggressive cancer therapies in children), technologies concerning diseases with strong interest groups involved (for example cochlear implants) or other "extraordinary" new technologies that appear to challenge commonly held values or everyday beliefs (like home care nurse robots) require more emphasis on the ethical analysis.
- b) The role of the HTA organisation and the intended purpose of the assessment especially in relation to national decision making and bodies providing guidance;
- c) Prevailing methodological expertise and experience with ethical analysis.

d) Time and resource constraints for the assessment.

Every HTA process should be performed considering general moral issues that have been stated in the introduction chapter. Preferably, ethical considerations should be introduced as early as possible in the process. The person responsible for the ethical analysis should ensure that the moral issues are considered by the whole group during the entire process.

## *Defining the focus of the overall assessment*

The focus within the topic, the specific questions to be answered, the study inclusion criteria and the primary outcome points for the analysis of the consequences of implementing a technology (e. g. efficacy, safety, effectiveness, cost implications) are defined by the entire working group. These choices are value laden and they need to be carefully scrutinized before proceeding to literature review as they can have a major impact on the content and conclusions of the HTA report.

It is important to consider, whether there are issues of potential ethical significance related to the disease or health problem as such – i.e. even before any factual considerations about the effectiveness or consequences of implementing / not implementing a technology. For example, some conditions might be considered “self-inflicted”, and issues related to embryos are likely to raise fundamental questions about the value of life and autonomy, and conflicts of interest (interest of embryo, of mother, of father).

## *Identification of all stakeholders*

The perspective of all relevant stakeholders should be involved in the process. The view of the stakeholders is optimally acknowledged already during the process (e.g. stakeholder hearing meetings) and not first during the external peer review process. It is usually fairly easy to identify the primary stakeholders for each technology - patients, clinicians, patient organizations, industry, providers etc. It is as important to identify also those stakeholders who can be indirectly affected if the technology/change is being implemented (e.g. change in the use of resources at emergency units may have a large impact on other patient groups); this may include the HTA agency itself. 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.

## *Answering the core set of questions*

Ethical evaluations can be conducted very differently depending on the resources in the HTA organization and the technology in question. It can, however, be conducted in a transparent way so that process is clearly defined and the objectivity of the analysis can be acknowledged.

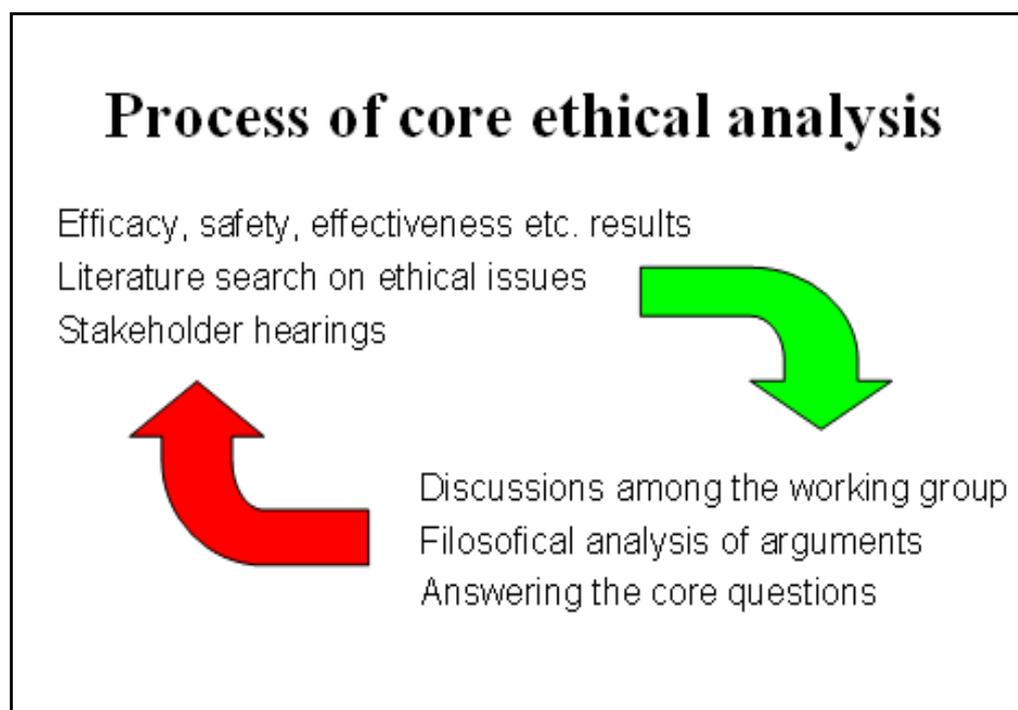
The core set of questions to be considered within an ethical analysis are presented at the end of this chapter. This approach is strongly influenced by the work of Hofmann (see above Value analysis of NKCHC). All questions are not relevant for all technologies and thus do not need to be answered every time. Nor are the questions in order of importance, or need to be answered in the same order as presented. Some issues deal with direct consequences of the implementation (simple facts, e.g. can the technology harm the patient). Many issues deal with questions that need careful consideration that will provide a thorough overview of the value-laden aspects that need to be taken into account when deciding on implementation (e.g. balance between benefit and harm). A minority of issues cover areas that lead to clear conclusions (e.g. whether legislation is fair and adequate).

The evaluation of the principal questions about the technology and consequences of implementing/not implementing a new technology are based on the information received from following sources:

- The ongoing assessment of efficacy, safety, effectiveness and cost-implications.
- Discussions among the working group. Discussions with experts are effective in identifying key issues and topics related to the questions, and help in planning the rest of the information gathering. Structured questions presented in the issues list need to be discussed but additional content specific ethical aspects may also be identified during the discussions.
- Literature search focused only on the technology in question may seldom give access to articles relevant to the ethical evaluation. A natural starting point is to include keywords related to ethics to the literature search needed to cover the other areas of the HTA process, to do a hand-search of published HTA reports (ethical considerations are often integrated in the reports), and an internet search for reports, proceedings and books etc. To perform a systematic literature review that will cover all of the ethical and moral issues identified during the process is, however, challenging. Ethically relevant issues are identified during the entire HTA process, and the literature searches thus commonly repeated when new ethically relevant issues are identified. The extended literature search should not be focused only on the technology in question but cover other related technologies with similar ethical challenges (see casuistry above). The detailed literature search should include all relevant sources on ethical aspects of the technology in question. A suggestion for databases and MeSH terms that can be useful has been identified by Droste et al (Droste et al 2003)
- Qualitative analysis of the expectations and fears of various stakeholders may reveal questions that cannot be identified by the content or methodological expert group or from the literature review. This information can be reached through stakeholder meetings or conducting primary studies.
- Philosophical analysis of the logic and coherence of the argumentation.

Information for answering the questions is gathered from several sources, and using several procedures. There is no clear starting point, but the information gathering can be seen as circular process where previous phases identify new needs and questions then answered by other sources (Figure 1). Thus, it may be useful to repeat some phases following new insights.

**Figure 1. Process of ethical analysis**



### *Presentation of the ethical analysis and evidence in a balanced fashion*

The morally relevant issues and moral conflicts have to be synthesized and reported transparently so that they can be considered when deciding upon implementation of technology. No single solution to every moral problem exists; neither is it possible to list moral issues according to a commonly agreed weighted value. Answers to the core set of issues may also reflect the wide variety in personal morals and values within the society. The methods described above in the methodology part can be useful tools for eliciting information, but they are probably more useful for analysing, processing and balancing the information and insights gathered during the ethical analysis. The core set of questions is intended especially for identifying ethically relevant issues.

The synthesis of ethical analysis has to be performed in an open way so that the interests of various stakeholders are kept as "unweighted" as possible, or the weighing is done transparently i.e. describing the procedure and participants of the analysis. Ideally, the decision on "whose values are to be weighted" need to be in the hands of the decision makers. The decision makers can be different within the same country between technologies and / or institutions and also between countries. Thus the ideal way to present the synthesis of the analysis may vary accordingly.

Ethical analysis on the consequences of implementing/not implementing the technology may be handled using an open framework (Autti-Rämö and Mäkelä 2007). The possible consequences of proceeding with or refraining from the implementation of the technology can be listed separately for each stakeholder in an open table as the answers for various parties may differ largely (table 2). The identified issues are not valued-weighted against each other but the table offers a transferable list of aspects that need to be appreciated in the final decision making process.

**Table 2. Example of 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				
Care Providers				
Other patient groups within the specialty				
Primary Health care providers				
Secondary Health care providers				
Tertiary health care providers				
Payers				
Society				
Producers/Industry				
Decision makers				
HTA organisation				

It is important to identify also those areas where values may differ significantly between various professions (eg. attitude towards the care of patients with nontreatable diseases or towards treatments of extreme cost). It is important that areas of ethical disagreement are clearly stated in the final document.

Ethical analysis is usually reported as a separate chapter, in order to assure transparent reporting of value issues. The ethical implications of implementing or refraining from the implementation of technology need, however, to be discussed in a balanced way so that the health policy makers have a wider view on all possible consequences of their decision. The open framework as presented in table 2 can be a helpful tool in this process. The decision to implement a new technology requires careful decision on the balance between benefit and harm, cost-effectiveness, reallocation of resources etc. Discussing the context-specific moral issues within the respective chapter (e.g. effectiveness, safety, and costs) may thus also help the decision makers to identify various scenarios and find the best for the common good.

### *Transferability of ethical analysis*

The ethical analysis and its outcome have to be described in an open way in order to judge their transferability. Many of the ethical implications are common to various nations but some value laden issues are likely to be country specific. Analyses relating to ethical principles, coherence or paradigmatic cases are likely to be more easily transferable than argumentation based on interactive approaches relying on local values, stakeholder attitudes and available health care resources.

### *Overlap with legal and societal evaluation*

Ethical analysis can not be separated from the evaluation of legal and societal aspects. These domains overlap the ethical analysis, though the angle of evaluation may differ. The legal framework forms a basis for professional ethics (e.g. abortion, prenatal screening, and euthanasia).

The societal consequences of implementing a technology may differ largely from those of primary outcomes at patient level (f.i. 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.

## Assessment elements

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optiona	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status
F0001	Ethical analysis	Principal questions about the ethical aspects of technology	Is the diagnostic technology a new, innovative technology,, an "add on" to a standard mode of care, intended as triage to other tests or a replacement of a standard?	The consequences of totally new types of diagnostic technologies are likely to be more difficult to predict than the consequences of replacing an old technology (for individual values, attitudes and expectations as well as for health care systems). Novel, innovative diagnostic technologies – tests for currently orphan disorders, new markers or new diagnostic approach for disorders with a currently established diagnostic path- may have far-reaching consequences on health care. They may require more emphasis on ethical analysis than replacing a test already in use with another testing the same diagnostic marker, although the literature and research base on the topic may be narrow.	3	2	Literature search Expert opinion	Mitcham 2004	technology description, organizational	Core
F0002	Ethical analysis	Principal questions about the ethical aspects of technology	Can the technology challenge religious, cultural or moral convictions or beliefs of some groups or change current social arrangements?	It is important to identify those groups within the society for whom the use of the technology may pose serious challenges due to their beliefs, convictions or current social arrangements (e. g. triple test during routine pregnancy examination in cultural groups that will not tolerate abortion). Identification of these conflicts and finding other, acceptable possibilities in these groups is important. Identifying the conceptions behind the beliefs and values may help put them in perspective, when considering the overall acceptability of the technology. Technology may also change generally accepted social arrangements by challenging traditional conceptions (e.g. preimplantation diagnostics and the concept of "design babys").	3	2	Literature search Expert opinion Stakeholder hearing	Ogletree 2004	Social	Core
F0003	Ethical analysis	Principal questions about the ethical aspects of technology	What can be the hidden or unintended consequences of the technology and its applications for different stakeholders.	In addition to intended use, the technology may be used for other purposes and have side-effects in addition to those following from the intended use. Diagnostic information often necessitate further action, so diagnostic technologies may have large impact on the health care processes and systems and on individuals. They may even change the concepts of disease and diagnosis. Unintended consequences are obviously difficult to predict, but the intended purpose and uses of the technology should be evaluated against the likely uses and consequences of the technology in the real world. New technologies tend to lead to new areas of inventions and give rise to new ethical questions (e.g. IVF and development of	3	2	Literature search Expert opinion Stakeholder	Ogletree 2004, Hofmann 2005b, Hofmann 2002b		Core

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optiona	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status
				genetic testing has led to questions of preimplantation genetic diagnostics (PGD). As presymptomatic and prenatal genetic tests have become available, the health care system has to be prepared to handle moral issues raised by true positive and false negative findings.) 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)						
F0017	Ethical analysis	Questions about effectiveness and accuracy	What are the proper end-point for assessment and how should they be investigated?	For diagnostic tests, clinical effectiveness should ideally be directly investigated, but this is not always fully possible so other endpoints may have to be used. In addition, diagnostic tests may have several aims (e.g. those related to knowledge without expected health effects). The acceptable and feasible endpoints (possibly several) for assessing diagnostic technologies must be carefully considered early in the analysis. The context-specificity of diagnostic technologies must be especially considered; for example, results of diagnostic technologies are rarely in practice interpreted without knowing the clinical and organisational situation of the patient, some technologies require extensive interpretative skills, and the practical consequences of diagnostic tests will depend on the population tested. The importance of context relates to what kinds of studies are deemed acceptable.	3	2	Other domains of analysis: accuracy, safety, effectiveness Expert opinion			
F0018	Ethical analysis	Questions about effectiveness and accuracy	Are the accuracy measures decided and balanced on a transparent and acceptable way?	Are the accuracy measures chosen so that they accord with the purpose of the HTA? How and by whom are cut-off values decided? How and by whom has balancing sensitivity and specificity been done? This should be done considering the moral value of different results – for example, high specificity is required if false positives have serious consequences.	3	3	Other domains of analysis: accuracy, safety, effectiveness Expert opinion			
F0004	Ethical analysis	Autonomy	Does the implementation or use of the technology challenge patient autonomy?	Patients have in most cases a right to autonomy, i.e. right to be self-governing agents. This requires the right to decide about things of importance to oneself on one hand, but also relevant information and a capability to understand the information, consider it in relation to personal values and decide accordingly. Thus, technologies and health systems may interfere with patient's right to autonomy directly or indirectly by influencing the decisional capacity. For example, a technology that does not allow itself to be understandably explained to the patient (e.g. diagnostic procedures for dementia) is potentially problematic, as are treatments that require patients to behave in a certain way (e.g. to abstain from	3	2	Literature search Expert opinion Stakeholder hearing	Miller 2004		Core

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optiona	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status
				alcohol prior to investigations). The practical challenge with diagnostic tests is that in order to be fully autonomous, the patient should understand not just direct risks of testing, but also all alternatives following different test results.						
F0005	Ethical analysis	Autonomy	Is the technology used for patients/people that are especially vulnerable?	The right and justification to use the technology for persons who are vulnerable (critically ill or have otherwise reduced decision making capacity, like children, mentally retarded, patients that have due to their illness/state limited decision making capacity, pregnant women etc) has to be clarified. 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 can not give informed consent to it?	3	3	Literature search Expert opinion Stakeholder hearing	Miller 2004		Core
F0006	Ethical analysis	Autonomy	Can the technology entail special challenges/risk that the patient/person needs to be informed of?	Is the common professional practice of discussing the technology with patients enough, or is special care needed with this technology? Should the patient be explicitly informed, for example, that false positive results may lead unnecessary further investigations and treatments with serious harms? The technology to be used in life-threatening situations may have life-threatening side effects (e.g. invasive techniques). Technology used to get exact information may have unexpected severe side-effects (e.g. miscarriage due to amniocentesis).	3	3	Literature search Expert opinion Registers	Miller 2004	Safety	Core
F0007	Ethical analysis	Autonomy	Does the implementation challenge or change professional values, ethics or traditional roles?	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 virtues and principles of medical and professional ethics challenge the professional integrity of the physicians or other health care professionals. Technologies that align with professional ethics are more likely to be implemented successfully. For example, people may require diagnostic tests for many reasons, even if the professionals think them unnecessary and potentially harmful.	3	2	Expert opinion	Hofmann 2005b Medical Professionalism Project 2002	Organisational Technology description	Borderline
F0008	Ethical analysis	Human Dignity	Does the implementation or use of the technology affect human dignity?	Especially technologies that are applied for persons with reduced autonomy may violate a person's dignity (children, mentally impaired, severely ill), i.e. challenge the idea that all human beings have intrinsic moral value, and should thus not be seen as means to others ends. Labelling people may also threaten their dignity; for example predictive tests may label healthy people as sick or	3	2	Literature search Expert opinion Stakeholder hearing	Kilner 2004		Core

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optiona	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status
				otherwise less worthy; handicapped people may be labelled by prenatal diagnostics which imply that their handicap is an indication for abortion.						
F0009	Ethical analysis	Human integrity	Does the implementation or use of the technology affect human integrity?	Technology can challenge human integrity by preventing (or even tempting) people (patients or professionals) to live according to their moral convictions, preferences or commitments. This is especially important for vulnerable patient groups. Integrity can also be seen as a coherent image or identity of oneself. Thus, for example, prenatal diagnostics might challenge the integrity of people who value new life as gift; cochlear implants are problematic for those, who do not see deafness as a disability. Institutions that discourage honesty or ethical conduct more generally are detrimental to integrity (for example, systems where lying about ones health state might lead to better treatment than being honest).	3	2	Literature search Expert opinion Stakeholder hearing	Kilner 2004		Core
F0010	Ethical analysis	Beneficence/ nonmaleficence	What are the benefits and harms for patients, and what is the balance between the benefits and harms when implementing and when not implementing the technology? Who will balance the risks and benefits in practice and how?	The decision to implement new diagnostic technology requires careful decision on the balance between benefit and harm, cost-effectiveness, reallocation of resources etc. When this decision has been made on the system level, the decision on individual patient level rests on both the professional who offers the technology and the patient who autonomously accepts the use of technology in her/his situation. The individual decision has to be based on objective information on possible benefit and risks. Risks are only justified to the extent they are needed to create benefits. If not proven otherwise, the individual patient is generally to be seen as the best judge of risks and benefits for her/himself.	3	2	Literature search Expert opinion Stakeholder hearing	Autti-Rämö 2007	safety Effectiveness	Core
F0011	Ethical analysis	Beneficence/ nonmaleficence	Can the technology harm any other stakeholders? What are the potential benefits and harms for other stakeholders, what is the balance between them? Who will balance the risks and benefits in practice and how?	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 (relatives, other patients, organisations, commercial entities, society etc.) Benefits and harms to individuals must be balanced with benefits and harms that can befall 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. 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. Changes in the availability of diagnostic tests may significantly alter the requirements placed on the health care system. Table 2 in the process description can be used to describe benefits and harms.	3	2	Literature search Expert opinion Stakeholder hearing	Autti-Rämö 2007 Beauchamp and Childress 2001	Organisational Social	Core
F0012	Ethical	Justice and	What are the	A new intervention may require reallocation of human resources,	3	2	Literature search	Sterba	Cost-effectiveness	Core

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optiona	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status
	analysis	Equity	consequences of implementing / not implementing the technology on justice in the health care system? Are principles of fairness, justness and solidarity respected?	funding and training. A large reallocation of resources may seriously jeopardize other patient groups (e.g. 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 for all stakeholders? Can the technology be applied in a way that there is equal access to those in equal need? How can this be guaranteed? Could potential discrimination or other inequalities (geographic, gender, ethnic, religious, employment, insurance) prevent access? 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. Are specific safeguards needed? How will possible caregivers' burden and well-being be influenced? Potential inequalities and discrimination should be justified.			Expert opinion Stakeholder hearing	2004 Daniels 2001	Organisational Social	
F0013	Ethical analysis	Justice and Equity	How are technologies presenting with relevantly similar (ethical) problems treated in health care system?	Clearly presenting how relevantly similar technologies 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 project. The similarity may be, for example, of medical, technological, economical, ethical, social, organisational or legal nature.	3	2	Littrature search Expert opinion	Hofmann 2005b		Core
F0014	Ethical analysis	Rights	Does the implementation or use of the technology affect the realisation of basic human rights?	Human rights exist both in ethics and legislation, most notably in the United Nations declarations and related statements, like the European Council Biomedicine convention. Basic human rights are universal and consider the most important goods, protections and freedoms. Classes of rights are civil and political rights, social rights, minority and group rights and environmental rights. For HTA, perhaps the most relevant are the rights to equality, non-discrimination, safety, adequate standard of living and health care. For example: -Right to life, liberty and security of person. -Right to a standard of living adequate for the health and well-being of himself and of his family, including medical care and necessary social services, and the right to security in the event of sickness, disability or old age -Right of the child to the enjoyment of the highest attainable standard of health and to facilities for the treatment of illness and rehabilitation of health. For diagnostic tests, issues of access to tests and treatments as	3	3	Literature search Law, rules and regulations Expert opinion Stakeholder hearing	Marks 2004	Social Legal	Core

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optiona	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status
				well as labelling and potential discrimination of diagnosed persons may be relevant issues.						
F0016	Ethical analysis	Legislation	Is legislation and regulation to use the technology fair and adequate?	Technology may lead to ethical problems that make current regulation inadequate. Diagnostic technologies are commonly differently regulated than treatments, especially medications. Ethical reflection is needed when considering what kind of regulation is needed. This consideration is done on the basis and in combination with the legal domain. Emphasis should be put on considering the ethically relevant aspects and consequences of current law, needs for legal regulation that have arisen from the ethical analysis, and a global assesment of the adequacy of the legislation based on all available information. For example, who has a right to get the results and for what purposes?	2	1	Law, rules and regulations Stakeholder hearing Expert opinion	Capron 2004	Legal	Borderline

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# *Organisational aspects*

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## **Domain description**

In the scope of health technology assessment, organizational issues have not been the visible ones, while the greatest focus has been pointed at the clinical aspects of health technologies (Banta 2003, Draborg 2005). However, organisational aspects are a significant part of HTA, because the focus here is on the delivery modes of technologies. The growing focus in HTA on the delivery modes indicate a recognition that many decisions on resource allocation are made within regional health authorities, hospitals, departments, and in clinical offices, where the organisation of provision of technologies are of crucial importance. Therefore the focus on organisational aspects reflects a need to find ways of influencing the behaviour of a diffuse group of managers and health professionals (Battista, 2006). Also policymakers on the national level need knowledge on organisational aspects when making decisions on the use of technologies. HTA can contribute with analysis of e.g. management, financing and controlling issues. Including organisational aspects in HTA can contribute to clarifying challenges and barriers in implementing health technologies, since the analyses typically include considerations on the unfolding of the respective technologies in health services.

## *Definition of 'organisation'*

Organisation has been defined as a consciously coordinated social unity (Robbins 1987). An organisation has rather clear boundaries and its activities, which target certain goals, are continuous. An organisation is formed in order to assign and carry out special tasks and coordinate these tasks (Schein 1985). The elements that constitute an organisation have been defined in many ways in different approaches, for example the physical structure, social relations, technology and organisational culture. A structure of the organisation defines its assignment of tasks, reporting systems and the mechanisms of interaction and coordination. In addition, other elements of society and its culture have influences on organisation and its function. Different types of organisations exist, e.g. the profit centre organisation, the matrix organisation and the network organisation. (Kristensen 2001)

The complexity of a health care system and especially its processes complicates the assessment of organisational issues. Objectives within an organization are often compromises and they develop over time. Various objectives and criteria may exist. Due to the multiplicity of objectives, organisational HTA -analysis will be less pre-determined and more complicated than for example economic analyses and clinical effectiveness analyses. In addition, the findings are expected to be more context-dependent and less transferable than e.g. in the effectiveness and safety domains of an HTA. The choice of the areas on which the assessment of organisational aspect will be focused should be guided by the information needs of the end users of the assessment (e.g. focus areas

demanded by decision-makers at the level of regional health authorities may differ from those of a hospital manager).

Organisational aspects include the intra-organisational level, inter-organisational level and health care system level. An example of intra-organisational level is how information about the new technology is provided to the patients in the organisation. Co-operation and communications between different organisations is an example of inter-organisational level, and setting down national objectives is an example of health care system level. At these levels, besides staff and patients, there are many stakeholders e.g. payers, providers and suppliers. These groups have usually different aims and expectations of the new technology. For example patients may not accept the new technology because it is uncomfortable, or personnel do not accept it because of safety aspects, or providers do not accept it because of expensiveness.

A new diagnostic technology can replace or supplement the old technology (MSAC, 2005). It can be used to confirm that a patient suffers from a particular disease or it may be used to exclude that this is not the case. From organisational view it is interesting to find out e.g. how the new technology changes patient management.

## *Topics*

The organisational domain considers what kind of resources (material artefacts, human skills and knowledge, money, attitudes, work culture, etc) have to be mobilised and organised when implementing a new technology, and what kind of changes or consequences the use can further produce in the organisation. The organisational domain includes issues of work processes (e.g. work flow and patient flow, staff, co-operation), structure (centralisation) , management(e.g. managerial structures), and culture (e.g. acceptance).

These topics and issues are probably the most important ones, but the relevance depends on the specific technology and needs to be considered as explained in the chapter "General design". In some technology there might be other more relevant topics and issues and if such are found, the model should be amended.

Different levels of health care (local/regional/national) have been taken into account while defining the issues. Some issues are relevant at all levels (e.g. approval of a new technology) and some mostly in one level, for example issues related to the staff which affect mostly in the hospital level. In addition, different viewpoints have been noticed. There are issues related to the patients in nearly all topics.

The domain might overlap with other domains especially with the domain of current use of technology (e.g. place of the technology), with the economical domain (e.g. finance issues), with the ethical domain (e.g. acceptance and accessibility) and with the social domain (e.g. patient issues).

## Methodology

### *Health care and HTA*

Health care is becoming increasingly complex. This complexity can be seen in the organisational issues of health care. In a complex system the activities of different agents are not always predictable and actions of one agent changes the context for the other agents. Furthermore, complex systems typically have fuzzy rather than rigid boundaries. Complexity science suggests that it is often better to use multiple approaches (Plsek and Greenhalgh 2001). Through different theoretical frameworks we can understand how various organisational functions operate. For example the collaboration between public health and clinical health can be explained by structuration theory (St-Pierre 2006).

Demands on the way of organizing and delivering health services have become greater. Therefore, health service research has become well-established in some parts of Europe and North America during the last 20 years. Health services research provides answers for example to the following questions: How should services be funded? Who should receive health services? How well are services being delivered? Along with Health Technology Assessment, research of service delivery and organisation (SDO), gives answers to these questions. There is no clearly defined boundary between HTA and SDO - on the contrary, they complement one another. For example HTA can provide evidence on the cost-effectiveness of one particular intervention and SDO research would be required to determine, where the most cost-effective setting (e.g. primary or secondary care) would be for the delivery of that intervention. (Fulop 2001) Also constructive technology assessment (CTA) - first described in the 1980's - takes into account the dynamics of technology such as e.g. practice organisation and financing and patient reactions (Douma 2007). CTA attempts to influence technological design and implementation to improve the effectiveness of the technology in clinical practice. There are also other theoretical areas which can be used, such as STS (Science and Technology Studies) and ANT (Actor-Network Theory).

Usually, it will be difficult to isolate and measure the output effects of given organisational initiatives. More realistic is to describe the various process dimensions in relationship between a technology and organisational behaviour. Organisational analysis can be seen as an analytical approach that focuses on the organisational preconditions and consequences of a technology (Dacehta 2007). Analysis of organisations cannot be defined by PICO but the unit of analysis should be demarcated to fit PICO in the best possible way. The natural starting point of an analysis of change in processes will be to map the current work-flow / patient-flow. Therefore, the methods for data collections may involve qualitative methods such as interviews or observations, or quantitative methods such as surveys. (Kristensen 2001)

### *Framework*

The implementation of new health care technology necessitates changes in the work processes and structures of an organisation. However, 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 (and social) issues that are conducted in HTA. The views are 1) the diffusion model and 2) the translation model which is a version of the loose approach called co-production of technology and its context (Kristensen 2001, Latour 1987; Bijker & Law 1992; Harbes (ed) 2005).

The diffusion model bases on a linear, unidirectional conception of causality. It assumes a causal order between variables; an independent variable technology with its "effects" (impact) on organisational and other social levels. It considers technology as an exogenous and independent entity which is separate from the social or organisational. It is a given object which stands outside or above the society, its organisations and actors. It supposes that technology stays constant and that it is the same technology which is diffused and transferred from the innovator to the different users, e.g. to hospitals.

The diffusion model assumes that a health technology can "travel" through the society and have an impact on its different levels (see Latour 1987). It supposes that a technology has an inner causal power that can affect and change the individuals (micro-level), the organisations such as hospitals or health care centres (meso-level) or the national and international systems (macro-level).

The Translation model is increasingly utilized in European technology and organisation studies (Kristensen 2001). The translation model sees technology as endogenous, as a part of the organisational and use process. Technology can not be separated from the organisation and its users; it is not an independent and stable entity. The translation model implies a view that technology does not stay constant during the implementation process. This follows from the idea that human activity is a part of the technology in question.

According to the translation model, it can be asked "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." This means that a technology does not causally affect the organisation and change its social structures, but that the organisation and its work processes and social structures have to be organized so that good results can be produced from the technology. Leavitt's (1965) model of organisational change from the sixties can be seen as early steps towards the translation model, but it may give more ontological autonomy to the different elements of an organisation than the translation model defined by the actor-network theorists (Callon 1991; Law 1992; 1994). Leavitt's model illustrates the importance of aligning task characteristics (autonomy, feedback, identity), structure characteristics (decentralisation, extrinsic rewards), technology environment (access to information technology, information technology use norm, required use of information) and motivational characteristics of people working in the organisation (intrinsic rewards and job variety) in order to effectively bring about change. Technology is broadly referred to as the work performed by the organisation. (Leavitt 1965)

The definition of organizational analysis of this paper is based on the loose approach called co-production of technology and its context and especially on the translation model. Its main thesis is that a technology needs a context or a network to function. In addition to the translation model, other approaches that form the co-production approach are for example constructive technology assessment (Schot 1992; Douma 2007), the systems approach (Hughes 1983) and social construction of technology (Bijker et al. 1987).

Both organisational and administrative perspective can be used in the organisational analysis (Kristensen 2007). Administrative analysis uses a managerial perspective (e.g. decision making, co-ordination and managerial tools) and organisational analysis deals with changes in relation to the executing /producing function (e.g. organisational conditions, change processes). There may be overlapping between these two approaches. Organisational perspective rises from Leavitt's model for organisational change and administrative analysis looks at administrative and managerial

structures. In this report, we use mix of both these perspectives. Organisational analysis is used in the topics of Process, Structure, and Culture. Administrative analysis is used mainly in the topic of Management, but also in some other topics.

## *Research methods*

### **Study types**

The complexities of health problems require gathering data by using a broad spectrum of qualitative and quantitative methods. Qualitative methods are more appropriate for certain evaluation questions and purposes, especially in the stage of implementation, in which a technology is getting embedded in the management of certain conditions. Furthermore, qualitative research can contribute to HTA by offering and summarizing the perspectives, meanings, values, and interests the different stakeholders have concerning a particular technology. (Leyes 2003) For example, it has been stated that breast cancer research which includes both qualitative and quantitative methods increases understanding about the organization and delivery of services (Gagliardi 2006).

When qualitative methods are used, the data is gathered in close proximity of a specific situation. Therefore, influences of the local context are taken into account. Because of this, qualitative methods are powerful for studying the meanings of people about events, structures, processes and so on. On the other hand, qualitative research has also been resisted and called unscientific and full of bias, and qualitative empirical data are judged unreliable, subjective and difficult to replicate. (Leyes 2003).

Qualitative methods include e.g. observation, interviews, content analysis of text, documents and written records, conversation analysis, photographs, and audio- or videotapes. Qualitative research has an interpretative approach which is based on flexible methods of data gathering in order to produce understanding of complexity, detail, and context. Individual approaches include one-to-one interviews, dyadic interviews, case study analyses, the Delphi technique and complaints procedures. Group-based methods include focus groups, concept mapping, citizens' juries, consensus panels, public meetings and nominal group techniques. Validity, reliability, generalisability, objectivity, acceptability to respondents and cost has been identified as the assessment criteria of qualitative methods. (Leyes 2003, Ryan 2001)

Interviews cover a spectrum of enquiry, such as unstructured interviews, interviews based on a theme guide and focus group interviews. Questionnaire or survey methods are tools which provide data by use of questionnaires. The questions could be posed verbally or by using standard interview forms (e.g. telephone interviews) or in written form as postal questionnaires. Prospective studies aim at predicting the users' attitudes and preferences to a new technology. The aim is to create a situation which promotes or renders it possible to make predictions based on collected opinions and preferences. The Delphi method and the Future workshops are examples of the prospective method. (Kristensen 2001)

A range of instruments to measure the culture of health organizations is available, but all of them have limitations in terms of their scope, ease of use, or scientific properties. There is no simple answer to the question of the best instrument. The answer depends on how we define "culture", "measurement" and "organization". Scott et al have reviewed quantitative instruments. They found thirteen instruments with differing characteristics. These adopt either a *typological* approach, in

which the assessment results in one of more “types” of organisational culture; or a *dimensional* approach, which describes a culture by its position on a number of continuous variables. The choice of instrument should be determined by how organisational culture is conceptualized by research team, the purpose of the investigation, intended use of results, and availability of resources. (Scott 2003)

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. (Mays 2000)

## **Study framing**

After defining relevant organizational topics relevant for the technology being assessed, a theoretical perspective that fits the co-production approach has to be chosen. Identifying the research problems and questions, it has to be taken into account that organisational analysis deals with the overall policy question and the organisational set-up. However, sometimes it has to pay attention to the patient group. For example, there are differences in work processes and staff groups dealing with Multislice CT for coronary artery disease patients and cancer patients (cardiologists / radiologists).

## **Sources of information**

The first step for selecting the relevant studies is to make a systematic literature search focusing on the organisational aspects. If there are no systematic reviews or meta-analysis, primary studies should be used.

To reduce publication bias, it is recommended that a wide range of sources of information should be searched (Bidwell 2003). These should include published literature, as well as grey literature, hand searching of journals, contacting experts and scanning reference lists of relevant papers. It is sensible to allow also studies made in the context of the diffusion model to be included in the assessment of organizational issues, since the co-production approach has not been used in the HTA for a long time and there are not many that kind of studies available. However, the studies made in the context of the diffusion model should be analyzed according to issues defined according to the co-production model approach. One should consider what kind of information can these studies provide and which are their weaknesses. Organisational studies could be found in different databases. Here are listed the most important databases and other sources of information. The following medical databases are often the most important ones for the organisational domain when conducting a core HTA: Medline, Premedline, Cochrane Library, HTA, DARE, EED, TRIP database (Turning Research Into Practice) and Cinahl which includes more qualitative studies. General science publishers' databases (browsing databases) such as Emerald Library, that includes administrative studies, could be useful. Science Direct and Ebsco Academic Search Elite are also browsing databases and are useful to check, as well as full-text databases such as Pub Med Central (PMC) and Bio Med Central (BMC). Educational database ERIC and Open Access databases OAIster are sometimes useful, and also the Web of Science database which includes e.g. conference papers. Gray literature can be found e.g. in the databases of Dissertational Abstracts and of Scirus

which includes reports of hospital studies and doctoral thesis. HealthSTAR is a Mixed Content database and includes administrative and hospital surveys. Social Science databases (Sociological Abstracts, Social Services Abstracts, Social Care on line / Caredata and SocINDEX) could be informative as well as PsycInfo, but the searches are likely to find many irrelevant studies. The database of GIN recommendations is also an important source of information. Selection of which databases to use depends on the context. 'Snowballing' and personal knowledge or personal contacts are also way of identifying especially qualitative studies (Cochrane 2008).

Registers and international, national and regional routine collected statistics can provide answers to some organisational issues (See chapter Health problem and Current Use of Technology). Also conference proceedings and manufacturers are in some respect important sources of information.

When necessary, a primary research could be carried out according to the co-production approach, but it will usually be very time-consuming. There are several possibilities of the study methods to choose from, e.g. interviews, questionnaires, observation, an analysis of written material. If the resources available for the assessment project does not allow carrying out own primary research, it can be useful to consult health care professionals or other content experts.

## **Quality assessment**

It is crucial to assess the quality of studies. Interpretation of the findings of a study depends on its design, conduct and analyses, as well as on populations, interventions and outcome measures. Quality criteria for assessment of different types of studies have been created (e.g. for experimental, observational and qualitative studies). In this report the focus is on qualitative research. Whilst the nature and application of procedures to minimise bias in qualitative research may be problematic, it is desirable and theoretically possible to have a structured approach to quality assessment. In qualitative research, many frameworks including a large number of appraisal criteria have been identified, for example the quality criteria made by Popay et al, Mays and Pope and BSA Medical Sociology Group. (CRD 2001) Spencer et al. have undertaken a review of many current appraisal frameworks and checklists (Spencer 2003). At present there is insufficient evidence to inform a judgement on the rigour or added value of various approaches. Cochrane Qualitative Research Methods group is contributing knowledge and practice in this area (Cochrane 2008).

The transferability of the research identified in literature searches, will have to be assessed very carefully, since this domain is in general to be considered highly context-specific. It is possible, that in many cases, the results from the literature review, can be considered to be hypothesis generating, and be useful for planning primary research in the own context.

## **Data extraction**

Data extraction can be a subjective process and therefore the design of these forms should be undertaken carefully (Kahn, 2001). The amount of information to be extracted should be directly related to the questions posed. 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.

## **Data synthesis**

Data synthesis collates and summarizes the results of included primary studies by generating a summary of study results (Khan, 2001). In quantitative data synthesis statistical methods are used to combine the results of the included studies (meta-analysis). The most commonly used graphical approach to express the quantitative results is forest plot. In non-quantitative synthesis tabulation of study characteristics and results are used. Qualitative evidence synthesis is a process of combining evidence from individual qualitative studies to create new understanding by comparing and analyzing concepts and findings from different sources of evidence with focus on the same topic interest. There are two broad approaches that can be used to integrated qualitative and quantitative findings: multilevel synthesis (synthesis is combined) and parallel synthesis (synthesis is juxtaposed alongside) (Cochrane 2008).

## **Assessment elements**

The organisational domain consists of four possible topics: Process, Structure, Management and Culture. In each topic there are two to five issues (specific questions within the topic), together 12 issues. These topics and issues are probably the most important ones, but the relevance depends on the specific technology and needs to be considered as explained in the chapter "General design". In some technology there might be other more relevant topics and issues and if such are found, the model should be amended.

Different levels of health care (local/regional/national) have been taken into account while defining the issues. Some issues are relevant at all levels (e.g. approval of a new technology) and some mostly in one level, for example issues related to the staff which affect mostly in the hospital level. In addition, different viewpoints have been noticed. There are issues related to the patients in nearly all topics.

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status 3=core 2=borderline 1=not core
G0001	Organisational aspects	Process	What kind of work flow and patient flow processes are needed?	A new technology could change current work tasks and processes (including also quality control). Work and patient processes should be described, and it should be explained what kind of activities a new technology might replace or reduce in the target organisation. Patient flow and changes required in patient path should be taken to account when implementing new technology. It is essential to know the change the use of the new technology generates to the performance of care.	3	2	Systematic reviews (and other studies), annual reports and statistics of the hospital, other qualitative research methods	Kristensen 2001, Kristensen 2007	(Current use)	3
G0002	Organisational aspects	Process	What kind of patient and relative involvement in treatment or care has to be mobilized?	A new technology may require changes in the distribution of tasks among the people involved in the treatment and care. Patients 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.	2	1		Kristensen 2007		2
G0003	Organisational	Process	What kind of staff, training and other human resources is required?	It has to be clarified what kind of staff is needed, and whether the existing staff can be trained or extra staff must be brought in. A new technology can bring along the need for extra staff when extending the ongoing activities in the organisation or when there is a demand for special expert knowledge. It must be considered if there will be a need to increase or decrease the amount of the staff. The implementation of a new innovation can mean change in job satisfaction. It could make some tasks monotonous or bring along new boring job descriptions. It is crucial that there is not just one person familiar with the new technology. If just one person has been trained for a new technology, there is a risk of losing know-how when he/she leaves the organisation (or moves to other tasks).	3	2	Systematic reviews (and other studies), reports of the hospital or hospital districts and other qualitative research methods	Busse 2002, Kristensen 2001, Kristensen 2007	Description	3
G0004	Organisational aspects	Process	What kind of co-operation and communication of activities have to be mobilised?	The use of technology can presume new co-operation and communication with other parts of the structure (e.g. other units) or outside the structure (e.g. other hospitals, pharmacies). The type of technology 'determines' the frequency of need for information exchange between different actors. Also interaction and communication with patients and their important others will change.	2	2	Systematic reviews (and other studies), reports of the hospital or hospital districts and other qualitative research methods	Kristensen 2001, Kristensen 2007, Senter for Medisinsk metodevurdering (SMM) 2003		2

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status 3=core 2=borderline 1=not core
G0005	Organisational aspects	Structure	What consequences the implementation of the new technology will have in respect of decentralisation or centralisation?	The location of use of the technology (primary - secondary - tertiary care) could vary between different countries depending on the system of organisational systems. (De)centralisation could have some economical and qualitative benefits. Centralisation could make a new technology more difficult to access. For example some expensive technologies are centralized to tertiary care units.	3	2	Systematic reviews (and other studies), reports of the hospital or hospital districts and other qualitative research methods	Busse 2002, Kristensen 2001, Kristensen 2007, Senter for Medisinsk metodevurdering (SMM) 2003	Current use, Description	3
G0006	Organisational aspects	Structure	What kinds of investments are needed (material or premises)?	The new technology could require many changes in the organisation e.g. premises must be according to the directions of the manufacturer. This could be very costly for the organisation. High costs of the new technology can influence the decision of purchasing the new technology. It is important to know which organisation(s) participate in the investments of a new technology and to what extent the other organisations take part in the running costs.	3	2	Systematic reviews (and other studies), reports of the hospital or hospital districts and other qualitative research methods Information from manufacturers	Kristensen 2007	Description	3
G0007	Organisational aspects	Structure	What is the likely budget impact of the implementation of the technology for the payers (e.g. government)?	When a new technology is introduced, the question about reimbursement quickly arises. Whenever a technology is reimbursed, there will be an impact on the health care budget. Budget impact analysis examines the likely impact of the reimbursement of a new technology on financial outlays from the perspective of the payers (e.g. government).	3	1	Systematic reviews (and other studies), reports of the hospital or hospital districts and other qualitative research methods			2
G0008	Organisational aspects	Management	What management problems and opportunities are attached to the new technology?	The issue concerns the administrative / managerial questions of the new technology: management of resources (e.g. investments), co-ordination (in relation to different levels), establishment of objectives, monitoring and control, evaluation and sanctioning.	2	2		Kristensen 2007		2
G0009	Organisational aspects	Management	Who decides which patients are to undergo a treatment and on what basis?	Procedurals about decisions about the patients who receive care could vary.	3	2	Systematic reviews (and other studies), reports of the hospital or hospital districts and other qualitative research methods	Kristensen 2007		3
G0010	Organisational aspects	Culture	How is the new technology	Acceptance should be looked at by different perspectives: by organisation, by personnel and by	2	2	Systematic reviews (and other studies),	Finohta's EUnetHTA	Ethical, Social	2

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status 3=core 2=borderline 1=not core
			accepted?	patients. A new technology could consist of elements which don't suit the image of the organisation. Also, the alternative ways to introduce a new technology into the organisation could influence problems e.g. resistance among staff and dysfunction of processes. Patients are usually very technologically-oriented. However, patients can resist a new technology itself or its implementation. Objective and understandable information on a new technology is important.			qualitative research methods	workshop 2006, Kristensen 2007		
G0011	Organisational aspects	Culture	How will the other interest groups of the new technology be taken into account in the planning / implementation of the new technology?	It may be useful to know who are the possible stakeholders of the particular technology, as well as what kind of co-operation there has been and what kind of interaction is needed. The stakeholders could be e.g. the pharmaceutical industry and companies offering new technologies, authorities (national / regional), administrative parties, municipalities, policy makers / decision makers, staff groups and patient organisation. One can also ask: Has the patient organisation taken part into the process? Has it been involved from the beginning (in the planning) or in the later stages for example as commentator? Furthermore, it is interesting to figure out what kind of co-operation exists between hospitals and companies offering new technologies and what kind of co-operation is needed.	3	1	Systematic reviews (and other studies), qualitative research methods	Kristensen 2001, Kristensen 2007, Senter for Medisinsk metodevurdering (SMM) 2003	Ethical	2

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# Social aspects

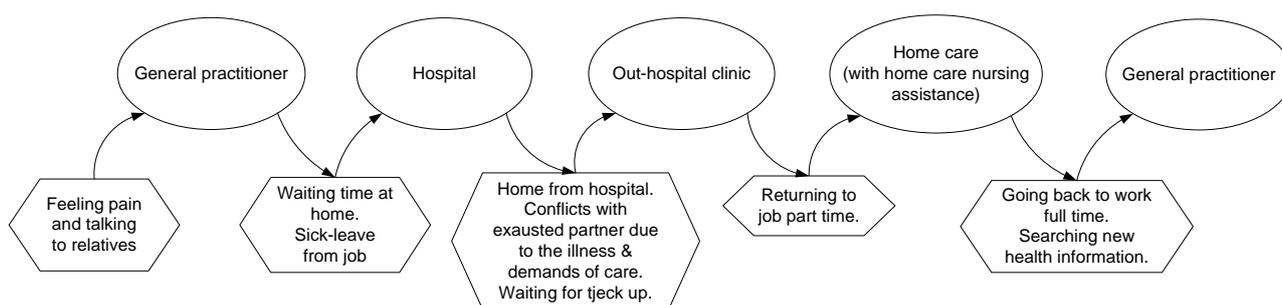
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## Domain description

### Definition

The social domain takes the patient as a point of departure in its analysis of the manifold social implications of health technology. The focus of the domain is on the diverse social arenas where the patient lives and acts during the period of sickness and treatment. Figure 1 illustrates the scope of social analysis by an example of a patient's itinerary in and outside the health services. A HTA may focus on a specific technology practiced for example in a hospital setting or in general practice, whereas other technologies received from health care may mainly be used and experienced in daily life settings.

The life of a patient takes place in various arenas (hospitals, general practitioner, everyday life, homes, schools, and workplace). The technology moulds and is moulded by all these sites. Irrespective of the site, where a certain technology is used, the implications of its use for a patient may extent far beyond the health care setting, e.g. the hospital or the general practitioner's consultation. The patients may have considerations, worries and experiences both before, during and after the health technology has been put to use. The social analysis is interested in all these aspects that surround the patient and his or her important others.



**Figure 1.** The scope of social analysis in an example: of patient's itinerary in and outside health care. Circles: Arenas within health care system.

## *Why social analysis is important*

Health technologies do not work in a vacuum. People who use technologies give them their specific meanings. Thus health technologies can be said to be used and understood by the people involved in them. This is how they gain their significance. (1, 2) Their perceptions are attached to feelings of hope, fear, or perhaps uncertainty as well as broader norms and values of society (3-5).

The patient is not just a patient but a human being with different roles in different life arenas – a family member, a citizen, an employee, a consumer etc. (1). The use of a new health technology may change these roles, skills and positions in both negative and positive ways. Considerations of power/empowerment/stigmatisation are therefore integral to a patient and social analysis of health technology (6-9).

Irrespective of the technology in question, the use of health technology always requires that the user mobilizes some kind of resources in his or her daily activities (for example some kind of action from him/herself or support from other people) in order to achieve satisfactory results with the technology. The technology does not produce the good results alone. Further, the use of technology always produces some kind of changes or consequences in different spheres of social life, which can be positive or negative, or even unexpected. The different meanings and implications of a technology are dependent on specific sites (10, 11). An assessment of patient and social aspects both in and outside the clinical encounter is therefore necessary. Overall, the social analysis reveals the resources needed when using a technology and the consequences of its use in patients life spheres so that those who will use the technology can anticipate them (12-14).

## *Scope of social analysis*

Figure 2 provides a view of different social aspects that are relevant from a patient's perspective (1). Some of these aspects overlap with other domains in this HTA Core Model, as the patient perspectives are highly relevant to many HTA domains. Thus, figure 2 should be seen as an analytical model with the patient in its centre. The model intends to show and map different patient aspects, which could be considered of relevance for a specific HTA analysis. In practise, patient's experiences of health technologies cannot be seen isolated. Only in an analytical perspective it is possible to narrow the focus to for example communicative topics (1). Having said that, the social domain choose mainly to focus on the individual topics, communicative topics, and topics of major life areas such as family life, work life, and leisure time. These topics are underlined in figure 2. Other topics of relevance for a social analysis such as the patient perspectives concerning ethical/political topics, are mainly considered to be discussed in the ethical analysis domain. Patient-related, patient perspectives on biological/physical topics are discussed in effectiveness and safety domain, and patient-related perspectives on economic topics are included in economic domain. In some situations these three topics could also be relevant to incorporate in the analysis of the social domain. Below there is a short introduction to the content of the different topics.

**Topics of main life areas:** This topic deals with those life areas (e.g. work life, family life, leisure time, cultural, religious etc) that somehow will be influenced by the use of the technology, what kind of support and resources is needed in these areas and what kind of changes the implementation and use of the technology will have for the patients functioning and roles in life.

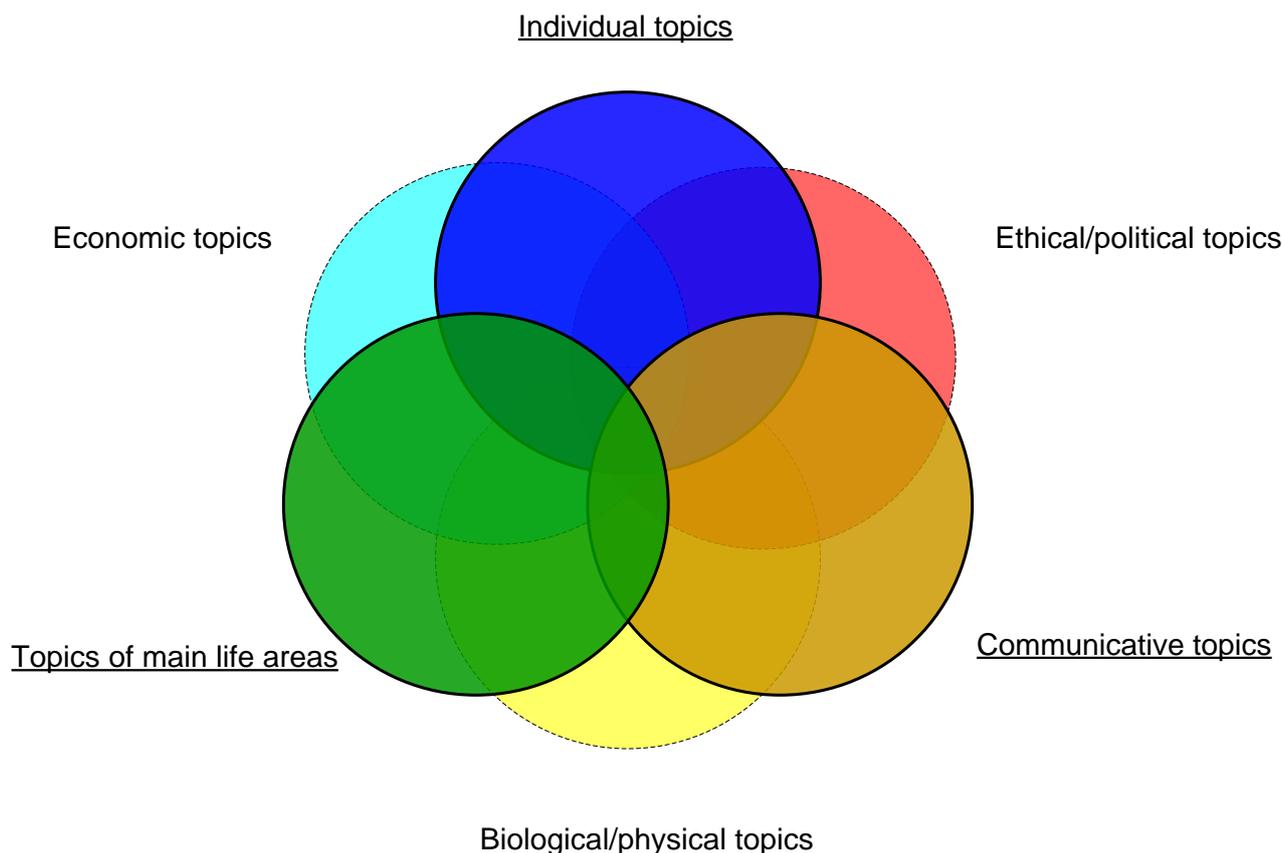
**Economic topics:** From a patient perspective this topic could deal with what short and long term financial resources the patient need to mobilize in order to use the technology (direct and indirect costs in relation to work, family life, leisure time and life style).

**Individual topics:** This topics covers how patients and important others react and act upon the technology and weather the use of the technology have any positive or negative consequences in that sense.

**Ethical/political topics:** This topic concerns weather the technology from a patient perspective entail ethical and/or political considerations, choices, dilemmas e.g. humiliation, stigmatization, tabooisation etc.

**Communicative topics:** This topic explores the patients and important others knowledge and understanding of the technology, the exchange of information from a patient perspective and limitations and possibilities for patients involvement in decision making.

**Biological/physical topics:** This covers whether, from a patient perspective, the technology leads to or might lead to side effects, pain and temporary or permanently reduced physical functioning.



**Figure 2.** Social aspects of relevance from a patient perspective in HTA. Modified from (1).

### *Analytical perspective*

The analysis of social aspects can be based on different theoretical perspectives from the social sciences (3, 4, 11, 15-19). The definition of social analysis of this paper is based on the loose

approach called co-production of technology and its context (20, 21). According to the approach, technology can include for example the hardware, methods and models used in performing work, the skills and knowledge of workers, and the activities of patients (and other lay people) on which work is performed and who utilize the technologies in their daily life. That is, the humans and their activities constitute and co-create technology as well (22). Technology is a network of human and non-human actors.

According to the co-production approach, it can be asked: "How many and what kind of resources (material entities, time, money, people, skills, knowledge, activities, etc.) must be mobilized and organized in order to produce satisfactory results from a technology?", that is, what kind of network of human and non-human elements has to be established in order for the technology to work. A new technology does not by itself improve the patient's health or quality of life. It is in the hands of the people as to how they use and thereby shape the technology. Among the people using and shaping the technology, one always finds the patient. In that sense patients have a very significant and active role as to how the technology works and what outcomes it brings. Even though a patient might seem very passive in receiving a certain treatment he/she still does a lot of "work" by for example accepting to be treated, indulging pain, managing uncertainty, behaving appropriately (or inappropriately) (23). When a given health technology is assessed it is therefore essential not just to focus on what consequences the use of a given technology might generate for a patient's life. It is also important to pay attention to how the patient by his or her way of approaching the technology contributes to its shaping (12).

### *Core questions*

The social analysis includes two kinds of questions. The first set of study questions focuses on what kind of resources (people, support, money etc.) has to be mobilized and organized from the point of view of a patient before, during and after the use of the technology in order to produce satisfactory results from the technology. The task of the assessment is to map and describe the possible resources needed. However, it is evident that there is no predefined combination of resources for a given technology that has to be mobilised.

The other set of study questions focuses on the experiences, actions and reactions of patients with respect to the technologies as well as on the change and consequences that the use of the technologies may further produce, e.g. with respect to a person's working capacity, social relationships, coping with illness and treatment or attitudes towards a person who uses the technology. The task of the assessment is thus to map and describe the possible experiences, actions and reactions towards the technologies and the consequences the use of a given technology may produce. It is again evident that the actions, reactions and consequences vary to some extent between different persons, surroundings, cultures and countries. The assessment should characterize the different and possible actions, reactions and consequences. The more specific questions of social analysis are listed in the assessment elements table.

### *Transferability*

Technologies are not, according to the co-production approach, universally true and thereby applicable wherever. They are constituted by and they work within networks of different human and non-human elements. Thus, to transfer any kind of technology means that the technology and its entailing network — the whole hybrid in fact — have to be re-built in a new place (24, 25). This is

equally true for more simple technologies, such as a single drug or a single device, as for complex interventions like disease management programmes.

Furthermore, technologies and patients change over time as people put the technology to use, get accustomed to it, find new ways of using it in combination with other technologies or practices etc. Hence an analysis of social aspects can never foresee the exact social implications and consequences of the use of a given technology. It may however, provide us with important knowledge of aspects that need to be taken into continuous consideration. In short, transferability of the social analysis results requires careful consideration of comparability of the social and cultural circumstances of the compiled data from the literature to the circumstances at hand.

## **Methodology**

### *Planning and conducting social analysis*

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. 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 (see Figure 2). 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. Figure 2 illustrates the relevant topics that one must consider when designing the social analysis. The assessment elements table contains more specific issues on each topic. These issues can serve as inspiration to study questions for the specific social analysis that is to be conducted.

### *Preliminary scoping/study framing*

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.

### *Answering the core set of questions*

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.

### *Literature review with thematic mapping*

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'.

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 (cross ref to 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. Malterud et al (26) or Hansen et al (27).

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? The appendix in this chapter provides an example model for data extraction (Appendix A).

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 (28-30). A critical interpretive synthesis on literature considering access to healthcare by vulnerable groups provides one example (31).

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.

### *Primary study*

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 a 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.

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.

## *Consultation*

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 health professionals' knowledge of their patients emanates from the punctual situations of their clinical encounter (narrow context, typically related to the meeting at the bedside or in the consultation). The amount of knowledge on the views of patients which a provider can gather in the clinical encounters is limited by the willingness of the patient and of the provider itself to talk and listen about these aspects. Even when health professionals talk with patients about issues concerning such aspects, the conversation is formed by their positions, power relations, patient's dependency on doctor's goodwill, time constraints, etc. Moreover, the kind of knowledge that is most relevant for an analysis of the social aspects often relates to aspects outside the meetings with health professionals. Hence patient's perspectives are often incompletely represented by health care professionals. Stakeholders may represent patient's perspective, but often does so with a political agenda.

## Assessment elements

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status 3=core 2=borderline 1=not core
H0001	Social aspects	Major life areas	Which social areas does the use of the technology influence?	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.	3	2,1	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.	(1)		2
H0002	Social aspects	Major life areas	Who are the important others that the use of the technology may affect in addition to the patient?	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)	3	2,1	See above			2
H0003	Social aspects	Major life areas	What kind of support and resources are needed or might be released as the technology is put to use?	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).	3	2,1	See above	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)	Organisational	2
H0004	Social aspects	Major life areas	What kinds of changes does the use of the technology generate in the patient's role in the major life areas?	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.	3,2	2,1	See above	ICF(32) activities and participation, interpersonal interactions and relationships (chapter 7, d710-779), community, social and civic life (chapter	Ethical Effectiveness, safety	2

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status 3=core 2=borderline 1=not core
								9:d910-d999), (5, 7, 33, 34)		
H0005	Social aspects	Major life areas	What kind of changes does the implementation and use of the technology mean for the patients physical and psychological functioning in his or her major life areas?	This issue is about the physical and psychological consequences the use of the technology may generate in the patient's main life areas e.g. on person's body functions and structures, activities on daily living, or performance at work, school, home or leisure time. This issue covers whether, from a patient perspective, the technology leads to improvements or harms (a cross reference to effectiveness, safety domain issues), or generates any other unexpected effects on functioning.	3	2,1	See above	ICF(32),(15)	Effectiveness Safety	2
H0006	Social aspects	Individual	How do patients and important others react and act upon the technology?	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).	3,2	2,1	See above	ICF(32) body functions: mental functions (chapter 1:b110-b199) environmental factors: attitudes (chapter 4., e410-499) , (3)	Effectiveness	2
H0007	Social aspects	Communication	What is patients' and important others' knowledge and understanding of the technology?	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.	3,2	2,1	See above		Current use Safety	2
H0008	Social aspects	Communication	How is the information regarding the use of the technology processed and exchanged?	This issue is about the exchange of information from a patient's perspective. What are patients' and significant others' questions? How do they receive answers?	3	2,1	See above		Organisational	2

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status 3=core 2=borderline 1=not core
				How is information provided and received?						
H0009	Social aspects	Communication	What are the consequences in decision making?	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.	3	2,1	See above		Organisational Ethical	2

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## Appendix: Data extraction sheet for social domain

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	

# *Legal aspects*

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## **Domain description**

Legal issues have not traditionally been considered as standard part of health technology assessment (later referred to as HTA) in most countries. However, as the norms of professional ethics are continuously codified into statutes and European Union is producing ever more health technology related legislation, the legal issues may form a substantial part of HTA in the future. Moreover, as the patients and health care professionals are allowed free movement within Europe, some evolution in harmonisation of legal regimes is likely to occur in the health care sector. At the same time one must bear in mind the national characteristics of legal and health care systems and be sensitive to the limits of exportation of HTA from one country to another.

Already today proper knowledge of relevant legal questions has significant consequences for the decision making in an HTA process, often perceived as part of sociological issues or so called socio-legal issues (Decker 2004, Møldrup 2002). The consideration of legal issues as an independent domain of HTA helps to focus the scrutiny to relevant legal sources, which may vary according to the nature of the technology in question.

The systematic consideration of legal aspects is also expected to contribute to the implementation of HTA results across the Europe. At the very least it will help to identify the (often) legal barriers which hinder the export and import of HTA results (Drummond & Weatherly 2000, Henshall et al. 2002, Hofman 2005, Terry 2004). The study of legal aspects during an HTA process is also likely to give insight into the areas of health care legislation where harmonisation is needed, and might provide tools for legislative and policy reforms.

The questions that arise in the legal domain pertaining diagnostics HTA can be roughly divided into five categories of issues which operate at different levels in health care:

- issues related to the central question of who the end-user of the diagnostic technology is
- issues directly related to the patient and his/her basic rights and freedoms, such as issues of autonomy, informed consent, privacy and confidentiality as well as his/her safety
- issues related directly to the technology in question such as proper authorisation, patent/license issues, price and reimbursement regulation and product safety, guarantee and liability issues
- issues related to the process of acquisition of the technology
- issues related to the health care policy at the local, national, European and/or international level

The weighing of the importance of different legal aspects varies depending on technology in question.

One reason why legal issues have not been considered elemental to HTA might be that the issues at stake overlap with e.g. ethics, societal aspects and safety. What separates the legal domain from these (and possible others) is, however, that matters within the legal domain are always codified in national, international and/or supranational legislation or has been agreed on in international conventions or is implicitly or explicitly agreed upon by the manufacturer (or seller) and buyer of the technology. In other words, for an issue to be considered a legal one, one must be able to point the legal source (stipulation, convention or agreement) that makes the issue legally relevant.

## Methodology

In short, legal approach to HTA entails the study of the compliance of a given technology and its anticipated use with relevant legal instruments. From a methodological point of view, it is important to recognise the compulsory legal sources that form the basic regulatory framework for any given question. In addition, the compulsory sources are often complemented by various so called soft law instruments which have been defined as “rules of conduct that are laid down in instruments which have not been attributed legally binding force as such, but nevertheless may have certain (indirect) legal effects, and that are aimed at and may produce practical effects” (Senden 2005). Legal dogmatics requires understanding of hierarchy and interaction of various national, international and European instruments and legal expertise is usually required to detect the relevant legal sources among the magnitude of laws, conventions, codes, guidelines etc. Thus, research on the domain of legal issues of the core model is most efficiently done by a person with a legal training, the best result probably obtained by a team with both legal and medical experts.

This section outlines the sources that can be considered as important in the context of HTA. The aim is not, and indeed cannot be, to give or even propose a binding legal solution to a given question, but to guide the HTA organisations/personnel in recognising the legal questions at the time when decisions about using the technology are made. Furthermore, the relevant legal sources will be provided at the end.

The different legal orders and/or regimes to be studied are:

1. International law
2. European law
3. National law
4. Relevant complementing soft law.

### *International law*

Although EUnetHTA is operating in Europe, many of the Member States are bound by international legal instruments. For instance, the European Patent Convention and the Conventions of the Council of Europe fall under international law. In addition, the World Trade Organisation's Agreement on Trade Related Aspects (TRIPS) is important to the European patent regime. Apart from the instruments issued by the Council of Europe, the direct relevance of international law to European HTA remains limited.

## The Council of Europe

All countries of the European Union are also members of the Council of Europe. Although often referred to as part of the European law, it is still an institute under international law and not part of the European Union. This means that the Council cannot issue any binding law unless the Member States consent to it. Council of Europe has been very active in the field of biomedicine and has given numerous recommendations. In addition, it is a platform for international conventions, the most fundamental one being the European Human Rights Convention (1950). The Convention is complemented and developed by the court practise of the European Court of Human Rights.

The central legal document related to health care issues is ‘the Convention for the protection of Human Rights and dignity of the human being with regard to the application of biology and medicine’ (ETS 164), hereafter referred as Biomedicine Convention, with its Additional Protocols, specifying the provisions of European Human Rights Convention in the field of modern biomedicine. Also various recommendations given by the Parliamentary Assembly or Committee of Ministers may need to be considered. These are referred to at the relevant sections of the text. Importantly, it may be necessary to investigate whether the European Court of Human Rights has given a relevant decision on the matter. New court decisions arise in constant manner, and information of these needs to be updated regularly.

A new Additional Protocol concerning Genetic Testing for Health Purposes to the Convention on Human Rights and Biomedicine was adopted on 7 May 2008. It is not legally binding upon the Members States until they ratify the protocol and implement it nationally. However, it gives immediately a very important signal for policy-makers about how to approach genetic tests. Article 7 of the Protocol states that a genetic test for health purposes may only be performed under individualised medical supervision of an appropriately qualified physician. This means that genetic tests targeted for laymen to be performed home are no longer allowed. The explanatory report states in points 64-65: *“This provision is driven by the concern, in particular, to enable the person concerned to have suitable preliminary information with a view to an informed decision regarding the carrying out of this test and, if appropriate, to have access to an appropriate genetic counselling. A precise evaluation of the situation of the person concerned, involving direct contact with him or her, is a determining element in that respect. A mere telephone conversation with a medical doctor, for example, does not allow for such an evaluation. The conduct of a genetic test for health purposes must be in response to a specific request made on the basis of a precise evaluation of the situation of the person concerned, carried out by a medical doctor”*. Hence, the aspect of who is going to be the end-user of a diagnostics medical device is an important legal question in HTA of diagnostic technology.

## European Union Law

The European Union has issued several directives that are relevant in the domain of legal aspects related to HTA of diagnostics. One of the most central is the Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices.

A search of EC legislation can be performed at the internet database EurLex (<http://eur-lex.europa.eu/>). By using the “simple search”-option, and a search combination “diagnostic\*” and

“medical”, one is led 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.

A good starting point is visit the homepage of the subject in question, such as Medical devices’ homepage of the European Commission which provides links to relevant legislation:

[http://ec.europa.eu/enterprise/medical\\_devices/index\\_en.htm](http://ec.europa.eu/enterprise/medical_devices/index_en.htm)

Furthermore, the judgements of the European Court of Justice may sometimes be relevant when interpreting community legislation. The search form is available on the internet (<http://curia.europa.eu/jurisp/cgi-bin/form.pl?lang=en>). In general, one must pay attention to using relevant terms of EU law when searching for cases. Among others, such terms as ‘state aid’, ‘marketing authorisation’, ‘personal data’, ‘essentially similar product’, ‘advertising’, ‘free movements of services’, ‘medicinal products’ and ‘medical device’ may be of relevance. Interpretation of the judgements requires legal expertise.

As a conclusion, to get a clear picture of the community legislation, good skills in both the law and information technology are needed.

### *National legislation*

Whereas the Regulations are directly binding upon all the Member States of the European Union, the countries are obliged to transpose the directives to their national legislation. The Member States have some choice as *how* to transpose the directives into national laws: they are only bound by the result to be achieved. Much of the health care related EU legislation is given as minimum directives. Purely national requirements may exist as they are allowed if they are not posing restrictions for the community markets. Also precedents of national Supreme Courts may be of relevance. The variety of national legislation obviously leads to differences from one country to another. Hence, concerning the transferability of HTA one needs to check the status of the relevant national legislation in order to evaluate the exact manner of implementation. Given the differences in legal cultures nationally, a local lawyer needs to be involved.

### *Soft law*

As mentioned above, soft law complements legally binding instruments and sometimes serves as the only guidance for a specific issue. It appears in all the legal regimes.

### *Agreements with and documentation provided by the technology supplier*

These will influence the division of risk and liability between the buyer (health care unit) and the supplier and are hence of economic importance to the health care unit in question. It seems unlikely that any uniform standard agreements emerge and the scrutiny of these documents is most reliably made by a legally educated person.

## *Legal literature*

In addition to these, a survey on legal literature may be conducted, for the legal concepts and their interpretation is also developed within legal science. At the European level such journals as e.g. *European Journal of Health Law; Health, Economics, Policy and Law; Medical Law International; Medical Law Review* and *Medicine and Law* may be scrutinised. Also national libraries' electronic databases can be used to search for relevant international and national monographs and articles on the technology/issue in question. Some literature is given in the references of this chapter, but the list is by no means comprehensive. Moreover, as legal doctrines evolve over time, literature search should be updated every time the model is used. An up-to-date textbook (e.g. Mason & Laurie 2005 or the latest, Hervey & McHale 2004) is a good starting point for a literary review.

## Assessment elements

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status 3=core 2=borderline 1=not core
I0030	Legal aspects	End-user	Who is the intended end-user of the technology?	Different requirements may apply depending on the answer. E.g. consumer Information, CE-marks, easiness of use, exactness of the results etc. are to be evaluated differently if the technology is intended to laymen's use.	3	3	In vitro diag. directive 98/79/EC; Council of Europe Gen testing protocol 2008	Directive 98/79/EC; Council of Europe Gen testing protocol 2008		
I0031	Legal aspects	End-user	Is the use of the diagnostic technology limited in legislation?	Some countries may have restricted the use of some diagnostic technologies.	3	1			Ethical aspects	
I0032	Legal aspects	End-user	Is the health care personnel using the technology according the professional standards?	Health care personnel are obliged to follow professional standards and apply methods that are generally approved. When considering their professional liability towards patients it is very important that they know the limits and possibilities of diagnostical methods.					Ethical aspects	
I0002	Legal aspects	Autonomy of the patient	Can patients understand the future implications of using/not using the technology?	It is important to provide information on the (evermore complex) technologies in such a manner that the patient can truly understand it.	3	2	Explanatory report to Biomedicine convention	Biomedicine Convention Art 5		
I0003	Legal aspects	Autonomy of the patient	Are there relevant optional technologies that future patients should be	The concept of informed consent includes also the possibility to consider other therapeutic options, if these are available.	3	2	Explanatory report to Biomedicine convention	Biomed conv Art 5		

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status 3=core 2=borderline 1=not core
			allowed to consider?							
I0004	Legal aspects	Autonomy of the patient	Is it possible to give future patients enough time to consider their decisions?	It is usually advised that the patient is given some time to think over the treatment decision, especially if the decision involves assimilating complex technical information or a tough weighing of risks and benefits of the procedure. It should be assessed beforehand if a given technology allows such time for consideration.	2	2				
I0005	Legal aspects	Autonomy of the patient	Is it possible to obtain an advance directive on the use of the technology?	If it is expected that the technology may be used in an emergency situation in the future it is advised that the patient is consulted beforehand and her opinion is recorded to the medical file as an advance directive on the use of a given technology.	2	1				
I0007	Legal aspects	Privacy of the patient	Does the use of the technology produce some additional (i.e. diagnostically or therapeutically irrelevant) information on the patient?	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 means further challenges to this principle.	3	3	Z vs. Finland (ECHR February 25, 1997); M.S. vs. Sweden (ECHR August 28, 1997); national legislation; legal literature	Directive 95/46/EC, EU FR Charter Art 8, Biomedicine Convention Art 10, CM Recommendation R (97) 5	Ethical aspects	
I0033	Legal aspects	Privacy of the patient	Does the use of the technology produce such information on the patient that is not directly relevant to the disease/condition that is being diagnosed or tested?	Modern biomedicine may produce (genetic) information from the relatives of the patient as well as on patient herself. 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.	3	1				
I0008	Legal	Privacy of the	Does the use	The results of a given diagnostic technology	2	2				

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status 3=core 2=borderline 1=not core
	aspects	patient	of the technology produce information that would be relevant for the relatives of the patient?	may indicate that the relatives of a patient may have a medical condition that would need to be addressed. The issue is on what conditions (if any) can the privacy of the original patient be broken in order to inform the relatives of their situation.						
I0009	Legal aspects	Privacy of the patient	Can the access to the patient data secured properly?	At the era of computer-based patient records it is crucial that the health care unit has taken appropriate measures to secure the patient databases. Negligence may lead to liability.	2	1		Directive 95/46/EC	Organisational aspects	
I0010	Legal aspects	Privacy of the patient	What levels of access to which kind of patient information exist in the chain of care?	During the therapeutic process many people may either need to get access or semi-accidentally get access to the personal medical data of patients. The delicacy of the information depends on the technology in question. Health care unit must be organised so that it minimises the number of people having access to patient data. Also other measures to minimise the risk of information leakage from health care unit must be taken.	1	1			Organisational aspects	
I0011	Legal aspects	Equality in health care	Is the technology equally accessible to all needing members in a given society?	This topic operates both at national and international level. 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. In many Constitutions equality of citizens covers also access to health care.	3	2		EU FR Charter Art 35, Biomedicine Convention Article 3, CM RecommendationR (2006) 18	Societal aspects	
I0012	Legal aspects	Equality in health care	Is the technology subsidized by the society?	Governmental interventions or the lack of them may affect to the expected number of patients.	2	1			Societal aspects, organisational aspects, economical aspects	
I0013	Legal aspects	Equality in health care	Is there a wide variation in the acceptability of the	Varying legal regimes may lead to health-care tourism across the borders, especially if the technology in question is controversial.	3	3	Europe-wide legal comparison		Societal aspects	

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status 3=core 2=borderline 1=not core
			technology across Europe?							
I0014	Legal aspects	Equality in health care	Is health-care tourism expected from/to other European countries?	Varying legal regimes may lead to health-care tourism across the borders.	2	3	C-158/96 (ECJ), C-372/04 (ECJ), Europe-wide legal comparison		Societal aspects	
I0015	Legal aspects	Authorisation & safety	Has the technology national/EU level authorisation?	Patient safety as expressed in product safety is one domain of health care technology assessment which clearly falls under the mandate of the European Union	3	3			Safety aspects	
I0016	Legal aspects	Authorisation & safety	Does the technology need to be listed in a national/EU register?	A European database of medical devices (EUDAMED) is under construction.	2	2			Safety aspects	
I0017	Legal aspects	Authorisation & safety	Does the technology fulfil product safety requirements?	The implication of findings in the safety domain should be discussed against the relevant European or national legal frameworks to ensure patient safety from using the technology:	3	3		Directive 93/42/EEC, Directive 95/2001/EC	Safety aspects	
I0018	Legal aspects	Authorisation & safety	Does the technology fulfil tissue safety requirements?	Many novel health technologies may utilise human cells or tissue (so called advanced therapy medicinal products). These products must fulfil the safety requirements issued by EC Directive 2004/23/EC.	3	3	COM 567 (2005) final	Directive 2004/23/EC	Safety aspects	
I0019	Legal aspects	Ownership & liability	Does the technology infringe some intellectual property right?	Issues in this topic are to be considered by the health care unit when considering the acquisition of a new technology. The wording of acquisition contract may affect liability sharing between the manufacturer and health care unit.	2	3	Manufacturer, patent data bases, EPO Web site	European patent convention (EPC), Directive 98/44/EC, national legislation		
I0020	Legal aspects	Ownership & liability	Does the introduction of the technology	As novel technologies build up on existing knowledge, the use of the technology may involve the payment of some additional fees	2	2	Manufacturer, patent data bases			

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status 3=core 2=borderline 1=not core
			presume some additional licensing fees to be paid?	to additional patent holders etc. In principle, the manufacturer should be able to clarify this to the health care unit/health care system in question.						
I0021	Legal aspects	Ownership & liability	What are the width, depth and length of the manufacturers guarantee?	The terms of the manufacturers guarantee are of importance to the health care unit as well as to the society's health care sector when considering whether it is economically and/or liabilitywise advantageous to introduce the technology or not.	3	3	Manufacturer			
I0022	Legal aspects	Ownership & liability	Is the user guide of the technology comprehensive enough?	The wording and clarity of the user guide of the technology can have legal effects on the liability issues in case the technology is not working as expected.	3	3	Manufacturer			
I0023	Legal aspects	Regulation of the market	Is the technology subject to price control?	As health care technology is essential to everyone at some point in their lives, its pricing may be regulated.	3	2	C-317/05 (ECJ), C-283/03 (ECJ)	Directive 1989/105/EEC		
I0024	Legal aspects	Regulation of the market	Is the technology subject to acquisition regulation?	Expensive technology is subject to acquisition regulation.	3	2		Directive 2004/18/EC		
I0025	Legal aspects	Regulation of the market	Is the marketing of the technology to the patients restricted?	As health care technology is essential to everyone at some point in their lives, the way by which it can be marketed to consumers may be regulated.	3	2	T-179/00 (ECJ)	Directive 1989/105/EEC , directive 1992/27/EEC		
I0026	Legal aspects	Legal regulation of novel/experimental techniques	Is the technology so novel existing legislation was not designed to cover its regulation?	Modern biomedical sciences produce novel technologies which may not always be unambiguously covered by existing provisions.	3	1				
I0027	Legal aspects	Legal regulation of novel/experimental techniques	How the liability issues are solved according to existing	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.	3	1				

ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=complete 2=partially 1=not	Information sources	Reference	Relations	Status 3=core 2=borderline 1=not core
			legislation?	This way the health care unit can prepare itself for the possible future legal proceedings.						
I0028	Legal aspects	Legal regulation of novel/experimental techniques	Are new legislative measures needed?	If the existing legislation is not satisfactory the introduction of a novel technology may require new legislative measures. At the level of a health care unit this may slow down the introduction, whereas at the level of the society it implies a need to use resources for preparing new laws.	2	1				
I0029	Legal aspects	Legal regulation of novel/experimental techniques	Is the voluntary participation of patients guaranteed properly?	Use of experimental technologies may not compromise patient safety. Patients must not be pressured into such treatments.	3	1		Biomedicine Convention Article 16		

## *Descriptions*

For each issue it is indicated whether it is of relevance in direct doctor-patient relationship (DP), for the health care unit (HCU) or at the level of national health care policy (HCP).

### **End-user of the diagnostic technology**

A very important question from the legal viewpoint is who the end-user of the technology is. For instance, increased markets for do-it-yourself genetic and other tests (such as HIV) vis-à-vis tests for clinical practise are subject to different requirements (e.g. Directive on in vitro diagnostics medical device 98/79/EY; Council of Europe protocol concerning genetic testing for health purposes). Both international and local medical communities are concerned about medical tests targeted for lay persons and require more stringent regulation especially on genetic tests (e.g, Wolfberg 2006, Human Genetics Commission 2007, Pearson 2008). Furthermore, the use of some diagnostic technology may be restricted in a given jurisdiction, e.g. predictive genetic tests on non-curable diseases may not be allowed for minors.

Health care personnel are obliged to follow professional standards and apply methods that are generally approved. When considering their professional liability towards patients it is very important that they know the limits and possibilities of diagnostic methods. HTA may on its part serve this purpose. When using, for instance, diagnostic device or a certain diagnostic test they should know about its clinical utility and clinical validity. The concept of clinical utility relates to the fact that a test should be beneficial for the tested person and in addition, if the benefit is established, the benefit should outweigh potential harm. Clinical validity means clinical sensitivity (positive in the affected) and specificity (negative in the controls), i.e., accuracy with which the test predicts the presence or absence of a clinical condition or predisposition (Ibarreta et al., 2003).

- Who is the intended end-user of the diagnostic technology?
- Is the use of diagnostic technology limited in legislation?
- Is the health care personnel using the technology according the professional standards

### **Autonomy of the patient**

The Nuremberg trial codified the principle of informed consent in biomedical research, and it was further strengthened after the Helsinki Declaration of the World Medical Association in 1964. Today the informed consent principle, being a central expression of the patient autonomy, is widely recognised also in everyday doctor-patient relationship. The paternalistic relationship has transformed into a discursive one where both parties are to express their opinions. The essential elements of informed consent can be summarised as follows

- i) the patient has given it without any external pressure
- ii) the consent is based on adequate information of the procedure, its benefits, risks, and options
- iii) the patient has had enough time to consider her decision.

Patient autonomy does not mean that doctor-patient relationship is a completely equal one, for the physician always acts as an educated expert when giving opinions and advice. The final decision on the use of any technology must not, however, be made against the expressed will of the patient. The

issues in this topic mainly concern the direct doctor-patient relationship, but depending on the legislation, also the health care unit may be liable of infringement of patient autonomy.

- Can the patient understand the implications of using/not using the technology? (DP)  
As scientific advancements are brought into clinical practise the information for the patient tends to become more complex and hence, more difficult for a layperson to evaluate. Therefore it is essential that each patient information sheet concerning novel technologies is carefully scrutinised in order to evaluate whether it is comprehensible for people not familiar with health care technologies. For the most complex or controversial technologies, person-to-person consulting may be needed in order to realise the patients' autonomy.
- Are there relevant optional technologies that the patient should be allowed to consider? (DP, HCU)  
Although novel health care technologies may represent the cutting edge know-how in treating patients, established methods may still remain useful. This is especially true if the known risks of the older and newer technology markedly differ, e.g. if the risks of newer technologies are not yet fully evaluated. Hence, in order to appreciate patient autonomy, it may be required to clarify the options and their therapeutic and risk implications to her, specifically comparing them to the technology which the physician is recommending. Again, legal responsibility may take place if relevant options are not discussed with the patient.
- Is it possible to give the patient enough time to consider his/her decision? (DP)  
With complex novel health care technologies with elaborate patient information sheets, it is advisable that patients are given enough time to familiarise with the written material before they need to reach a conclusion on the use of the technology. Also, patients should have the opportunity to see a specific counsellor (e.g. a trained nurse specialised in patient advising) if they have some detailed questions about the technology. If the decision about the use of technology is likely to be a hasty one, appropriate procedures to ensure maximum possible patient understanding should be prepared beforehand.
- Is it possible to obtain an advance directive on the use of the technology? (DP, HCU)  
Advance directives have their own problems, and the legal ones have been recognised for a long time. These include first and foremost the issues of i) with complex real-life medical situations it is often difficult to formulate such an advance directive that would be indisputably applicable it either being too wide or too narrow in scope ii) the advancement in medical know-how may render the directive useless and iii) as the time between the giving of advance directive and the real situation gets longer it is more difficult to decide whether it expresses the patients will at the situation-at-hand. Recognising these problems, it may still be useful to obtain an advance directive on the use of a given technology, if it is likely that the acute need for the use of technology might be a rushed one or that the patient may be unconscious at the time of decision making.

*Literature:* Appelbaum et al. 2001, Jones 1999, Lötjönen 2006, MacLean 2006.

## **Privacy of the patient**

Privacy of the patient, which can also be expressed as a principle of confidentiality, is one of the central and most established principles of medical profession and medical law, dating back to

Hippocratic Oath. The measures needed to protect privacy are ever more important in the era of computer-based patient records and increasing knowledge of genetic factors in disease emergence.

- Does the use of the technology produce such information on the patient that is not directly relevant to the disease/condition that is being diagnosed or tested (HCU)  
Use of modern medical technologies may produce diagnostically or therapeutically irrelevant information on the patient. The health care unit needs to have established policy on how to handle this information. Issues that need to be concerned are i) is this data to be saved or discarded ii) who has access to this data iii) should the access to this extra data be more limited than to the at-the-time medically relevant data and iv) if the extra data reveals some new adverse condition on the patient how and by whom this information is made known to the patient. In especially point ii) national laws may apply.
- Does the use of the technology produce some additional (i.e. diagnostically or therapeutically irrelevant) information on the relatives of the patient? (HCU)  
This issue has obvious similarities to the above one, but needs to be considered separately as in the era of increasing genetic knowledge also adverse information on the relatives of the patient may emerge when using a given health care technology. The major difference is that it is not at all clear whether this information should be revealed to the relative in question or not. Again, national laws may apply.
- Does the use of the technology produce information that would be relevant for the relatives of the patient (DP, HCU)  
Sometimes (especially) genetic diagnostics can reveal information that would be relevant to the relatives of the patient. It must be assessed when the information is of such relevance for the relatives' health and wellbeing that the privacy of the primary patient can be broken.
- Can the access to the patient data be secured properly? (HCU)  
One essential part of the patient privacy today, computer-based patient records being more of a rule than an exception, is the technical security of the patient record files. The level of technical security may affect the liability of the health care unit on any information leakage and following breach of patient privacy.
- How many people in the chain of care need to get access to the patient information? (HCU)  
As the number of people that have access to patient data straightforwardly correlates with the possibility of information leakage it is advisable to keep this number as low as rationally possible. The accuracy of this evaluation may affect the liability of the health care unit on any information leakage and following breach of patient privacy.

*Literature:* Case 2003, Kienle 2001, Laurie 2003, Leith 2006, Terry 2003.

## **Equality in health care**

Equality in health care is one of the central aims of the Human Rights and Biomedicine Convention of the Council of Europe. Many European constitutions have also established both equality and right to adequate health care as basic rights of all people. However, as new technologies tend to be expensive the equality in health care is threatened at least on two levels. Firstly, the technology may not be (at least easily) available to all citizens and secondly, the use of an expensive technology in one sector of health care may reduce the resources available to other health care sectors. Moreover, some technologies might be morally controversial, and if a given technology is forbidden in one country, its citizens may migrate to health care units of a permissive country for the treatment. This

further induces inequality, as only to patients able to cover for their own expenses can rely on this 'health care tourism'. Also the equality in the receiving country is threatened if its health care units are crowded with foreign patients.

- Is the technology equally accessible to all needing members of society? (HCP)
- Is the technology subsidized by the society? (HCP)
- Is there a wide variation in the permissibility of the technology across Europe? (HCP, HCU)
- Is health-care tourism expected from/to other European countries? (HCP, HCU)

*Literature:* Hervey 2007, Hoedemaekers & Dekkers 2003, Oliver 2007, SEC (2006) 1195/4

## **Authorisation & safety**

Patient and product safety are the two areas of health care technology assessment where the European Union has the authorization to issue legal measures. Hence, the issues in this topic are mostly governed by EU directives. The safety problems are regulated via diverse standards, authorisations, and other administrative measures required. One must bear in mind, however, that directives are always implemented in a somewhat different way in different jurisdictions. Health care related directives may also be so called minimum directives, that is, Member States are entitled enact stricter provisions if they so want. Therefore also the national legislation must be examined.

- Has the technique proper national/EU level authorisation? (HCU)
- Does the technology need to be listed in a national/EU register? (HCU)
- Does the technology fulfil product safety requirements? (HCU)
- Does the technology fulfil tissue safety requirements? (HCU)

*Literature:* Altenstetter 2003, Hodges 2004, Lierman 2001, Permanand 2006

## **Ownership & liability**

Although patents in biotechnology are controversial in general, also many health care technologies are protected by intellectual property rights. These can increase the actual cost of using the technology in question and can hence affect the acquisition decision of the health care unit. When considering the acquisition of a new medical device, it is also advisable to pay detailed attention to such things as the manufacturers guarantee and e.g. the comprehensiveness of the user manual, for these may have an impact on the liability allotment between the manufacturer and the health care unit in case of device malfunction.

- Does the technology infringe some intellectual property right? (HCU)
- Does the introduction of the technology presume some additional licensing fees to be paid? (HCU)
- What are the width, depth and length of the manufacturers guarantee? (HCU)
- Is the user guide of the technology comprehensive enough? (HCU, DP)

## **Regulation of the market**

As use of medical services and technologies is literally vital for most people at some point of their lives, its marketing means to the general public may be restricted by the legislation. Also, to render the technology available for all patients, the state may regulate the price that health care unit is allowed to charge from the patients. These may have an effect on the purchase decision of the health care unit. Complex medical devices may be so expensive that they are subject to either national or EU level acquisition regulation.

- Is the technology subject to price control? (HCU, HCP)
- Is the technology subject to acquisition regulation? (HCU, HCP)
- Is the marketing of the technology to the patients restricted? (HCU, HCP)

*Literature:* Altenstetter 2003, Lierman 2001, Permanand 2006

### **Legal regulation of novel/experimental technologies**

Due to rapid progress in biomedical sciences, it is likely that novel health care technologies not covered by any specific legislation emerge. When considering the use of such technologies the health care unit must be aware of the legal void and ensure that liability issues are clearly settled beforehand. The use of experimental technologies does not diminish the health care unit's responsibility of its patients, and appropriate measures to ensure patient safety and their voluntary participation to the experimental procedures must be taken. At the level of society, the introduction of a novel health care technology may call for new legislation.

- Is the technology so novel that no legal rules are directly applicable? (HCP, HCU)
- How the liability issues are solved according to existing legislation? (HCU, HCP)
- Are new legislative measures needed? (HCU, HCP)
- Is the voluntary participation of patients guaranteed properly? (DP, HCU)

*Literature:* COM 567 (2005) final

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COM 567 (2005) final. Commission proposal for a regulation of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.

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.

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 medicinal products for human use.

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.

Directive 2001/104/EC of the European Parliament and of the Council of 7 December 2001 amending Council Directive 93/42/EEC concerning medical devices.

Directive 2001/95/EC of the European Parliament and of the Council of 3 December 2001 on general product safety.

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.

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 implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000 amending Council Directive 93/42/EEC as regards medical devices incorporating stable derivatives of human blood or human plasma.

Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices.

Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions. 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.

Council Directive 93/42/EEC of 14 June 1993 concerning medical devices.

Council Directive 92/27/EEC of 31 March 1992 on the labelling of medicinal products for human use and on package leaflets.

Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices.

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.

Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

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Council of Europe

Convention for the protection of Human Rights and dignity of the human being with regard to the application of biology and medicine: Convention on Human Rights and Biomedicine CETS No.: 164.

Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes, adopted on 7 May 2008. (CETS No still open).

Recommendation R (97) 5 of the Committee of Ministers to Member States on the protection of medical data.

Recommendation R (2006) 18 of the Committee of Ministers to Member States on health services in a multicultural society.

### **Web sites**

CURIA (The search page for case law of the European Court of Justice)

<http://curia.europa.eu/jurisp/cgi-bin/form.pl?lang=en>

COUNCIL OF EUROPE Treaty Office

<http://conventions.coe.int/>

EMA Product Safety Announcements

<http://www.emea.europa.eu/htms/human/drugalert/drugalert.htm>

EMA Marketing Authorisation Withdrawals and Suspensions

<http://www.emea.europa.eu/htms/human/withdraw/withdraw.htm>

European Medical Devices Database (EUDAMED) homepage

<http://eudamed.cec.eu.int/>

European Patent Convention

[http://www.european-patent-office.org/legal/epc/pdf/epc\\_2006\\_v5\\_bm\\_en.pdf](http://www.european-patent-office.org/legal/epc/pdf/epc_2006_v5_bm_en.pdf)

European Patent Office – Search page for European patents

<http://www.epo.org/patents/patent-information/european-patent-documents.html>

EUR-Lex (The legislation of the European Union)

<http://eur-lex.europa.eu/en/index.htm>

HUDOC (The search page for the case law of the European Court of Human Rights)

<http://cmiskp.echr.coe.int/tkp197/search.asp?sessionId=9831593&skin=hudoc-en>

Medical devices homepage of the European Commission

[http://ec.europa.eu/enterprise/medical\\_devices/index\\_en.htm](http://ec.europa.eu/enterprise/medical_devices/index_en.htm)