eunethta

EUnetHTA

INTERIM TECHNICAL REPORT – WP4

Appendices

YEAR 2011

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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA Joint Action WP4

Working Groups

of the HTA Core Model, its applications and core HTAs

The development of the HTA Core Model and its applications (i.e. the individual "models"), as well as the production of core HTAs require participation of several people from all over Europe and even further. This document outlines the main working groups and their relations for the EUnetHTA Joint Action 2010-2012. Policies regarding the maintenance and development of the HTA Core Model as well as production of core HTAs beyond that period will be defined within WP4 of the JA. The working groups outlined in this document may provide a useful organizational structure for future developments, but should not be seen as a permanent structure prior to more detailed considerations regarding the structure, participants and policies.

HTA CORE MODEL DEVELOPERS

In the previous EUnetHTA project (2006-2008), the HTA Core Model was developed by two types of developers. Basic principles and solutions were discussed and decided on in two international "General Design Teams" (GDT) that guided the development of the two model applications ("HTA Core Model for medical and surgical interventions" and "HTA Core Model for diagnostics technologies"). The two GDTs were operational during two different periods since the two model applications were designed one after the other (and not in parallel). Participants of these teams were people from WP4 member agencies and shared interest in the overall development work. The two GDTs consisted to a large extent – but not completely – of the same persons. The Lead Partner's internal coordinating team prepared matters for the GDT to discuss, suggested solutions and took care of practical tasks after decisions were made.

The experts of various domains formed the other type of developers. They worked within "domain teams" (DT) and defined the contents of each domain for each model application. "Content" here refers to the introductory texts and methodological guidance within each domain and definition of assessment elements. As was the case with GDTs, there were two different DTs working on each domain of the two model applications. The persons within each DT were partially the same.

CORE HTA PRODUCERS

Two pilot core HTAs were produced in the previous project. As was the case with the model developers, the core HTAs were each produced by one GDT and several DTs (one for each domain). Again the teams consisted only partially of the same persons between the two core HTAs.

NEW STRUCTURE FOR JOINT ACTION 2010-2012

While the aforementioned structure delivered what was expected within the 2006-2008 project, the experience has brought forward some needs for refinement. The key challenge is to create such an organizational structure that supports the development and management of the relatively complex "Core HTA Structure", which consists of the HTA Core Model (i.e. ontology, methodological guidance and reporting structure), various model applications (e.g. model for assessment of diagnostic technologies) and the resulting core HTAs. Such tasks include for example the production of new model applications, updating of already existing applications and developing and refining the more generic features of the HTA Core Model. For that purpose a more permanent structure than the earlier application-specific or core HTA -specific GDTs is needed.

Therefore, a new *Coordination Working Group* (CWG) will replace the old General Design teams. CWG will discuss and decide on all major decisions regarding the HTA Core Model and information produced through using it. The CWG should be viewed as the body for making final decisions within JA WP4 2010-2012. The decisions may need further endorsement by the EUnetHTA Executive Committee and/or Plenary Session. The CWG will be set up for the period of the current Joint Action and its structure and mandate will be reconsidered for further periods.

The following table defines Working Groups (WG) and their tasks within JA WP4:

Name of WG	Period	Tasks	Members
Coordination (CWG)	2010-2012	Discussion and major decisions[1] on basic principles, technical solutions and policies related to • the HTA Core Model, • its applications, • online tool & service, • relevant processes • core HTA structure • SAG involvement Production and approval of relevant guidance documents. Final approval of different model applications together with each application's Editorial team. Focus of GD here is adherence of applications to basic principles and structure of the HTA Core Model and interoperability of applications. Editorial board of the Handbook. Final approval of the 2 core HTAs produced within the JA. Come up with and collecting of relevant ideas on improvement and utilization of the system. See appendix 1 for more detailed tasks. Internal teams within THL and AGENAS will act as more active operational unit, collecting and bringing up topics, preparing them for discussion in the WG Coordination and implement decisions.	12 (+ 1-8 observers) in total ACTUAL MEMBERS: 2 from WP4 LP (Kristian Lampe and Iris Pasternack) 2 from WP4 Co-LP (Marina Cerbo and Mirella Corio) 2 from WP4 Strand A agencies focusing on online tool & service: Iñaki Imaz (ISCIII) and Gottfried Endel (HVB) 2 from WP4 Strand A agencies focusing on screening application: Lidia Becla (AHTAPol) and Nick Crabb (NICE) 4 from WP4 Strand B agencies (producing core HTAs): Wim Goettsch (CVZ), Katrine B. Frønsdal (NOKC), Stefan Mathis (LBI-HTA) and Finn Kristensen (NBoH) OBSERVERS*: 1 from LPs of WP1, WP5, WP6 and WP7 ** Irina Cleemput (WP6, KCE) and representative of HAS (WP7, to be confirmed) Up to 4 invited external experts (primarily some persons of the previous project 2006-2008) CHAIRS: Chairs***: Kristian Lampe and Marina Cerbo Vice-chairs***: Iris Pasternack and Mirella Corio * Observers from those WPs that

[1] Major decisions are decisions that have an important impact on the structure or use of the HTA Core Model as well as of information created through using the Model. The decisions and approvals of this working group should be seen as "final" for WP4 within the Joint Action and for its deliverables, not for the whole EUnetHTA. More general approval by the EUnetHTA Collaboration needs to be sought through relevant mechanisms, e.g. the Executive Committee or Plenary Session. Formal decisions (endorsements etc.) for the EUnetHTA Collaboration as a whole may take place after the completion of the JA period, i.e. end of 2012. WP4 will seek always, however, to find solutions that can be endorsed by the whole EUnetHTA Collaboration.

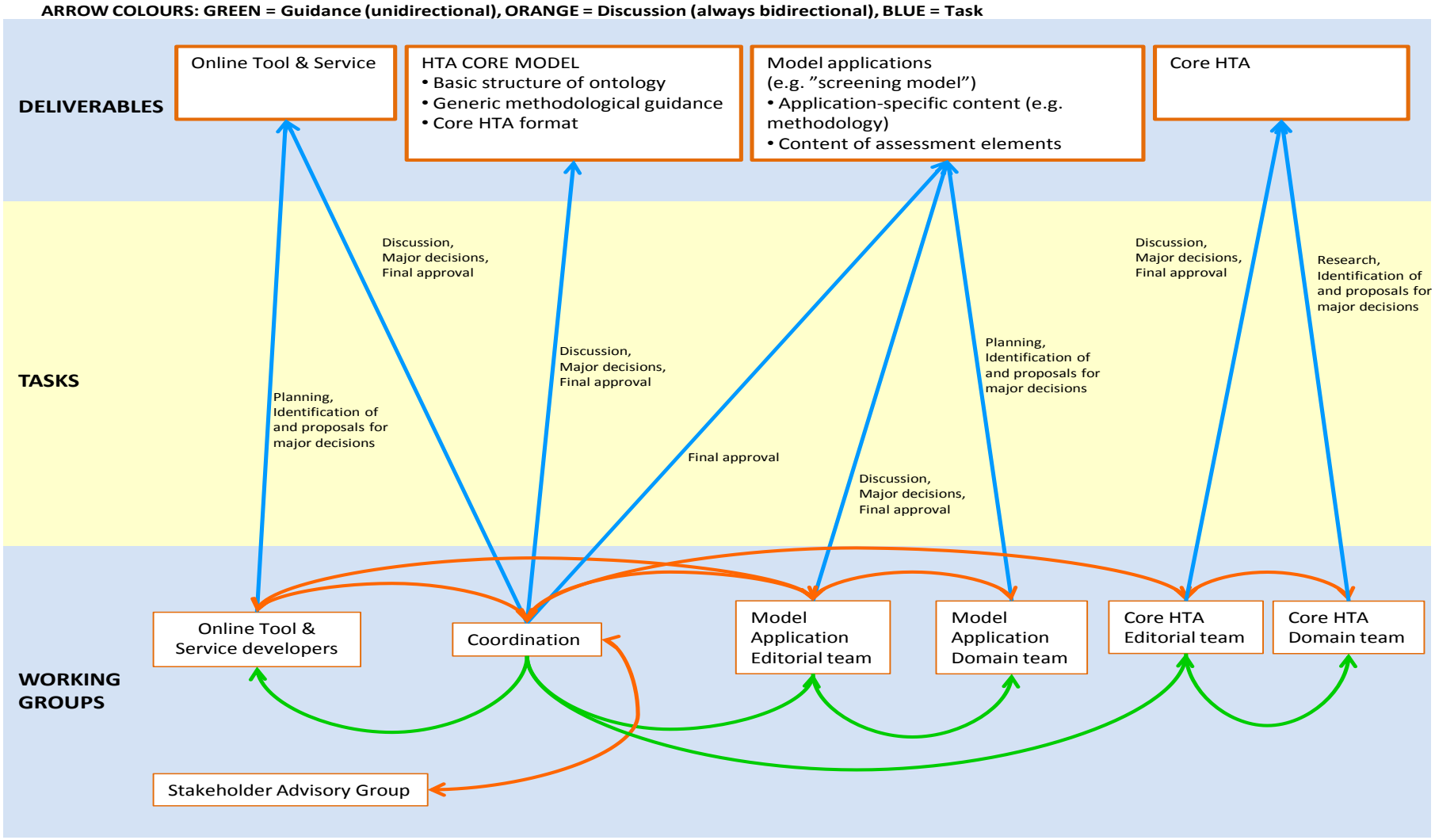
Name of WG	Period	Tasks	Members
			have a more direct link to WP4 are invited to view materials and participate in discussions. They do not have voting right. ** Possible status as actual member of CWG overrides status as an observer, i.e. the latter is not needed. Applies to lead of WP1 (NBoH) and WP5 (CVZ). *** THL will chair topics relevant for the whole WP and Strand A, AGENAS will chair topics relevant for Strand B
Online tool & service developers	2010-2012	Development and testing of • The online tool & service • Structure and format of Core HTAs and other structured information within the core HTA database. Discussion and formulation[2] of basic principles, technical solutions and policies related to • the HTA Core Model, • its applications, • online tool & service, • relevant processes • core HTA structure Production of the Handbook Come up with and collecting of relevant ideas on improvement and utilization of the system. See appendix 1 for more detailed tasks.	Persons from WP4 Strand A agencies focusing on online tool & service Chair: Kristian Lampe Vice-chair: Representative of an AP participating in the work
Editorial team of screening application	2010-2012	Discussion and major decisions on basic principles and solutions related to the HTA Core Model application for screening technologies. Production of relevant guidance documents. Final approval of the whole application together with the CWG.	Persons from WP4 Strand A agencies focusing on screening application Chair: Iris Pasternack Vice-chair: Representative of an AP participating in the work

[2] This working group has a more "hands on" role in the development work. Major decisions are made through CWG, since it represents a wider user community.

Name of WG	Period	Tasks	Members
Domain teams of screening application	2010-2012	Development and testing of the various domains of the HTA Core Model application for screening technologies. Approval of each respective domain, together with the Editorial team, prior to final approval by Editorial team and CWG.	Persons from WP4 Strand A agencies focusing on screening application Primary investigators: CUR Sunya-Lee Antoine TEC Katrine Bjørnebek Frønsdal SAF Iris Pasternack EFF Petra Schnell-Inderst ECO Suvi Mäklin ETH Mirella Marlow ORG Ulla Saalasti-Koskinen SOC Alessandra Lo Scalzo LEG Ingrid Wilbacher
Editorial team of pharmaceutical application	2010-2012	Discussion and major decisions on basic principles and solutions related to the HTA Core Model application for pharmaceuticals. Production of relevant guidance documents. Final approval of the whole application together with the CWG.	Persons from WP5 agencies focusing on pharmaceutical application 1 person from WP4 LP (Iris Pasternack) Chair: CVZ, Wim Goettsch Vice-chair: HAS Mira Pavlovic
Domain teams of pharmaceutical application	2010-2012	Development and testing of the various domains of the HTA Core Model application for pharmaceuticals. Approval of each individual domain, together with the Editorial team, prior to final approval by Editorial team and CWG.	Persons from WP5 agencies focusing on pharmaceutical application Primary investigators: CUR Iris Pasternack TEC Bernardette Rossi, DPPM SAF Marc van de Casteele, RIZIV EFF Anna Bucsics, HBV ECO - ETH Daiga Behmane, CHE ORG Rossella Di Bidino, A.Gemelli SOC Payam Abrishami, CVZ LEG Hans Seyfried, HBV
Editorial team of core HTA 1 (on genetic testing in cancer)	2011-2012	Discussion and major decisions on basic principles and solutions related to the content of core HTA 1. Final approval of the whole core HTA 1 together with the CWG.	Persons from WP4 Strand B agencies focusing on core HTA 1 Chair: Thomas Oliver Jefferson Vice-chair: Heike Raatz

Name of WG	Period	Tasks	Members
Domain teams of core HTA 1 (on genetic testing in cancer)	2011-2012	Production of content for each domain of core HTA 1. Final approval of each respective domain's contents, together with the Editorial team, prior to final approval by Editorial team and CWG.	Persons from WP4 Strand B agencies focusing on core HTA 1 Primary investigators: CUR Sunya-Lee Antoine TEC Antonio Migliore SAF Iris Pasternack EFF TO BE DECIDED ECO TO BE DECIDED ETH Isaura Vieira ORG Jennifer Butt SOC Marco Marchetti LEG Marco Marchetti
Editorial team of core HTA 2 (on AAA screening)	2011-2012	Discussion and major decisions on basic principles and solutions related to the content of core HTA 2. Final approval of the whole core HTA 2 together with the CWG.	Persons from WP4 Strand B agencies focusing on core HTA 2 Chair: Thomas Oliver Jefferson Vice-chair: Katrine Bjørnebek Frønsdal
Domain teams of core HTA 2 (on AAA screening)	2011-2012	Production of content for each domain of core HTA 2. Approval of each respective domain's contents, together with the Editorial team, prior to final approval by Editorial team and CWG.	Persons from WP4 Strand B agencies focusing on core HTA 2. Primary investigators: CUR Stefan Mathis-Endenhofer TEC Daniela Pertl SAF Iñaki Imaz EFF Katrine B. Fronsdal ECO Suvi Mäklin ETH Gottfried Endel ORG Janek Saluse SOC Anne Lee LEG Ingrid Wilbacher
Stakeholder Advisory Group (SAG)	2010-2012	Review and feedback on key WP4 documents prior to public consultation. Details outlined in the following EUnetHTA Joint Action documents: Stakeholder Involvement Policy and Stakeholder Involvement Procedure (SOP), as well as in WP4 3-year work plan.	Representative of Stakeholder Forum participants Chairs*: Kristian Lampe and Marina Cerbo Vice-chairs*: Iris Pasternack and Mirella Corio *THL will chair topics relevant for the whole WP and Strand A, AGENAS will chair topics relevant for Strand B

Figure 1. Working groups, deliverables and tasks



Appendix 1: Immediate needs for CWG discussion and decisions

Working Groups

- Composition of Editorial Teams (ETs): "Which persons from WP4 strand A/B agencies should be members of ET?" "Is the composition of ETs always the same or could it change, depending on the specific product (Core Model applications, Core HTA1, Core HTA2)?" "How will they be nominated?"

  PROPOSAL: ETs are composed by Primary Investigators of the 9 domains (involved in the specific product development); so it is not necessary a nomination process since the role of PI will assign automatically the membership at the ET.

HTA Core Model

- Clarification of basic concepts of the Core HTA Structure
- Reference management in Model and Core HTAs
- Authorship in model texts
- Reconsidering importance and transferability and the meaning of Core, and instructing Model authors on it
- The problem with distinguishing generic and application specific and how to solve it
- Should we include evidence tables as tools?
- Should we go for GRADE?

Core HTAs

- Peer review and editing
- Authorship in updates
- Should methodologies be always reported issue specific instead of domain specific as they usually are now?

EUnetHTA Joint Action WP4

Policies for HTA Core Model and its use

including policies for producing, publishing, storing, retrieving and using structured HTA information and Core HTAs

July 2011

CONFIDENTIAL

This document outlines the policies that JA WP4 will define during Joint Action 2010-2012 as part of its official deliverables. Policies are divided into five groups that steer the A) production, B) publishing, C) storing, D) retrieving and E) using any information produced through the WP4 deliverable "Online Tool & Service". Letters A-E indicate the group, and policies are numbered within each group.

Various options for each policy are presented in this document as a table. Whenever options constitute a continuum from "open use" to "restricted use", the options are presented in an order from liberal to more restrictive.

The crafting process has two main phases. First the various (plausible) options for each policy are identified, alongside with comments on the consequences of each policy ("Pro" and "Con"). In the second phase WP4 agencies are asked to indicate their preference for each option. The goal is to find a set of policies that reflect the overall values and principles of EUnetHTA and adheres to the overall business model of the Network. On the one hand the policies need to balance between an overall trend for *free flow of information and transparency*, and on the other hand the requirements of the Network's *financial sustainability*. Also in situations where a policy cannot accommodate both these principles, a clear choice needs to be defined.

The policies will be defined in a process that contains the following steps (basics were agreed on in the WP4 workshop in Helsinki in March 2010):

1. Agreement on which policies will be developed and on the overall crafting process.
   M11-12, Confirmed in Rome in November 2010 and over email afterwards

2. Mapping and discussing a) plausible options for each policy, b) results of WP4 Strand B analyses
   M17-18, Discussions in Rome in November 2010 and online survey among WP4 participants

3. Find out agencies preferences, i.e. which options are best for each policy
   M19-21, Online survey among WP4 participants

4. Agreement on policies within WP4
   M22, Consideration and proposal by WP4 Coordination work group
   Review and comments by WP4 participants

5. Consultation of WP4 Stakeholder Advisory Group (WP4 SAG) (NEW STEP, AFTER SETUP OF SAG)
   M23, Review and commentary through email

6. Public consultation
   M23, Online survey

7. Final approval by EUnetHTA Executive Committee
   M24

8. Final approval by EUnetHTA Plenary Assembly
   After M24

The policies agreed on by M24 will be revisited in May 2012 (M29), to allow all EUnetHTA agencies consider their appropriateness in the current situation of their agencies and the overall concepts defined within WP4. Further refinement will be carried out only if necessary. Final versions will be ready by the end of 2012 (M36).

TERMS AND CONCEPTS

Readers of this document should be aware that terms and concepts often have a different meaning depending on the context. The work HTA Core Model uses in many cases terms that already exist (e.g. "protocol") which may or may not have the same meaning as in some other setting (e.g. medical research). In some cases completely new terms have been coined (e.g. "core HTA").

The EUnetHTA may still choose to redefine these terms or use different terms for concepts presented here. Hence these should not be seen as a final vocabulary of WP4 or EUnetHTA as a whole. But for the purposes of this policy paper, the following terms and concepts (including their meaning in this context) are used in this document:

HTA Core Model is a framework for structured production and presentation of HTA information as assessment elements. The HTA Core Model enables collaborative production and sharing of information. It consists of a) an ontology for HTA, b) methodological guidance and c) a common reporting structure. The ontology provides a basis for structured research protocols. The answers to questions defined by a protocol are answered using the available methodological guidance and reported using the common reporting structure.

Assessment elements are the basic unit of the HTA Core Model. Defines a piece of information that describes the technology or the consequences of implications of its use, or any other implication that is relevant for the assessment, such as the patients and the disease for which it is applied. All assessment elements within the HTA Core Model form a common pool of elements that can be utilized by different applications (see below).

HTA ontology constitutes a formal representation of knowledge within HTA, defined as assessment elements and their relations. It does not contain methodological guidance.

Application of the HTA Core Model is built for assessing a specific kind of health technology. Different kinds of technologies (e.g. surgical interventions or pharmaceuticals) may require different questions to be asked in an assessment and the answers to the questions may require different kind of methodological guidance. Different applications all draw from the same pool of assessment elements, but not all elements are used in all applications.

Methodological guidance exists on two levels within the HTA Core Model. Domain-specific guidance provides general advice about how to answer research questions within a specific domain (e.g. effectiveness or ethics). More specific guidance may be available for answering questions within individual assessment elements. Various Core Model applications (see above) may contain different kind of guidance. All guidance is included in the applications of the HTA Core Model, not in the ontology.

Online Tool & Service is the deliverable under construction within WP4. It constitutes of a Tool with which one can use the HTA Core Model to produce and publish HTA information and a Database of information (a.k.a. the "Service") that has been produced using the Tool and that is available for various purposes.

Information systems in this document refer to any information system (including but not limited to "tools" and databases), in any format (e.g. electronic or paper format) that considers utilizing the HTA Core Model or parts of it.

Core HTA information refers in this document to any information that is a) produced using the Online Tool and b) made available through the Service. Some of the information is included in collections that follow a standard, "official" EUnetHTA template. For example core HTAs have a specific and extensive structure (see below). Other, more limited collections may be made available as official templates, such as rapid reviews. On the other hand, some of the information in the Service has been produced in a more ad hoc manner as "free selection of assessment elements" (e.g. if someone wants to use only one or few assessment elements to answer a very limited question). There may or may not be a need to distinguish between the official templates and other information when it comes to policies. Notice also, that the appropriateness of this term will be considered further within the Joint Action. It is used here for the purposes of this questionnaire and respondents should look more at the definition of it when responding.

Official EUnetHTA templates -> See "Core HTA information".

Core HTA is an assessment that a) has been conducted using the HTA Core Model and b) has considered all core elements of all 9 domains. A Core HTA is an extensive collection of information that contains also some standard text chapters, such as a common introduction and a summary that draws together key findings of various domains, but does not make recommendations on technology use.

(Project) protocol is the overall plan of producing any core HTA information. It defines – among other things – persons participating in a project, research questions that will be answered and possibly methodology used in answering.

Terms of Use are defined in a public document available to users of the HTA Core Model and the Online Tool & Service. The document defines in concise format the terms according to which the deliverables can be used. Terms are based on the more extensive policy document crafted within WP4 (i.e. this work).

Unauthorized use of the HTA Core Model is regarded as any use that violates the Terms of Use.

Commercial use is use in any manner that is primarily intended for or directed toward commercial advantage or private monetary compensation. This includes any use in a setting where the HTA Core Model is used for producing information made available only against a fee, or where the Model is used in information systems available only against a fee (including but not limited to systems used for producing HTA information). Notice that "commercial use" and "non-commercial use" are to some extent controversial terms and hence this definition may need reconsidering.

EUnetHTA Partners are organizations with full membership in EUnetHTA (same as Joint Action Associated Partners). See http://www.eunethta.net/Public/About_EUnetHTA/Organisation2/

EUnetHTA Associates: Organizations with limited membership in EUnetHTA (e.g. Joint Action Collaborative Partners). See http://www.eunethta.net/Public/About_EUnetHTA/Organisation2/

EUnetHTA Token is used here to represent a "currency" that is not money, but some other form of value or contribution that could be defined and used within the Network. EUnetHTA Token does not exist at the moment and would require a more general approval within the Network. For example an organization might have access to the Online Tool & Service only if the organization itself feeds information into the system as well. The Token in this context may be regarded as something that can be counted ("credits") or

something that cannot be counted. The POP database utilizes the latter approach in the sense that only agencies that provide information into the database can use it.

LIST OF POLICIES

Section A. The HTA Core Model

1. Availability of the HTA Core Model and its applications

Note 1: The following parts of the HTA Core Model may require separate decisions: a) the ontology (i.e. list of assessment elements and their relations), b) different applications (e.g. model for assessing diagnostic technologies)

Note 2: Section A is not about information produced through using the HTA Core Model (core HTAs, rapid reviews, any other compilations of structured HTA information)

Note 3: Whenever the HTA Core Model or its applications are made public, there is a possibility that its contents are taken for unauthorized use somewhere else. There is no 100 % secure way of preventing this, we can just make it more or less difficult to "steal".

Policy A1-1: Who can access the HTA Core Model and its applications?

Option ID	Option	Pros	Cons
a	All contents of the HTA Core Model are available to anyone in electronic format (e.g. HTML/XML) and as PDF documents.	• Transparency • Enables use in other tools	• All contents can easily be "stolen" for settings where Terms of Use are ignored
b	All contents of the HTA Core Model are available to anyone, but only as PDF documents. Other formats (e.g. HTML/XML) are available to anyone only through separate request and registration.	• Transparency • More difficult – but not impossible – to utilize for unauthorized purposes	• Requires some administrative effort when responding to requests
c	All contents of the HTA Core Model are available to anyone, but only as PDF documents. Other formats (e.g. HTML/XML) are available only to EUnetHTA Partners and Associates through separate request and registration.	• Transparency • Difficult – but not impossible – to utilize for unauthorized purposes	• Advanced utilization restricted to EUnetHTA Partners and Associates
d	Only the applications are available to anyone as PDF documents. The ontology is not distributed beyond the Online Tool & Service.	• Good control of contents	• Only partial transparency • Difficult to utilize in other tools
e	Only the applications are available to anyone as PDF documents. The ontology is available to anyone only through separate request and	• Transparency • Possible to use in other tools	• Requires some administrative effort when responding to

	registration.		requests
f	Only the applications are available to EUnetHTA Partners and Associates as PDF documents. The ontology is not distributed beyond the Online Tool & Service.	• Good control of contents	• Poor transparency • In any case not 100 % safe against unauthorized use
g	All contents of the HTA Core Model are available only through the Online Tool & Service for those who have access to it. Only parts of the Model that the user currently needs are available for viewing. The complete Model and its applications are not available to anyone except a small group defined by EUnetHTA Executive Committee.	• Good control of the contents	• Poor transparency • Not 100 % safe against unauthorized use

Policy A1-2: Who can distribute the HTA Core Model and its applications?

Note: Choosing option a or b of this policy renders options c-g of policy A1-1 impossible.

Option ID	Option	Pros	Cons
a	Anyone (including commercial and non-commercial parties) can distribute the HTA Core Model and its applications either as original or modified versions.	• Possibly more effective distribution	• Difficult or impossible to control versions • More effective distribution questionable as bandwidth or server space are not likely to become an obstacle
b	Anyone (including commercial and non-commercial parties) can distribute the HTA Core Model and its applications as original unmodified versions.	• Possibly more effective distribution	• Difficult or impossible to control versions • More effective distribution questionable as bandwidth or server space are not likely to become an obstacle
c	Only sites controlled by EUnetHTA or one of its member agencies can distribute the HTA Core Model and its applications. EUnetHTA decides on the distribution location (one or more) and may grant distribution rights to other trusted parties.	• Original versions in one or few places, hence good control of versions • Easy to point to official versions	•

2. Terms of use of the HTA Core Model

Note 1: A separate document "Terms of Use" is available since 2008. It will be updated to reflect the policies defined in this broader policy document.

Note 2: These policies outline general rules about using the HTA Core Model. More specific policies for core HTA information are available in sections below. Use of the Model within the Online Tool & Service is defined in sections B-E of the policies.

Policy A2-1: What kind of information can be produced with the HTA Core Model?

Note: This policy does not limit use of the HTA Core Model in settings were limitations can be seen as either illegal or otherwise unreasonable, such as the following settings: a) normal citation rights for those who have authorized access to the Model, b) scientific works that analyze different research methodologies or tools available for health research, as long as the Model has been accessed in an authorized manner.

Option ID	Option	Pros	Cons
a	Anyone can use the HTA Core Model for producing any kind of information, as long as they have authorized access to it.	• Flexibility	• Easy possibility for inappropriate use (e.g. false versions of the Model or its applications being distributed, false core HTAs used for marketing purposes, applications that use only parts of the Model to achieve an inappropriate goal)
b	The HTA Core Model can be used for producing non-commercial scientific information on health technologies (e.g. HTAs, literature reviews or other scientific studies). Use for any commercial purposes is not permitted.	• In accordance with overall EUnetHTA values	• Some potential for information production is lost
c	The HTA Core Model can be used for producing non-commercial scientific information on health technologies (e.g. HTAs, literature reviews or other scientific studies). Use for any commercial purposes requires specific free license that is available for free to anyone.	• Flexibility	• Perhaps very difficult to follow-up whether commercial use in reality follows overall Terms of Use
d	The HTA Core Model can be used for	• Income for EUnetHTA	• Perhaps very difficult

	producing non-commercial scientific information on health technologies (e.g. HTAs, literature reviews or other scientific studies). Use for any commercial purposes requires specific license that is available against a fee to anyone.		to follow-up whether commercial use in reality follows overall Terms of Use

Policy A2-2: Should the information produced through using the HTA Core Model be made publicly available?

Option ID	Option	Pros	Cons
a	Any information produced through using the Model must be made publicly available either on the Internet or as paper format. No fees must be collected from end-users of the produced information. COMMENT: THIS IS FROM THE CURRENT VERSION OF TERMS OF USE (published 31 Dec 2008)	• Facilitates free flow of information	• Makes it impossible to use the Model in work that is published in a journal that requires fee-based subscription.
b	Any information produced through using the Model must be made publicly available either on the Internet or as paper format. No fees must be collected from end-users of the produced information. An exception to this rule is use of the Model in scientific research, where the results are published as articles in scientific journals (that may or may not be available for free). COMMENT: MODIFIED VERSION OF CURRENT TERMS OF USE. THE NEED TO REFINED THIS PART HAS BEEN IDENTIFIED IN PRACTICE	• Facilitates free flow of information	•

Policy A2-3: Which version of the HTA Core Model should be used?

Note: This policy outlines general rules about using the HTA Core Model. More specific policies may be available below for core HTA information.

Option ID	Option	Pros	Cons
a	The HTA Core Model and its applications should always be used unaltered and in their most recent version available. In cases where the Model is updated during an ongoing work, users of the Model may choose whether they	•	• Creates confusion particularly in studies that take a long time to complete.

	want to finalize their work using the version they originally started with, or whether they will adjust their work to the updated version. COMMENT: THIS IS FROM THE CURRENT VERSION OF TERMS OF USE (published 31 Dec 2008)		
b	The HTA Core Model and its applications should always be used unaltered and in their most recent version available. In cases where the Model is updated during an ongoing work, users of the Model may choose whether they want to finalize their work using the version they originally started with, or whether they will adjust their work to the updated version. The version used must be indicated in the final work. COMMENT: MODIFIED VERSION OF CURRENT TERMS OF USE.THE NEED TO REFINED THIS PART HAS BEEN IDENTIFIED IN PRACTICE	• Flexibility	•

Policy A2-4: How should use of the HTA Core Model be disclosed?

Option ID	Option	Pros	Cons
a	The origin of the model is disclosed in the final products of the assessment as the EUnetHTA project and related documentation COMMENT: THIS IS FROM THE CURRENT VERSION OF TERMS OF USE (published 31 Dec 2008)	• Acknowledge original source of methodology	• Vague
b	Use of the HTA Core Model should always be disclosed in the final product(s), such as reports, articles or other documents, or in other information systems, through including the following text in the final product(s): *"The HTA Core Model®, developed within EUnetHTA (www.eunethta.eu), has been utilized when producing the contents and/or structure of this work. The following application of the Model was used: INCLUDE NAME AND VERSION OF APPLICATION HERE."* COMMENT: MODIFIED VERSION OF CURRENT	• Acknowledge original source of methodology • Explicit • Increases transparency about which methodological guidance was used.	•

	TERMS OF USE.		

Policy A2-5: Can the HTA Core Model be used as part of information systems and other tools?

Note 1: The HTA Core Model or parts of it (such as the ontology or reporting structure) could be utilized by a variety of information systems, such as databases, electronic patient records, or decision support systems.

Note 2: This policy is limited to using the HTA Core Model, but not information produced through utilizing the Model. The latter is considered in other policies (see below).

Note 3: The contents of a "license" would need to be crafted separately. That has not been done yet.

Option ID	Option	Pros	Cons
a	The Model and its information structure can be utilized in academic, governmental and other non-commercial information systems that are built for production and publishing of HTA information, provided that all other policies are followed. Use for any commercial purposes is not permitted.	• Broad and flexible non-commercial use possible.	• Information systems are often designed by commercial bodies and hence a lot of potential for bringing HTA results into system is lost. • Potential for income for EUnetHTA is lost.
b	The Model and its information structure can be utilized in academic, governmental and other non-commercial information systems that are built for production and publishing of HTA information, provided that all other policies are followed. Use for any commercial purposes requires a specific license that is available for free.	• Both non-commercial and commercial use possible.	• Requires some administrative work • Potential for income for EUnetHTA is lost.
c	The Model and its information structure can be utilized in academic, governmental and other non-commercial information systems that are built for production and publishing of HTA information, provided that all other policies are followed. Use for any commercial purposes requires a specific license that is available against a fee/token.	• Both non-commercial and commercial use possible. • Income for EUnetHTA	• Requires some administrative work

Policy A2-6: Does use of HTA Core Model require registration?

Note: different approach may be preferred for two types of use: producing information (as within one single project), or as part of an information system.

Option ID	Option	Pros	Cons
a	No registration is needed for any authorized use.	• Flexibility	• Not possible to follow-up use of the Model
b	Registration is recommended but not obligatory for any authorized non-commercial use. Commercial use must be registered.	• Flexibility • Possible to partly follow-up use of the Model	• Not possible to fully follow-up use of the Model
c	Registration is recommended but not obligatory for producing information through using the HTA Core Model for non-commercial purposes. Use of the Model as part of any information system (both non-commercial and commercial) requires registration. Any other commercial use must be registered.	• Possible to partly follow-up use of the Model	• Not possible to fully follow-up use of the Model • Some administrative work required
d	All authorized use requires registration.	• Possibility for good follow-up of use.	• Possibly very heavy administrative processes required.

3. Managing and updating the HTA Core Model and its applications

Note: these policies are about the official version of the HTA Core Model and its applications. They do not apply to local modifications of these (should those be permitted).

Policy A3-1: Who updates the HTA Core Model and its applications?

Option ID	Option	Pros	Cons
a	Anyone can update the HTA Core Model and its applications through a "Wikipedia-like", non-controlled, interface.	• Very many potential updaters	• Virtually impossible to control the quality of contents
b	Staff of EUnetHTA Partners and Associates may update the HTA Core Model and its applications through a "Wikipedia-like", non-controlled, interface.	• Very many potential updaters	• Difficult to control the quality of contents
c	Applications are updated through self-nominated, ad hoc expert groups that review existing applications at irregular intervals (or	• Many potential updaters • Coordinated effort	• Poor or no coordination between applications

	never).	within an application	• No control of contents and expertise of developers • May result is seriously outdated applications
c	Applications are updated through self-nominated expert groups that periodically review existing applications.	• Many potential updaters • Good control of contents • Coordinated effort within an application	• Poor or no coordination between applications • No control of contents and expertise of developers
d	Applications are updated through (self-nominated) expert groups that periodically review existing applications. An editorial board oversees the whole HTA Core Model and approves proposed changes.	• Many potential updaters • Good control of contents • Coordinated effort within an application • Coordinated effort across all applications • Good control of contents	• Some administrative work required • No control of expertise of developers
d	Applications are updated through expert groups (nominated by an editorial board) that periodically review existing applications. An editorial board oversees the whole HTA Core Model and approves proposed changes.	• Many potential updaters • Good control of contents and expertise of developers • Coordinated effort within an application • Coordinated effort across all applications • Good control of contents	• Some administrative work required

Policy A3-2: Who can suggest changes to the HTA Core Model and its (already existing) applications?

Option ID	Option	Pros	Cons
a	The following parties can suggest changes: • Expert groups developing a completely new HTA Core Model application • Expert groups updating an existing HTA Core Model application		

	•		
b	The following parties can suggest changes: • Expert groups developing a completely new HTA Core Model application • Expert groups updating an existing HTA Core Model application • Anyone who wants to contribute to improving an existing HTA Core Model application • Anyone who has access to an existing HTA Core Model application, or has used such an applications		

Policy A3-3: How often are the HTA Core Model and its applications updated?

Note: Some conceptual and technical features of the HTA Core Model that have not been fully decided on yet have a great impact on this policy. Hence this policy will be defined only after those decisions have been made.

Section B. Production of core HTA information

1. Topic selection

Policy B1-1: Who can propose topics for official EUnetHTA templates (e.g. core HTAs)?

Option ID	Option	Pros	Cons
a	Anyone can propose topics through the EUnetHTA website, possibly organized as a periodic call		
b	Only EUnetHTA Partners and Associates can propose topics through relevant tools.		
c	EUnetHTA Partners and Associates, as well as Stakeholder Forum members can propose topics through relevant tools.		
	EUnetHTA Partners and Associates can propose topics through relevant tools. In addition, members state governments can propose topics through the European Commission (DG SANCO)		
d	EUnetHTA Partners and Associates as well as Stakeholder Forum members can propose topics through relevant tools. In addition, member state governments can propose topics through the European Commission (DG SANCO).		

Policy B1-2: How are topics suggested for official EUnetHTA templates (e.g. core HTAs) prioritized and selected?

Option ID	Option	Pros	Cons
a	Any research group that otherwise fulfils relevant requirements and follows policies may start a core HTA project. A list of proposed topics may be made available by EUnetHTA, but no effort is made to steer topic selection.	• Broader coverage	• High risk of duplication • Risk of projects of local interest • Risk of limited depth

b	Any research group that otherwise fulfils relevant requirements and follows policies may start a core HTA project and choose a topic independently. An effort is made by EUnetHTA to identify and promote topics of common interest and utility, but choosing those topics is not mandatory for research groups. Other EUnetHTA tools are also utilized in this process (POP database, EVIDENT). EUnetHTA may (or may not) choose joint topics for core HTAs produced within the Network.	• Facilitate projects of common interest • Low risk of duplication due to coordination by EUnetHTA • Information needs may be covered through a centralized mechanism, but it is not mandatory.	• Some extra work
c	All Core HTA topics are defined and decided on by a centralized EUnetHTA mechanism that will be defined in more detail later.	• Good control of core HTA topics, concerted effort	• Lot of information production potential may be lost.

Policy B1-3: What kinds of collections of information should the Online Tool & Service contain?

Option ID	Option	Pros	Cons
a	Both information that follows official EUnetHTA templates (e.g. core HTAs and rapid reviews) and other information (e.g. on single or freely selected sets of assessment elements)	• Broader overall coverage	• Possibly difficult to manage quality and other aspects
b	Only information that follows official EUnetHTA templates (e.g. core HTAs and rapid reviews)	• All information included in standard formats with good coverage • Easier to manage quality	• Potential to produce information reduced

2. Producers

Note 1: All official guidance of EUnetHTA regarding stakeholder involvement and commercial parties applies in all options.
Note 2: Publication process is defined in another policy below.

Policy B2-1: Who is allowed to use the Online Tool and submit information to be published in the Service according to official EUnetHTA templates (including core HTAs)?

Option ID	Option	Pros	Cons
a	Anyone	• Possibility for large volumes of information	• Where is the added value for EUnetHTA member agencies? • How can the expertise and honesty of producers be guaranteed? • Poor reliability level without very detailed peer-review
b	Anyone except producers of health technologies or parties that are involved in their sales or promotion	• Possibility for large volumes of information • Exclusion of most biased producers	• How can it be confirmed that someone is not really a producer or seller? • Poor reliability level without very detailed peer-review
c	Any non-commercial party	• No commercial interest in production	• How can the status of each party regarding their commercial interests be checked? • Poor reliability level without very detailed peer-review
d	Only EUnetHTA partners and associates	• Added value for members • Good reliability level	• Limited volumes of information
e	Only EUnetHTA partners	• Added value for members • Good reliability level	• Greatly limited volumes of information • Why would associates be interested in the network if the cannot participate in information production?

Policy B2-2: Who is allowed to use the Online Tool and submit information (e.g. on single assessment element) that does not follow the official EUnetHTA templates to be published in the Service?

Option ID	Option	Pros	Cons
a	Anyone	• Possibility for large volumes of information	• Where is the added value for EUnetHTA member agencies? • How can the expertise and honesty of producers be guaranteed? • Poor reliability level without very detailed peer-review
b	Anyone except producers of health technologies or parties that are involved in their sales or promotion	• Possibility for large volumes of information • Exclusion of most biased producers	• How can it be confirmed that someone is not really a producer or seller? • Poor reliability level without very detailed peer-review
c	Any non-commercial party	• No commercial interest in production	• How can the status of each party regarding their commercial interests be checked? • Poor reliability level without very detailed peer-review
d	Only EUnetHTA partners and associates	• Added value for members • Good reliability level	• Limited volumes of information
e	Only EUnetHTA partners	• Added value for members • Good reliability level	• Greatly limited volumes of information • Why would associates be interested in the network if the cannot participate in information production?

Policy B2-3: What expertise is required from those involved in producing information that follows official EUnetHTA templates?

Option ID	Option	Pros	Cons
a	No requirements	• Flexibility	• Possibly incompetent producers
b	At least one expert EITHER on the topic (e.g. medical specialist, nurse, physiotherapist, engineer, clinical chemist, microbiologist) OR on the domain's typical methodology (e.g. an ethicist in ethical analysis domain) should participate actively as investigator in each domain.	• Some expertise present	• Expertise limited to topic or research methods
c	At least one expert BOTH on the topic (e.g. medical specialist, nurse, physiotherapist, engineer, clinical chemist, microbiologist) AND on the domain's typical methodology (e.g. an ethicist in ethical analysis domain) should participate actively as investigator in each domain.	• Expertise on both topic and methods present	• Expertise limited to two persons
d	At least two experts on BOTH the topic (e.g. medical specialist, nurse, physiotherapist, engineer, clinical chemist, microbiologist) AND on the domain's typical methodology (e.g. an ethicist in ethical analysis domain) should participate actively as investigator in each domain.	• Expertise on both topic and methods present	•

Policy B2-4: What expertise is required from those involved in producing information that does not follow official EUnetHTA templates?

Option ID	Option	Pros	Cons
a	No requirements	• Flexibility	• Possibly incompetent producers
b	At least one expert EITHER on the topic (e.g. medical specialist, nurse, physiotherapist, engineer, clinical chemist, microbiologist) OR on the domain's typical methodology (e.g. an ethicist in ethical analysis domain) should participate actively as investigator in each domain.	• Some expertise present	• Expertise limited to topic or research methods

c	At least one expert BOTH on the topic (e.g. medical specialist, nurse, physiotherapist, engineer, clinical chemist, microbiologist) AND on the domain's typical methodology (e.g. an ethicist in ethical analysis domain) should participate actively as investigator in each domain.	• Expertise on both topic and methods present	• Expertise limited to two persons
d	At least two experts on BOTH the topic (e.g. medical specialist, nurse, physiotherapist, engineer, clinical chemist, microbiologist) AND on the domain's typical methodology (e.g. an ethicist in ethical analysis domain) should participate actively as investigator in each domain.	• Expertise on both topic and methods present	•

Policy B2-5: What kind of organizational structure is required from Core HTA producers; is the contribution from one HTA agency enough?

Option ID	Option	Pros	Cons
a	No specific requirements, as long as requirements in Policy B2-4 are met.		
b	One organization may do the research work and another organization may provide reviewers.		
c	At least two organizations from two different countries should participate actively in the project by providing researchers. Reviewers can be from these or other organizations.		
d	At least two organizations from two different countries should participate actively in the project by providing researchers. Reviewers should come from other organizations in one or two other countries.		
e	At least three organizations from three different countries should participate actively in the project by providing researchers. Reviewers can be from these or other organizations.		
f	At least four organizations from four different countries should participate actively in the project by providing researchers. Reviewers		

	can be from these or other organizations.		
g	At least five organizations from five different countries should participate actively in the project by providing researchers. Reviewers can be from these or other organizations.		
h	At least seven organizations from five different countries should participate actively in the project by providing researchers. Reviewers can be from these or other organizations.		
i	At least seven organizations from seven different countries should participate actively in the project by providing researchers. Reviewers can be from these or other organizations.		

3. Protocol design

Note 1: All production of core HTA information with the Online Tool & Service requires setting up a "project" within the Tool. The project starts with designing a protocol that contains the questions that are to be answered in the project. The protocol must be marked "completed" by the project group before the research commences and any results can be entered. Likewise the results must be marked completed prior to the official publication process can proceed.

Note 2: The smallest "project" may find an answer only to one single question (defined by one assessment element).

Policy B3-1: Does a project protocol require some form of approval before it is accepted into the Online Tool & Service?

Option ID	Option	Pros	Cons
a	No approval is needed.	• Flexible	• Poor control of content
b	Approval of protocol by a body appointed by EUnetHTA (e.g. editorial board) is required for any project that follows official EUnetHTA templates (core HTAs, rapid reviews, etc.) and is not lead by a EUnetHTA Partner or Associate	• Control of content that follows official templates from the beginning	• Requires administrative work and expertise
c	Approval of protocol by a body appointed by EUnetHTA (e.g. editorial board) is required for any project that follows official EUnetHTA	• Good control of content that follows official templates from	• Requires administrative work

	templates (core HTAs, rapid reviews, etc.)	the beginning	and expertise
d	Approval of a protocol by a body appointed by EUnetHTA (e.g. editorial board) is required for any project not lead by a EUnetHTA Partner or Associate, irrespective of its format. Projects lead by EUnetHTA Partners or Associates do not need their protocols approved.	• Good control of content from the beginning	• Requires administrative work and expertise
e	Approval of a protocol by a body appointed by EUnetHTA (e.g. editorial board) is required for any project not lead by a EUnetHTA Partner, irrespective of its format. Projects lead by EUnetHTA Partners do not need their protocols approved.	• Good control of content from the beginning	• Requires administrative work and expertise
f	Any project protocol needs to be formally approved by a body appointed by EUnetHTA (e.g. editorial board)	• Good control of any content from the beginning	• Requires administrative work and expertise

4. Answering research questions

Policy B4-1: How should the multinational environment of EUnetHTA be taken into account when producing core HTA information?

Option ID	Option	Pros	Cons
a	There are no requirements. Core HTA information can be produced as any information for national/regional settings.	• No change to agencies' current research methods	• Possibly poor transferability and other utility of produce information in other settings
b	Core HTA information can be produced either a) through making a reasonable effort to produce information that is likely to be useful in contexts beyond producers' own setting, or b) as any information for national/regional settings. In the latter case (b), a warning of potentially high context-dependence must be included.	• Flexibility • Disclaimers present	• Possibly poor transferability and other utility of produce information in other settings • No particular demands for information that can be expected to be useful, since it is produced with tools created by the Network itself. • No agreed mechanism

			for contextualisation.
c	When producing information through official EUnetHTA templates (e.g. core HTA), a reasonable effort must always be made to produce information that is likely to be useful in contexts beyond producers' own setting. Information that does not follow official templates can be produced as any information for national/regional settings.	• Information in EUnetHTA templates likely to be useful in many countries	• "Reasonable effort" is a vague definition, leaves much room for interpretation
d	Irrespective whether the information follows or does not follow official EUnetHTA templates (e.g. core HTA), a reasonable effort must always be made to produce information that is likely to be useful in contexts beyond producers' own setting.	• Likely to be useful in many countries	• "Reasonable effort" is a vague definition, leaves much room for interpretation
e	An analysis that comprises the situation or context in each European country should be carried out for all products that follow official EUnetHTA templates (e.g. core HTA).	• Likely to be useful in many countries	• Extensive amount of work
f	An analysis that comprises the situation or context in each European country should be carried out for all products, irrespective whether they follow or do not follow official EUnetHTA templates (e.g. core HTA).	• Likely to be useful in many countries	• Extensive amount of work

5. Updating Core HTAs and other information within the Online Tool & Service

Note: Updating in this context means that a new version of any information piece included in the Service is produced (e.g. answer to a question defined by a specific assessment element). It will amend, not replace the old one. Technical solutions are sought to allow linking from older information to newer information.

Policy B5-1: Who may update core HTA information?

Option ID	Option	Pros	Cons
a	Anyone who has access to the Online Tool & Service can update core HTA information, provided that other relevant policies are followed and that origins of each piece of information can be traced back to its original source, references and author.	• Many potential updaters • Potential fast updating	• Intellectual property rights need to be defined clearly so as not to be accused for plagiarism.
b	Only original producers may update any	• Good control of contents and IPRs	• Probably an illegal request, as if one

	information.		would not be allowed to repeat scientific research to confirm earlier results. • Very rigid system, information production potential wasted.
c	Only original producers may update any information for a period that is specifically agreed on (e.g. 2 years). After the period anyone who has access to the Online Tool & Service can update core HTA information, provided that other relevant policies are followed and that origins of each piece of information can be traced back to its original source, references and author. Original authors may also release the information for free updating even before the period is over.	• Many potential updaters • More likely to be updated sooner or later	• Intellectual property rights need to be defined clearly so as not to be accused for plagiarism.

Policy B5-2: How often are core HTAs updated?

Option ID	Option	Pros	Cons
a	No time requirements are set and no extra efforts are made to ensure updates. All depends on the topics and various parties' needs.	• No obligations	• Possibly a lot of outdated information
b	No time requirements are set, but a follow-up mechanism is designed to identify those core HTAs that would most likely benefit from updating and specific calls within EUnetHTA are made for updating them.	• Very few obligations • Identification of most relevant topics	• Some research and administrative work required
c	EUnetHTA commits to update selected core HTAs once every two years (until the topic becomes obsolete).	• There is often a core HTA available for most relevant topics	• Substantial amount of research work required • Some administrative work required • Information often becomes outdated within 2 years, particularly with new technologies
d	EUnetHTA commits to update selected core HTAs once per year (until the topic becomes	• There is often a core HTA available for most	• Substantial amount of research work

	obsolete).	relevant topics • Currency of information	required • Some administrative work required
e	EUnetHTA commits to update all core HTAs once every two years (until the topic becomes obsolete).	• There is often a core HTA available for most relevant topics	• Substantial amount of research work required • Some administrative work required • Information often becomes outdated within 2 years, particularly with new technologies
f	EUnetHTA commits to update all core HTAs once per year (until the topic becomes obsolete).	• There is often a core HTA available for most relevant topics • Currency of information	• Substantial amount of research work required • Some administrative work required

Policy B5-3: How often is such core HTA information updated that does not follow official EUnetHTA templates (e.g. on single assessment elements)?

Option ID	Option	Pros	Cons
a	No time requirements are set and no extra efforts are made to ensure updates. All depends on the topics and various parties' needs.	• No obligations	• Possibly a lot of outdated information
b	No time requirements are set, but a follow-up mechanism is designed to identify those pieces of information that would most likely benefit from updating and specific calls within EUnetHTA are made for updating them.	• Very few obligations • Identification of most relevant topics	• Some research and administrative work required
c	EUnetHTA commits to update selected pieces of information once every two years (until the topic becomes obsolete).	• There is often information available for most relevant topics	• Substantial amount of research work required • Some administrative work required • Information often becomes outdated within 2 years, particularly with new technologies

d	EUnetHTA commits to update selected pieces of information once per year (until the topic becomes obsolete).	• There is often information available for most relevant topics • Currency of information	• Substantial amount of research work required • Some administrative work required
e	EUnetHTA commits to update all pieces of information once every two years (until the topic becomes obsolete).	• There is often information available for most relevant topics	• Substantial amount of research work required • Some administrative work required • Information often becomes outdated within 2 years, particularly with new technologies
f	EUnetHTA commits to update all pieces of information once per year (until the topic becomes obsolete).	• There is often information available for most relevant topics • Currency of information	• Substantial amount of research work required • Some administrative work required

Section C. Publishing of core HTA information

1. Authorship

Policy C1-1: How is authorship defined in core HTA information?

Option ID	Option	Pros	Cons
a	No authorship is granted to authors and contributors.	• Very flexible	• Probably illegal, as certain IPRs cannot be revoked • Does not encourage people to contribute
b	Authorship and contributorship is defined within each project separately.	• Flexible	• May make it difficult to update information or define policies as different parts have different authorship principles.
c	Authorship and contributorship follow the requirements of ICMJE, http://www.icmje.org/ethical_1author.html.	• Follows a well-recognized international standard • Same rules for anyone, consequently "authors" mean approximately the same thing in all other documentation and policies.	• Updating information requires specific consideration.

2. Quality assurance

Policy C2-1: What quality assurance procedures are used for publishing Core HTAs and other information?

Note: EUnetHTA may choose to have different types of information available: some of it more endorsed by the network through a rigorous editorial process ("peer reviewed information endorsed by EUnetHTA") and some not endorsed at all ("caveat emptor, use at own risk").

Option ID	Option	Pros	Cons
a	None. Each research group that fulfils the requirements outlined in policy group 2B can publish their work.	• Flexible • No administrative work	• Impossible to guarantee quality of content • Likely to gather low quality information into the Service
b	Any collection of information that follows official EUnetHTA templates (e.g. core HTA, rapid review) is subject to approval by an editorial board. Other collections (e.g. free selection of assessment elements) can be published without approval by an editorial board.	• Relatively flexible • Relatively good control of official template sections	• Users may find it difficult to distinguish between the two types. Challenge for interface design. • It may be very difficult for editorial board to judge quality of information • Heavy dependence on the original producers' own quality management processes.
c	Any collection of information that follows official EUnetHTA templates (e.g. core HTA, rapid review) is subject to external peer-review and approval by an editorial board. Other collections (e.g. free selection of assessment elements) can be published without peer-review or approval by an editorial board.	• Good quality of content within official template sections • Official template sections may seek status of peer-reviewed literature	• Users may find it difficult to distinguish between the two types. Challenge for interface design. • Administrative work required.
d	All information that is produced is subject to approval by an editorial board.	• Relatively good control of official template sections	• It may be very difficult for editorial board to judge quality of information • Heavy dependence on the original producers' own quality management processes.
e	All information that is produced is subject to external peer-review and approval by an editorial board.	• All contents may seek status of peer-reviewed literature	• Administrative work required • Time-consuming

3. Intellectual property rights

Policy C3-1: How are intellectual property rights of authors respected in core HTA information?

Note: this policy is intertwined with policies in group B3 (updating information), as one of the key challenges of the whole core HTA structure is in utilizing and updating already existing information. Certain level of flexibility is required from authors to enable improved utility of existing information.

Option ID	Option	Pros	Cons
a	Intellectual property rights of authors are respected in any core HTA information. Authors must, however, give a permission to freely reuse and modify any information they have produced in any other collection of core HTA information included in the Online Tool & Service.	• Very flexible • Existing information easy to reuse	• Potential for serious IPR clashes and accusations for plagiarism
b	Intellectual property rights of authors are fully respected in any core HTA information. Authors must, however, give a permission to freely reuse any information they have produced (in its original format) in any other collection of core HTA information included in the Online Tool & Service.	• Very flexible • Existing information easy to reuse • Fewer risks for IPR disputes	• Authors must be careful in using existing information but not changing it.
c	Intellectual property rights of authors are fully respected in any core HTA information. Normal citation rights are respected, but there is not explicit permission to reuse and/or modify existing information.	• Little risk for IPR disputes	• Difficult to reuse already existing information.

Policy C3-2: How are intellectual property rights of third parties respected in core HTA information (e.g. figures or tables from original articles)?

Option ID	Option	Pros	Cons
a	Intellectual property rights of third parties are fully respected in any core HTA information. Authors of core HTA information are responsible for acquiring necessary permissions.	• Simply has to be done like this.	
b	other options?		

Section D. Storage of core HTA information

1. Duration

Policy D1-1: For how long will core HTA information be stored?

Note: these policies assume that EUnetHTA will continue to exist as an organization and that it continues to support the maintenance of the Online Tool & Service.

Option ID	Option	Pros	Cons
a	Any core HTA information will be stored in the Online Tool & Service in a fully reusable format for a minimum period of 5 years after its publication. After this period the information will be archived in electronic format in a separate archive maintained by EUnetHTA (archive needs to be further defined).	• Information that is likely to be outdated is readily removed from the Service	• Update of information more difficult for those contents that have been archived
b	Any core HTA information will be stored in the Online Tool & Service in a fully reusable format for a minimum period of 7 years after its publication. After this period the information will be archived in electronic format in a separate archive maintained by EUnetHTA (archive needs to be further defined).	•	• Update of information more difficult for those contents that have been archived
c	Any core HTA information will be stored in the Online Tool & Service in a fully reusable format for a minimum period of 10 years after its publication. After this period the information will be archived in electronic format in a separate archive maintained by EUnetHTA (archive needs to be further defined).	• Easy to check results of earlier studies and the foundation of earlier policy decisions	• Update of information more difficult for those contents that have been archived • Considerable share of information is or starts to be outdated • Outdated information may be misleading and unethical
d	Any core HTA information will be stored in the Online Tool & Service in a fully reusable format for a minimum period of 20 years after its publication. After this period the information will be archived in electronic	• Easy to check results of earlier studies and the foundation of earlier policy decisions	• Update of information more difficult for those contents that have been archived • Considerable share of

	format in a separate archive maintained by EUnetHTA (archive needs to be further defined).		information is outdated • Very outdated information may be misleading and unethical

Section E. Retrieval and utilization of core HTA information

Note 1: EUnetHTA may choose to collect a fee for using core HTA information. The fee does not need to apply to all users and all content. Neither does the fee need to be the same for all types of use (non-commercial vs. commercial). In addition to money, the fee may also take a form of other contribution, e.g. one may require that users of the Service also produce something into the service.

Note 2: The term "fee" in the policy below is used for any kind of reimbursement, whether in money or information provision or something else. If non-monetary reimbursement is used, a clear trading policy needs to be defined in a separate process.

Note 3: The following table is used below while considering access:

User	*Type of information and possible reimbursement*					
	Official collections (core HTAs, rapid reviews etc.)			*Other types of information (e.g. free selection of elements)*		
	Free	*Money*	*Other "fee"*	*Free*	*Money*	*Other "reimbursement"*
Anyone						
EUnetHTA Partners (equals current Associated Partners)						
EUnetHTA Associates (including current Collaborative partners, possibly others)						
Researchers for scientific purposes						
Commercial users						

1. Access to core HTA information

Policy E1-1: Who should be allowed to browse and utilize core HTA information?

Note: access and possible reimbursement can be defined separately for various groups and purpose of use.

Option ID	Option	Pros	Cons
a	Anyone can access all core HTA information.	• Transparency • Easy to check the background of local reports that are based on core HTAs	• No added value for Network members
b	Anyone can access all such core HTA information that follows official EUnetHTA templates (core HTAs, rapid reviews). All other core HTA information is available only to EUnetHTA Partners and Associates.	• Partial transparency • Easy to check the background of local reports that are based on core HTAs • Added value for Network members	•
c	Anyone can access all such core HTA information that does not follow official EUnetHTA templates (core HTAs, rapid reviews). All information that follows official EUnetHTA templates is available only to EUnetHTA Partners and Associates.	• Partial transparency • Added value for Network members	• Difficult or impossible for others than people from Network agencies to check the background of local reports that are based on core HTAs
d	Only EUnetHTA Partners and Associates can access core HTA information.	• Added value for Network members	• No transparency • Difficult or impossible for others than people from Network agencies to check the background of local reports that are based on core HTAs

Policy E1-2: Is browsing and utilization of core HTA information free of charge for EUnetHTA Partners and Associates?

Note: access and possible reimbursement can be defined separately for various groups and purpose of use.

Option ID	Option	Pros	Cons
a	Browsing and utilization of all core HTA information is free for EUnetHTA Partners and	• Added value for Network members if	• Risk for imbalance between production

	Associates.	fees are collected from others	and utilization ("leeching") • Potential income to EUnetHTA from Partners and Associates lost
b	Browsing and utilization of all core HTA information is free for EUnetHTA Partners. Associates must pay a monetary fee for browsing and using any information.	• Added value for Partners if fees are collected from others • Some monetary income	• Risk for imbalance between production and utilization ("leeching") • Requires that fees are collected from all EUnetHTA-members as well. • Administrative work required • Potential income to EUnetHTA from Partners lost
c	Browsing and utilization of information contained in official EUnetHTA templates (core HTAs, rapid review, etc.) is free for EUnetHTA Partners and Associates. Other information is available against a monetary fee.	• Some monetary income	• Risk for imbalance between production and utilization ("leeching") • Administrative work required
d	Browsing and utilization of information contained in official EUnetHTA templates (core HTAs, rapid review, etc.) is free for EUnetHTA Partners and Associates. Other information is available against a non-monetary fee ("EUnetHTA token").	• Some incentive to produce more information	• Risk for imbalance between production and utilization ("leeching") • Administrative work required
e	Browsing and utilization of information contained in official EUnetHTA templates (core HTAs, rapid review, etc.) is free only for EUnetHTA Partners. Other information is available to Partners only against a monetary fee. Associates must pay a monetary fee for any information.	• Some monetary income	• Risk for imbalance between production and utilization ("leeching") • Administrative work required
f	Browsing and utilization of information contained in official EUnetHTA templates (core HTAs, rapid review, etc.) is free only for EUnetHTA Partners. Other information is available to Partners only against a non-monetary fee ("EUnetHTA token"). Associates must pay a non-monetary fee ("EUnetHTA	• Some incentive to produce more information	• Risk for imbalance between production and utilization ("leeching") • Administrative work required

	token") for any information.		
g	No information is free. All is available against a non-monetary fee "EUnetHTA token" (except information produced by one's own organization).	• Substantial incentive to produce more information	• Administrative work required • May slow down acceptance of the whole concept
h	No information is free. All information is available against a monetary fee (except information produced by one's own organization).	• Potential for substantial income	• Administrative work required • May slow down acceptance of the whole concept

Policy E1-3: Is browsing and utilization of core HTA information free of charge for others than EUnetHTA Partners and Associates?

Note: access and possible reimbursement can be defined separately for various groups and purpose of use.

Option ID	Option	Pros	Cons
a	Browsing and utilization of all core HTA information is free for all.	• Transparency	• Risk for imbalance between production and utilization ("leeching") • Potential income to EUnetHTA from Partners and Associates lost • No added value to Network members
b	Browsing and utilization of all core HTA information is free for non-commercial organizations. Commercial organizations must pay a monetary fee for browsing and using any information.	• Transparency towards non-commercial parties • Some monetary income	• Risk for imbalance between production and utilization ("leeching") • Administrative work required • Potential income to EUnetHTA from non-commercial organizations lost • Difficult to define access rights to individual persons, i.e. do we require that access is always granted based on

			person's employment?
c	Browsing and utilization of information contained in official EUnetHTA templates (core HTAs, rapid review, etc.) is free for anyone. Other information is available against a monetary fee.	• Some monetary income	• Risk for imbalance between production and utilization ("leeching") • Administrative work required
d	Browsing and utilization of information contained in official EUnetHTA templates (core HTAs, rapid review, etc.) is free. Other information is available against a non-monetary fee ("EUnetHTA token").	• Some incentive to produce more information	• Risk for imbalance between production and utilization ("leeching") • Administrative work required
e	Browsing and utilization of information contained in official EUnetHTA templates (core HTAs, rapid review, etc.) is free only for non-commercial organizations. Other information is available to non-commercial organizations only against a monetary fee. Commercial organizations must pay a monetary fee for any information.	• Monetary income	• Risk for imbalance between production and utilization ("leeching") • Administrative work required
f	Browsing and utilization of information contained in official EUnetHTA templates (core HTAs, rapid review, etc.) is free only for non-commercial organizations. Other information is available to non-commercial organizations only against a non-monetary fee ("EUnetHTA token"). Commercial organizations must pay a non-monetary fee ("EUnetHTA token") for any information.	• Some incentive to produce more information	• Risk for imbalance between production and utilization ("leeching") • Administrative work required
g	No information is free. All is available against a non-monetary fee "EUnetHTA token" (except information produced by one's own organization).	• Substantial incentive to produce more information	• Administrative work required • May slow down acceptance of the whole concept
h	No information is free. All information is available against a monetary fee (except information produced by one's own organization).	• Potential for substantial income	• Administrative work required • May slow down acceptance of the whole concept

2. Publicity level of different production phases

Note 1: All production of core HTA information with the Online Tool & Service requires setting up a "project" within the Tool. The project starts with designing a protocol that contains the questions that are to be answered in the project. The protocol must be marked "completed" by the project group before the research commences and any results can be entered. Likewise the results must be marked completed prior to the official publication process can proceed.

Note 2: "Public" in this context means that something is available to all those who have access to the Online Tool & Service. Depending on other policies it may mean completely public (i.e. any internet user can access it) or limited publicity (i.e. only for those who can access core HTA information either for free or against a fee).

Note 3: Instead of making either the protocol or the results completely public, specific access rights may be given to a more limited group of people (e.g. reviewers within the project group or external peer-reviewers).

Note 4: The smallest "project" may find answer only to one single question (defined by one assessment element).

Policy E2-1: When using the Online Tool, at which phase does the project protocol become available to people beyond the project group?

Option ID	Option	Pros	Cons
a	Project protocol is public from the moment the project group enters anything protocol-related in the Online Tool & Service. Uncompleted protocol status is indicated.	• Fast exchange of information	• Risk of low-quality information circulating • Risk of misunderstandings
b	Project protocol is public from the moment the project group marks it completed in the Online Tool & Service.	• Fast exchange of information	• Risk of low-quality information circulating • Risk of misunderstandings
c	Project protocol is public whenever the project group decides to make it public. Possible uncompleted protocol status is indicated.	• Possibility for fast exchange of information	• Risk of low-quality information circulating • Risk of misunderstandings
d	Project protocol is public whenever the project group decides, but only after it has been marked completed.	• Better control of content	• Slows down exchange of information to some extent
e	Project protocol is public whenever the project group decides to make it public. Uncompleted protocols are visible only to EUnetHTA Partners and Associates. Possible	• Possibility for fast exchange of information • Added value for Network members	• Tight control may impede dissemination

	uncompleted protocol status is indicated.		
f	Project protocol is public for EUnetHTA Partners and Associates when it has been marked completed. It becomes fully public after it has been formally approved by EUnetHTA (defined in other policies).	• Good control of content • Added value for Network members	• Administrative work required
g	Project protocol is public only after it has been completed and it has been formally approved by EUnetHTA (defined in other policies).	• Good control of content	• Slows down exchange of information • Administrative work required

Policy E2-2: When using the Online Tool, at which phase do project results become available to people beyond the project group?

Option ID	Option	Pros	Cons
a	Any results (including single assessment elements) are public from the moment the project group enters anything results-related in the Online Tool & Service.	• Fast exchange of information	• Risk of low-quality information circulating • Risk of misunderstandings
b	Any results (including single assessment elements) are public from the moment the project group marks them completed in the Online Tool & Service.	• Fast exchange of information	• Risk of low-quality information circulating • Risk of misunderstandings
c	Any results (including single assessment elements) are public from the moment the project group marks them completed in the Online Tool & Service, but only to EUnetHTA Partners and Associates. Others can access results only after the whole project has completed the official approval process (defined in other policies).	• Fast exchange of information	• Risk of low-quality information circulating • Risk of misunderstandings
d	Full or partial results may be made public by the project group, but those will be labelled "preliminary results" (or something similar) until a formal approval has been completed (defined in other policies).	• Possibility for fast exchange of information	• Risk of low-quality information circulating • Risk of misunderstandings
e	Full or partial results may be made public to EUnetHTA Partners and Associates by the project group, but those will be labelled "preliminary results" (or something similar) until a formal approval has been completed (defined in other policies). Others may not	• Possibility for fast exchange of information	• Some risk of low-quality information circulating • Some risk of misunderstandings

	access information that has not been formally approved.		
f	Results are public whenever the project group decides to make them public, but only as a full collection of the project (not single assessment elements). Results that do not have a formal approval are marked as "preliminary".	• Better control of content	• Slows down exchange of information
g	Results are public to EUnetHTA Partners and Associates whenever the project group decides so, but only as a full collection of the project (not single assessment elements). Results that do not have a formal approval are marked as "preliminary" and they are not available to others.	• Good control of content	• Slows down exchange of information
h	Project results are made public only after the full collection from a project is formally approved, if approval is required (defined in other policies).	• Good control of content	• Slows down exchange of information

3. Utilization of core HTA information in local products

Policy E3-1: On what terms can various parties use the information stored in the Online Tool & Service for local HTA reports?

Option ID	Option	Pros	Cons
a	All terms are defined in section A. No other terms exist for information within the Online Tool & Service	• Simple principle	• Potential for adding relatively easily important information is missed
b	In addition to the terms defined in section A, users of information that originates from the Online Tool & Service are urged to assist further users of the same information by providing a summary of the final conclusions of their local report. The summary will be included in the Online Tool & Service and linked to the information it was based on.	• Information on local considerations on e.g. relevance and transferability may be very useful in other contexts as well.	• Many may omit providing the information if it is voluntary
c	In addition to the terms defined in section A, users of information that originates from the Online Tool & Service must assist further users of the same information by providing a	• Information on local considerations on e.g. relevance and transferability may be	•

	summary of the final conclusions of their local report. The summary will be included in the Online Tool & Service and linked to the information it was based on.	very useful in other contexts as well. • Visibility of the steps taken to contextualise information will facilitate evolution of adaptation methods.	

E-meeting Comm Rules

- Raise hand **to make comment – leader will give the microphone**
- To talk you must be given a microphone **(when given a microphone,** a mike sign **appears to the left of your name in the participants area).** Press and HOLD Ctrl or F12 key **to be heard**
- **Respond to** yes/no questions by using green check for “yes” or red cross for “no**” (located at the top of your e-meeting screen)**
- **If you have** a problem transmitting the sound, please use text chat option **to communicate with the leader and the audience .** E-meeting leader monitors **the text chat and take up your question into the discussion.**
- If experiencing tech problems**:**
  - Check your internet connection (3-4 green boxes in the lower right corner of your e-meeting screen – good connection, if yellow or red – bad connection)
  - try to log out of the session (select File in the upper left corner, then Exit) and log into the e-meeting again
  - if problems persist – contact tech support:
  - ***Centra Tech Support - +44 1344 38 2999 (Contract name – National Board of Health Denmark)***

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WP4 and WP4-SAG feedback for screening model

WP4 E-meeting for screening model participants

May 12 2011

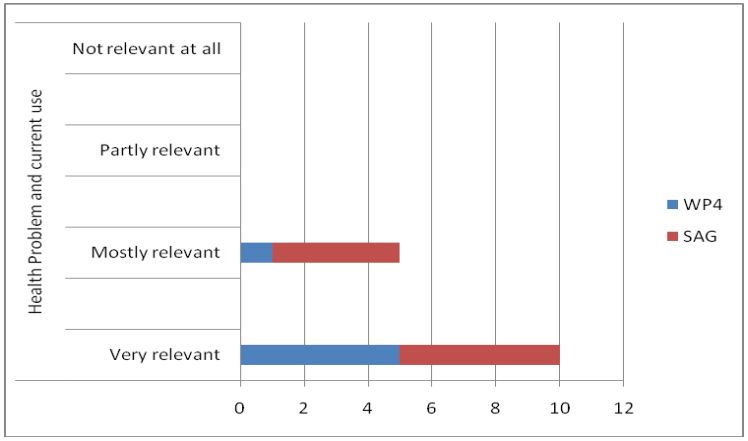
Agenda May 12 2011

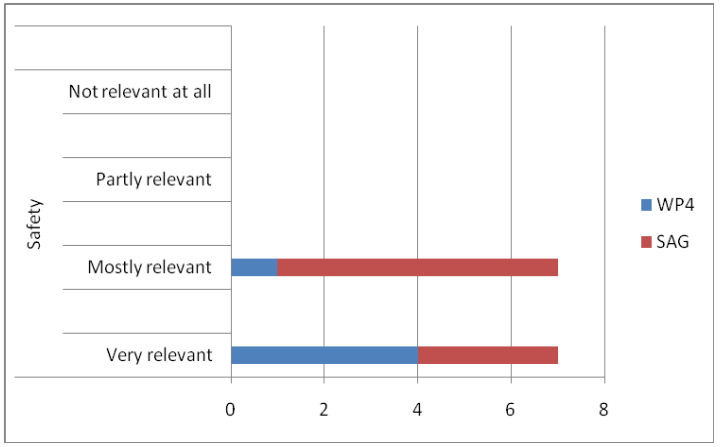
- **Overview of WP4 and WP4 SAG feedback**
- **List of pending improvements**
  - How to handle them?
- **Timing of the Public consultation**
- **How did this project go?**

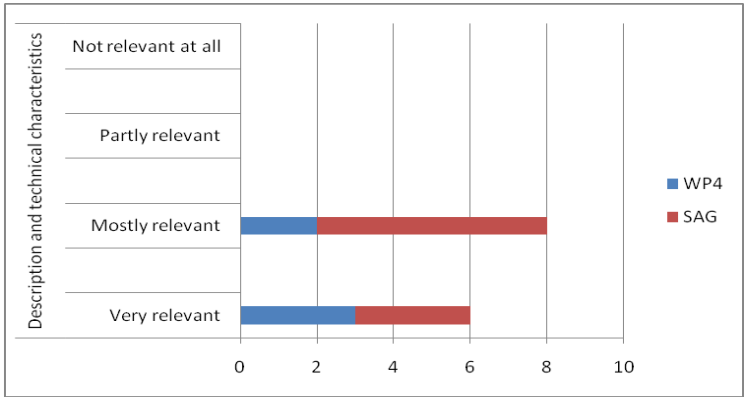
Numbers

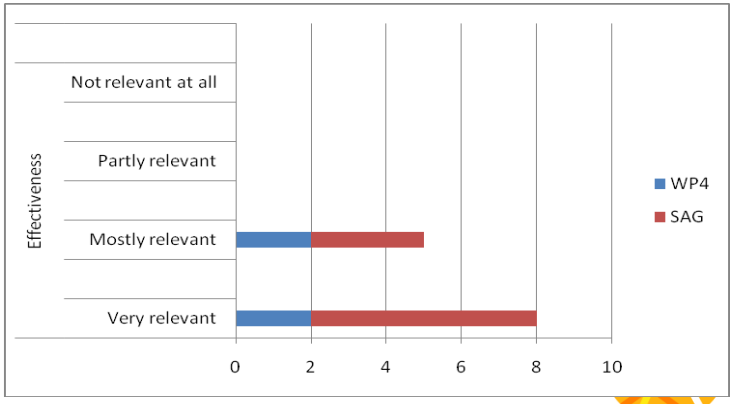
- **16 individuals from 9 WP4 member agencies commented the screening model (there are 15 APs and 6 CPs active in screening model, the responses came from 5 active APs, and 4 other WP partners)**
  - 24 general comments
  - 65 domain specific comments
- **11 out of 12 SAG members responded**
  - 17 general comments
  - 175 domain specific comments

How relevant is the set of questions for assessing screening technologies? Domains 1-4









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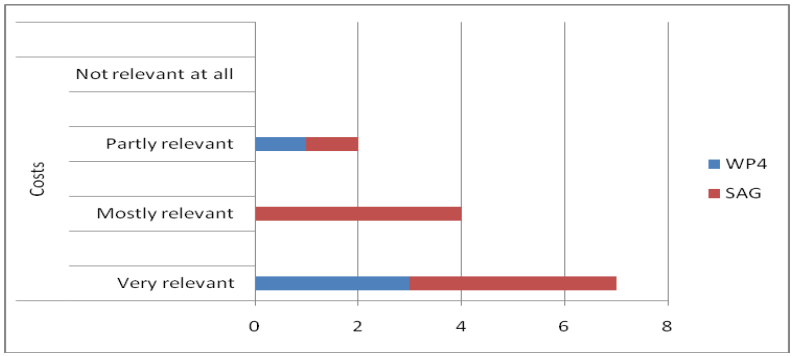
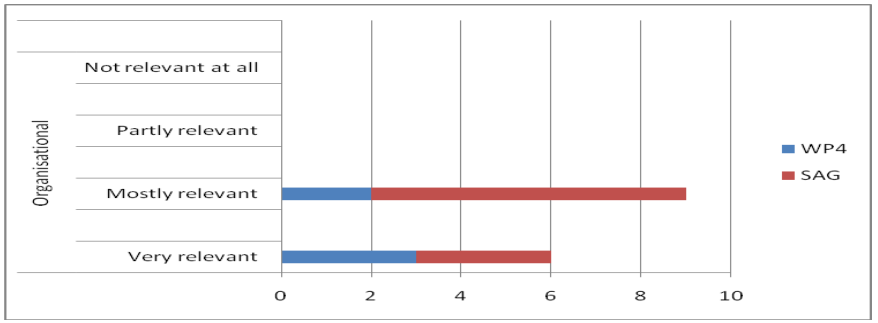
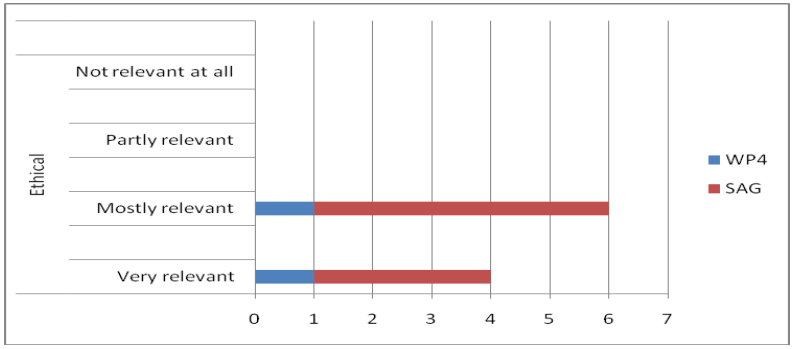
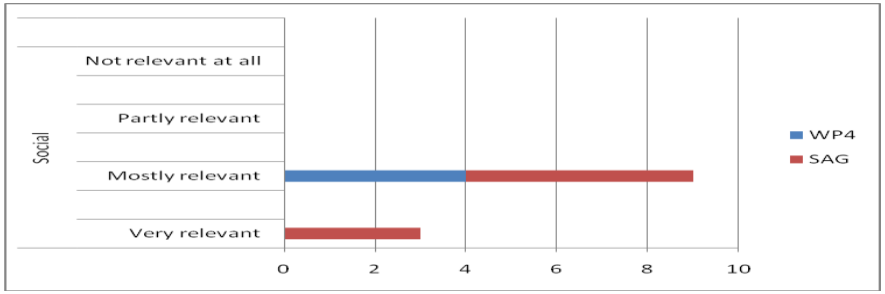
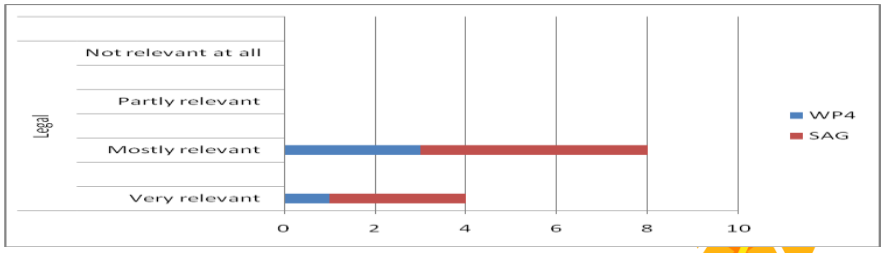
How relevant is the set of questions for assessing screening technologies? Domains 5-9











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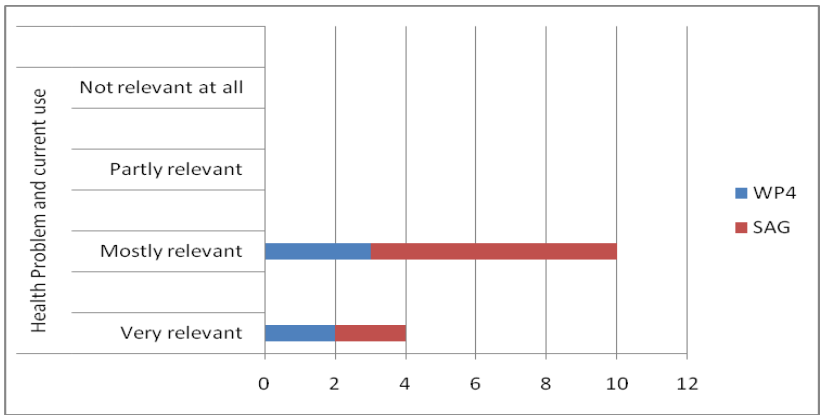
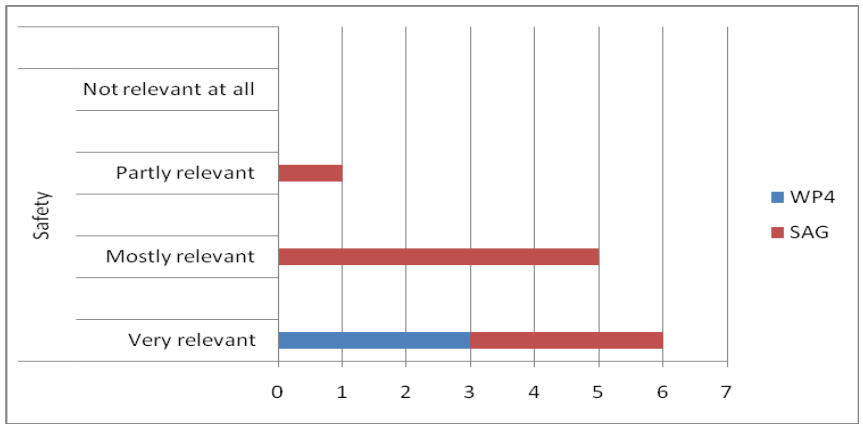
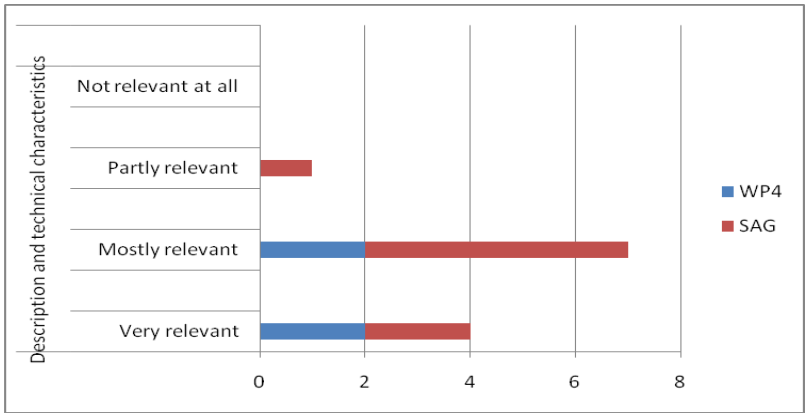
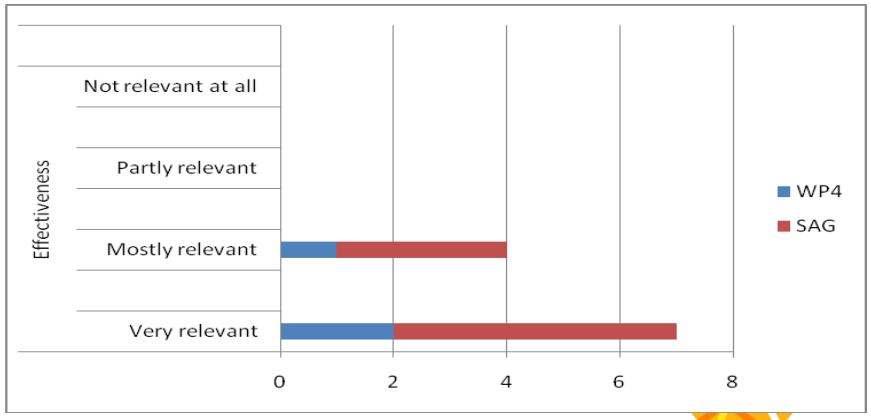
How well do the Methodology section and the Information sources fields in the Assessment elements table guide the HTA doer? Domains 1-4









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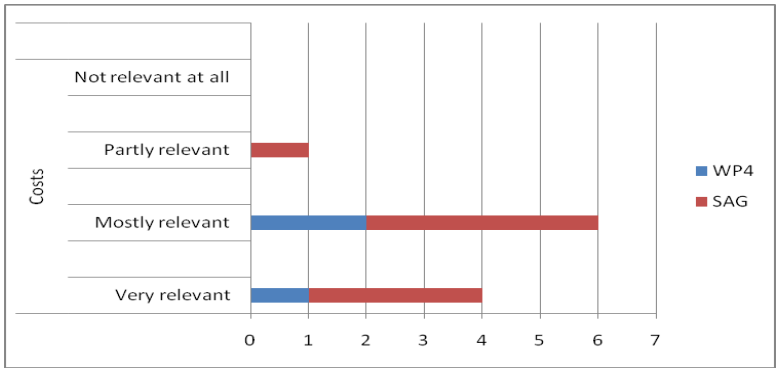
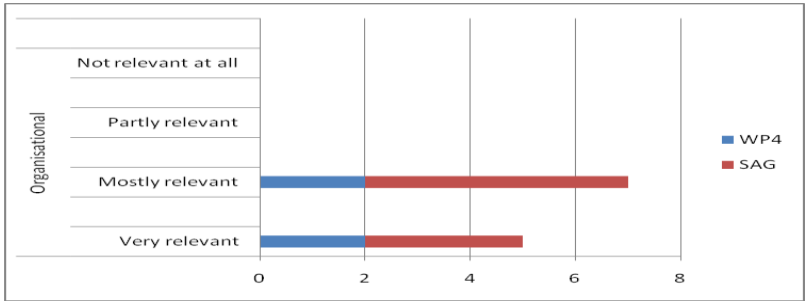
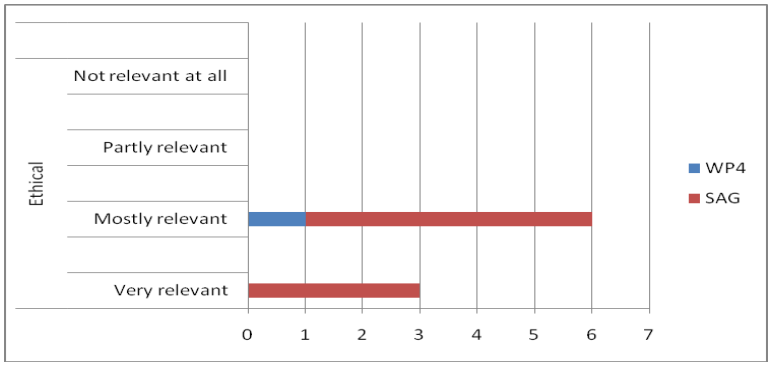
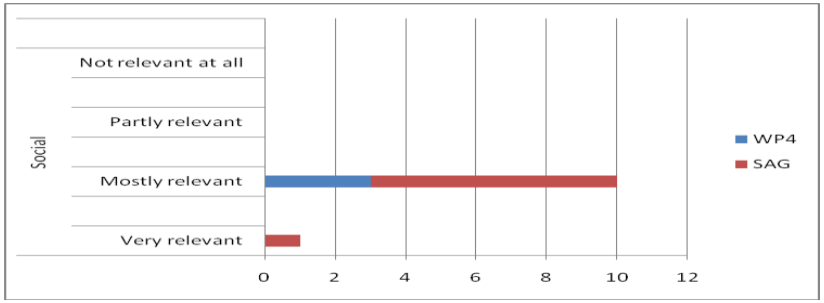
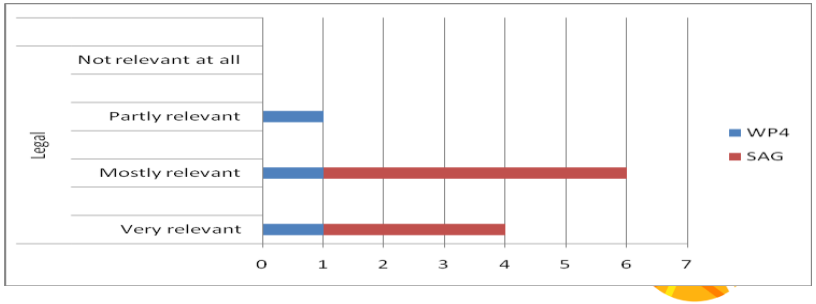
How well do the Methodology section and the Information sources fields in the Assessment elements table guide the HTA doer? Domains 5-9











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List of pending improvements: Introduction section and general

- **Definition of screening: motivation, examples**
- **Coherence between methodology text and Information sources - field in AE-table needs to be improved**
- **Reference column: add references, explain if ref missing**
- **List of abbreviations**
- **Screening glossary**
- **Coverage >reimbursement**
- **Generalisability vs transferability**
- **Post licensing assessment only?**
- **The role of GRADE**
- **Place safety domain after effectiveness domain**

How to proceed with the domain specific pending improvements?

- **1 HPCU**
  - Amend Appendix 1
  - Add links of regulatory institutions
  - Definition prognosis/natural course
- **2 DTC**
  - Amend Appendix 1
- **3 Safety**
  - Concept of harm
- **4 Effectiveness**
  - Update of certain methodology issues
  - Add evidence generation
  - Other smaller things

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How to proceed with the domain specific pending improvements?

- **5 Costs**
  - None
- **6 Ethical**
  - Person/patient term check
  - Add text of challenges
- **7 Organisational**
  - 2 new issues
  - Check methodology table
  - His > his/her
- **8 Social**
  - Define “satisfactory results”
- **9 Legal**
  - none

Timing of public consultation?

- **Determine what to do now (during JA) and what to leave to JA2**
- **After the “now” issues have been corrected we may proceed to the public consultation**

Feedback of the process

- **‘Time spent’ collected**
- **Should we collect some more information?**

Minutes of e-meeting 12.5.2011. Topic: finalising the screening model

Date: May 12 2011
Organiser: WP4A, chair Iris Pasternack
For: Screening model participants
Agenda:

- Overview of WP4 and WP4 SAG feedback
- List of pending improvements. How to handle them?
- Timing of the Public consultation
- Should we gather feedback from you about this project?

Minutes:
Iris presented overview of WP4 and SAG feedback to the screening model. The feedback was quite encouraging; most responders held the assessment elements relevant and methodological guidance useful. See pp-slides for more info.
We went through the list of pending improvements (those suggestions that the investigators did not implement yet). Although we are behind of schedule, we intend to implement as much of the pending improvements as we can manage. It was left for coordination and editing team to discuss the timeline and the extent of work for domains. Coordinator and CET will also discuss the extent to which the pending improvements for the Introduction section and general comments will be implemented or moved on. It was proposed that we aim at starting the Public consultation in September.
We had earlier collected information on how much time each participant has used for screening model. 30 out of 68 participating individuals responded, the amount of working days they declared was 230. Additionally, the missing information (n=38) was estimated by the coordinator to be 99 days. Altogether we used approximately 330 working days to prepare the screening model.
Iris proposed to gather additional feedback from the project participants. There were no objections. The aim and content of this kind of survey needs to be discussed in more detail in WP4, and communicated with WP3.

Event:	Screening model e-meeting
Subject:	
Start Time:	12/5/11 1:00 PM (GMT +01:00) Amsterdam, Berlin, Bern, Rome, Stockholm, Vienna
Duration:	1h 30m
Leader:	Iris Pasternack
Report Date:	12/11/11 11:18 AM (GMT +01:00) Amsterdam, Berlin, Bern, Rome, Stockholm, Vienna
Attended:	15
Played Back:	0
Absent:	40
Total Attendance Time:	19h 20m

First Name	Surname	Status	Time Connected

payam	abrishami	Absent	00m
andreas.gerber@iqwig.de	mailto:?bcc=andreas.gerber@iqwig.de&body=	Absent	00m
anne.stich@iqwig.de	mailto:?bcc=anne.stich@iqwig.de&body=	Absent	00m
Sunya-Lee	Antoine	Attended	1h 14m
Heidi	Anttila	Absent	00m
Ilona	Autti Ramo	Absent	00m
Lidia	Becla	Attended	1h 01m
Angelica	Carletto	Attended	22m
Marina	Cerbo	Attended	2h 24m
Americo	Cicchetti	Absent	00m
claus.loevschall@stab.rm.dk	mailto:?bcc=claus.loevschall@stab.rm.dk&body=	Absent	00m
Belen	Corbacho	Absent	00m
mirella	corio	Attended	35m
corio.agenas.it	corio.agenas.it	Absent	00m
Nick	Crabb	Absent	00m
Chris	De Laet	Absent	00m
Katrine	Frønsdal	Absent	00m
Paolo	Giorgi Rossi	Absent	00m
rish	harrington	Absent	00m
jderksen@cvz.nl	mailto:?bcc=jderksen@cvz.nl&body=	Absent	00m
JHeymans@cvz.nl	mailto:?bcc=JHeymans@cvz.nl&body=	Absent	00m
juha.koivisto@thl.fi	mailto:?bcc=juha.koivisto@thl.fi&body=	Absent	00m
Raul	Kiivet	Absent	00m
Kristian	Lampe	Attended	1h 04m
Chris	Lawinski	Absent	00m
Jaana	Leipälä	Attended	1h 07m
Aurora	Llanos	Absent	00m
Alessandra	Lo Scalzo	Absent	00m
lotte.groth@stab.rm.dk	mailto:?bcc=lotte.groth@stab.rm.dk&body=	Absent	00m
Suvi	Mäklin	Attende	1h 06m

		d	
Marco	Marchetti	Absent	00m
Mirella	Marlow	Absent	00m
antonio	migliore	Absent	00m
mruggeri@rm.unicatt.it	mailto:?bcc=mruggeri@rm.unicatt.it&body=	Absent	00m
nea.malila@cancer.fi	mailto:?bcc=nea.malila@cancer.fi&body=	Absent	00m
Marco	Oradei	Absent	00m
Camilla	Palmhøj Nielsen	Absent	00m
Iris	Pasternack	Attended	1h 14m
rosaria	perrini	Absent	00m
pietro.refolo@rm.unicatt.it	mailto:?bcc=pietro.refolo@rm.unicatt.it&body=	Absent	00m
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Teresa	Queiro	Attended	14m
Heike	Raatz	Absent	00m
Pirjo	Rasanen	Absent	00m
Ulla	Saalasti-Koskinen	Attended	1h 13m
Dario	Sacchini	Absent	00m
Janek	Saluse	Attended	1h 14m
samuli.saarni@thl.fi	mailto:?bcc=samuli.saarni@thl.fi&body=	Absent	00m
Stefan	Sauerland	Attended	3h 51m
Petra	Schnell-Inderst	Absent	00m
Petra	Schnell-Inderst	Absent	00m
Sinikka	Sihvo	Absent	00m
sirpa.soini@thl.fi	mailto:?bcc=sirpa.soini@thl.fi&body=	Absent	00m
Eva	Turk	Attended	1h 17m
Leonor	Varela Lema	Attended	1h 24m

HTA Core Model® Online

Handbook

The EUnetHTA Joint Action is supported by a grant from the European Commission

IMPORTANT NOTE ON THIS DOCUMENT:

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Version: 1.3

Date: 20 Oct 2011

Version history: -

Table of contents

1 Introduction

This Handbook is written primarily for people who use the HTA Core Model to conduct assessments, i.e. to produce HTA information. Future versions will include more specific advice on using the information produced.

The Handbook is divided into three sections.

Section 1 contains a general introduction to the HTA Core Model and its applications. It is necessary background reading for understanding how the system is designed and how it functions. Details are kept to a minimum, however.

Section 2 is a practical guide for using the HTA Core Model to produce a health technology assessment. The guidance is written primarily for the HTA Core Model Online Tool, where the production process is divided into five phases, each of which is explained in detail. Phases 1 and 2 result in a research protocol that is used for performing the research (phase 3) and that serves as the basis for reporting of results (phases 4 and 5). Most guidance is relevant also for situations where the HTA Core Model is used without the Online Tool.

Section 3 provides methodological guidance for performing the actual research (phase 3). Guidance is available both on general and domain-specific levels.

Any feedback on the Handbook is welcome, please send it to eunethta@thl.fi.

1.1 Basic concepts

Any health technology assessment contains a vast amount of information on the technology that is the object of the assessment. The HTA Core Model divides this information into standardized pieces, each of which describes one or more aspects of the technology that is likely to be useful when considering the adoption or rejection of the technology. These pieces of information are referred to as *assessment elements*. The elements that are most likely useful for international sharing of information are defined as *core elements*. Each assessment element contains a question that is referred to as *issue* and that defines in a generic manner the aspect of technology that one should consider.

There are two main options for utilizing the Core Model. The *primary* option leads to production of a Core HTA, which is a collection of all core elements complemented by more general sections of text. The *secondary* option is to utilize a free selection of elements. While the free selection may be more appealing in the sense that it allows the user to focus only on topics of local interest, one should notice that very important aspects of technology may be omitted in the process. The choice also reduces the overall usefulness of the pool of structured HTA information.

The following basic concepts define the HTA Core Model and its derivatives and applications.

HTA Core Model: A structured manner of creating and presenting HTA information as assessment elements. Some elements are prioritized over others to support European collaboration through defining them as "core elements".

Assessment element: The basic unit of the model. Defines a piece of information that describes the technology or the consequences of implications of its use, or any other implication that is relevant for the assessment, such as the patients and the disease for which it is applied. Each assessment element contains an "issue", which is a question that should be answered in an HTA. Not all issues, however, are relevant to all technologies/settings, and hence their relevance is considered separately for each assessment. Elements are defined through a combination of domain, topic and issue.

Domain: A wide framework within which technology is considered. It provides an angle of viewing the use, consequences and implications of technology. A standard set of domains is used in the HTA Core Model.

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

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 always expressed as a question that can be answered through answering one or more research questions.

Application of the HTA Core Model: Different kinds of technologies (e.g. surgical interventions or pharmaceuticals) may require different questions to be asked in an assessment and the answers to the questions may require different research methods. An application of the HTA Core Model is built for assessing a specific kind of health technology. Different applications all draw from the same pool of assessment elements, but not all elements are used in all applications. Currently three applications exist, one for medical and surgical interventions, another for diagnostic, and third for screening technologies. More applications will be developed in the future.

Element card: Each assessment element is connected to an element card, which provides tangible

information on the element and its relations to other elements. A card may provide advice on how to answer the question defined by the element. Two characteristics within a card (importance and transferability) define whether an element is a "core element" or "non-core element". While assessment elements are generic (i.e. one element can belong to several applications of the HTA Core Model), element cards are application-specific (i.e. the cards describing an element within different applications may be different).

Structured HTA information: Information on any aspect of health technology that has been created through answering the issues defined in the assessment elements of the HTA Core Model.

Core HTA information: Any information on a technology that has been produced through answering the issue defined in a core element, or a collection of such information. This information is very likely to be useful in the European context (i.e. also in another country) due to its importance and/or transferability.

Core HTA: An actual assessment that a) has been conducted using the HTA Core Model and b) has considered all core elements of all 9 domains. (Note: through this consideration some elements may be defined as irrelevant, but that should be documented). A Core HTA contains a chapter that draws together key findings of various domains, but does not make recommendations regarding the use of technology. Through the wide scope, focus on core elements and the summary chapter, a Core HTA gives an overview of a technology that is likely to be useful in the European context. A Core HTA can be used as a basis for producing local HTA reports that take into account local circumstances (e.g. epidemiology, organisation, resources, values).

1.2 Domains of HTA

The HTA Core Model employs a multidisciplinary view of HTA. Any technology that is being assessed is considered through domains, each of which provides a wide framework for the analysis. Brief definitions of the domains follow. More detailed information on domains is available in Section 3.

1.2.1 Health problem and current use of technology

Domain describes the health problems of the populations the technology is used for, the epidemiology, the burden of disease on individuals and the society caused by the health problem. It also provides the baseline description of the availability and patterns of use of the technology, and describes the alternatives and regulatory status of the technology.

1.2.2 Description and technical characteristics of technology

Domain details and separates the technology in question from related technologies, and gives an overall understanding on functioning of the technology under assessment, including investments and information needed for use.

1.2.3 Clinical effectiveness

Domain describes the efficacy or effectiveness of the technology in terms of health outcomes, function and patients' quality of life. As direct evidence from randomised controlled trials (RCT) is not available or sufficient in all assessments, there are also questions related to indirect measures, such as accuracy and change-in-management.

1.2.4 Safety

Domain considers the direct and indirect harms due to the technology itself (e.g. invasiveness) or to the use of the technology (e.g. proper patient selection or learning curve), or to particular patient susceptibility (e.g. pregnancy). In addition to patient safety, the harms of the technology posed to the families and close ones of the patient, health care professionals, public and the environment, are considered.

1.2.5 Costs and economic evaluation

Domain identifies, measures, values and compares the costs and outcomes of technologies being considered to inform value-for-money judgments about the intervention. The main aim is to provide information in order to improve decision-making in the health care sector regarding priority-setting between different health technologies.

1.2.6 Ethical analysis

Domain considers prevalent social and moral norms and values relevant for the technology in question. Ethical questions are addressed both with regard to the technology itself and with regard to the consequences of implementing or not implementing a health technology. In addition, the moral and ethical issues inherent in the entire HTA process are identified and evaluated.

1.2.7 Organisational aspects

Domain focuses on the delivery models of the technology, resources, management and cultural issues within variety of stakeholders in the intra-and inter-organisational level and in health care system level. The assessment of the organisational issues is highly context-dependent because of the inherent complexities of the health care system and multiplicity of objectives.

1.2.8 Social aspects

Domain focuses on the patients' and his or her significant others' considerations, worries and experiences before, during and after the health technology has been put to use. It describes how the technology moulds and is moulded in diverse social arenas (hospitals, general practitioner, everyday life, homes, schools, and workplace), and what specific meanings people give to the technology.

1.2.9 Legal analysis

Domain scrutinizes relevant legal sources in national or international legislation and conventions. It describes the implicit and explicit agreements of the manufacturer (or seller) and buyer of the technology. It includes questions on basic rights of patients, such as autonomy, informed consent, privacy and confidentiality, and legal requirements such as authorisation, guarantee, and regulation of market.

2 Production of Core HTAs and structured HTA information

2.1 Introduction

This section is written for those who conduct HTAs using the HTA Core Model and hence produce information on technologies that may be useful beyond the original location or setting in which the HTA was conducted.

The process is divided into five phases that are explained below. The project and its participants are defined in phase 1 and the assessment protocol designed in phase 2. Phase 3 contains tools for the research phase, where answers to the questions are sought. After finding answers, the process continues in submitting the results of the research in the online database of structured HTA information (phase 4) and publishing the results (phase 5). An editorial process precedes the final publication.

Some general policies are defined at the end of this section.

Before proceeding, go to http://www.corehta.info to use the online tool.

2.2 Production phases

2.2.1 Phase 1: Project definition

Online:
1. Select PROJECTS from top menu.
2. Select "Start new project".

The assessment you want to conduct is first defined as a project on the general level. This includes definition of the technology, its assessment and scope.

The following information should be provided:

- Name of project
- Name of technology
- Application: which application ("model") of HTA Core Model will be used? Additional to the actual applications, a "short model" with two domains only is available for testing purposes.
- Project type: select whether you will a) produce a Core HTA, ie. a full package of Core HTA information (as defined by the EUnetHTA Collaboration), including a summary of findings (recommended selection), or b) apply a free selection of assessment elements
- Project leader rights
- Scope: description of the technology and the comparator

Project scoping

Creating a common scope for the whole project is essential. All domain teams should consider it throughout the assessment in order to ensure that analysis within different domains is targeted at the same scope. Extent of analysis may differ between domains, but they all should take the common scope into consideration, whenever feasible. Further adjustments to the project scope may be done at domain level at a later phase (see "domain framing" below).

Scoping is divided into three sections

- Technology
- Indication
  - Target condition
  - Target population
  - Purpose of use
- Comparison

Technology

The authors should describe the technology detailed enough to distinguish it from relevant other technologies. There is possibly need to restrict the scope e.g. to the newer device generations (e.g. studies published year 2000 or later) or certain types (e.g. multi-slice CT with >64 slices).

Indication

The technology can be used in multiple indications and purposes. Therefore it is essential to carefully define the context in this particular assessment.

- Describe the **target condition**, disease or other health condition. Provide ICD-10 code and MeSH-terms for it.
- Describe the **target population**; are there possible age or sex limits, do we target healthy individuals (as in prevention) or patients with certain disease? Are we interested in all patients with the disease, or those who have low or moderate or high risk of having the disease. Provide MeSH-terms.
- Describe the **purpose of the use** of the technology; whether it is aimed at preventing, screening, diagnosing, treating, triage (ruling in or ruling out), treating or monitoring the condition. Provide

MeSH-terms.

Comparison

The technology can be compared to e.g. another specific technology, management pathway without the technology, usual care, not doing anything, or a placebo intervention. This should be described detailed enough to distinguish it from other relevant comparators. Provide MeSH-terms.

Online:
Save the changes before proceeding to other pages by selecting one of the available buttons at the bottom of the page.

Project participants and roles

The user starting the project will become the project leader. A project may in addition have an unlimited number of users participating in various roles listed below. The roles of each participant are defined separately for each domain.

	Primary investigator	Investigator	Informatician	Reviewer
Evaluate assessment element relevance and formulate research questions of a particular domain	Yes	If incomplete		
Define framing of a particular domain	Yes	If incomplete		
Enter research question answers of a particular domain	Yes	If incomplete		
Enter results of a particular domain	Yes			
Complete a particular domain by locking it	Yes	Yes		
Mark research question answer of a particular domain complete	Yes	Yes		
Mark results of a particular domain complete	Yes			
Unlock a particular domain	Yes			
Mark research question answer of a particular domain incomplete	Yes			
Mark results of a particular domain incomplete	Yes			
Read relevance evaluation, research questions, framing and results of a particular domain	Yes	Yes	Yes	Yes
Enter the methods of a research question answer of a particular domain	Yes	If incomplete	If incomplete	
Enter the methodology and references of a particular domain	Yes		If incomplete	

Note: the project leader can be given full rights to all domains (equivalent to being a primary investigator) in Phase 1. Alternatively, the project leader can be given specific roles in all or some of the domains by adding him/her as a participant to the project.

Online tool:
The project home page shows a list of all participants and their roles. Existing roles can be edited directly by clicking the *Edit* link.
Click *Add new participant* on the project home page to search for users to add as new participants. Each user found by your search has an associated link for adding the user and editing the roles.

The remaining text in the handbook defines the production of a Core HTA. Guidance on free selection of assessment elements will be included later, as that is not the primary use of the HTA Core Model.

2.2.2 Phase 2: Protocol design

This phase can be divided into four steps that lead into formulation of the final Core HTA protocol.

1. The relevance of each core element in the context of the technology is considered, and the selected issues are translated into practical research questions that are answered in the Core HTA.
2. A specific framing for each domain may be defined, as these may differ across domains.
3. Each domain is locked once the research questions and framing are complete.
4. The protocol is reviewed and locked.

Online:
Choose "Protocol design" from left margin. This opens the main page of protocol design.
Choose "Edit" from the table to access various steps for each domain. Remember to save changes using the buttons at the bottom of each subpage you edit.
You may click on the Identification number of each assessment element at any time to view its Element card for more information on the element.

Selecting relevant issues

A Core HTA project should start this phase by involving the Ethical aspects domain team actively in the discussion. The idea is to provide guidance and arguments for the relevance assessment and the research question formulation. What are the identified and possible ethical implications when using this technology? What should be researched? This discussion forms a substantial part of the ethical analysis in Core HTA, but also guides the work in other domains.

After that the team(s) should go through all the core elements of the model, one by one, and for each element make a selection of the following:

- Relevant
- Irrelevant

The issues defined as relevant will be studied in the assessment. Elements can also be tagged as "consider later" to allow flexibility in the working process. The "Clarification" link connected to each element provides more details on the issue.

The relevance is based on considering whether the issue presented within the element is relevant in the context of the particular technology that is being assessed. One should be practical: not to try to find "artificial" relevance, but not to reject issues too easily as irrelevant either. Defining the relevance of *core* elements is an obligatory process. A brief justification should always be provided for those core elements that are regarded as irrelevant. The final Core HTA will include this information, as it may be useful for its users.

The text of *non-core* elements is written in gray and each such element is additionally marked with text "not core" in front of the identification number. Defining the relevance of non-core elements is optional. One may include non-core elements in a Core HTA protocol whenever needed.

Research question formulation

This phase should result in a list of practical and answerable questions.

The issues of assessment elements are generic in nature, as they are intended to be useful in various settings and for various technologies. The relevant issues must be translated into one or more research questions. One should formulate research questions according to the research tradition of each domain. Notice that not all issues require thorough scientific research to be conducted, e.g. a systematic literature review. Some

issues may be answered e.g. through finding the information in a suitable register (e.g. whether a technology is approved for use). You may save and re-edit the relevance of assessment elements and research questions within a domain as many times as you want.

Online:
The tool automatically suggests a research question if you mark an assessment element relevant. The suggested question is simply the same as the issue with the word *technology* replaced by the name of the technology you had provided earlier in the Project definition phase. You can choose to use it without modifications or *Edit* it first.
Click *Add more* to define more research questions. You can choose to ignore the question suggested by the system by adding questions yourself.
Existing questions can be edited or removed by clicking the *Edit* link beside each question.

Relations between issues and possible overlaps

In this phase the coordinator of the Core HTA project and authors in the domain teams should consider the relations between the issues and possible overlap across various domains. Although the research questions may look very similar at first glance, they still might have different angle to the assessment and therefore require different information sources and approach (e.g. legal requirements versus ethical considerations related to patients' rights to receive balanced information). Still, there may be common sources of information and assessment methodologies that the domain teams would benefit sharing. Sometimes it may be necessary for certain domain to wait for the information from another domain before starting their own work in findings answers. In order to avoid double work, the teams should map the relations, both content and time related, and discuss how to sequence or share some parts of the assessment. There are certain principles already identified in earlier projects:

- The Health problem and current use domain should start early together with the Description and technical characteristics domain. The provide information essential to all other domains.
- Next start effectiveness and safety domains. They most probably share information and require each others' information.
- Organisational domain should also start quite early while the information it provides is essential for Costs domain
- Costs domain start their work when the results from effectiveness and organisational domain are available.
- Social domain requires information at least from safety and ethical domains.
- Legal domain requires information from the two first domains and organizational and ethical domain.
- Ethical domain requires information from all domains and its work should last throughout the project.

Domain framing

Whenever possible, all domains should consider the commonly defined project scope. The common scope is usually specific and thus quite narrow. Therefore, at least in some domains there may be a need to look at the technology from a broader frame. Otherwise the issue would be graded as irrelevant for assessment. For example, in a Core HTA comparing drug eluting and bare metal stents in coronary artery disease, a researcher in Social domain assessing patient experiences might want to explore stents in general or compared to bypass operation. On the other hand, it may be necessary, especially in rapid assessments, to keep the project scope strictly, and exclude issues that are not relevant for the scope.. Notice also that the there are several questions where no comparison is required (e.g. what are the known risk factors of the condition?).

The basic rules are:

1. Omitting completely the predefined project scope (certain Technology, Indication and Comparison), i.e. excluding these from the analysis, is not allowed

2. Extending the frame around the often quite narrow definitions in the project scope is allowed. You may select a broader group e.g. for the technology (CT instead of multislice CT), or target population (all coronary artery disease patients instead of severe cases only).

Viewing and locking protocol

You can view the protocol at any time during the design process. The protocol may be missing some of the unfinished content or content that you have no rights to view, until the design process is fully completed and the protocol has been locked.

The complete Core HTA protocol contains the following:

- A list of research questions that the Core HTA project should seek answers to
- Domain-specific methodological guidance
- Issue specific guidance for information sources
- A list of assessment elements that were regarded as irrelevant in the context of the technology under assessment and brief notes on such choices.

Based on the Core HTA protocol the research group should define a more detailed research plan that includes all the common parts of such a plan. Methodological guidance within the Core HTA protocol should be useful in this process.

Locking the protocol indicates that the project moves to the next phase, i.e. finding answers to the questions defined by the protocol. A locked protocol may not be altered unless it is unlocked first. Only the project leader may unlock the protocol.

Online:
View the protocol by clicking one of the links at the bottom right corner in Phase 2.
To lock the protocol, first make sure that all individual domains have been locked in Phase 2 (by clicking the *Lock* button beside each domain), then finally click the *Lock* button at the bottom right corner in Phase 2.
The protocol can be unlocked by clicking the *Unlock* button at the bottom right corner in Phase 2.

2.2.3 Phase 3: Research

In this phase the questions defined by the Core HTA protocol are answered through research that is appropriate for each domain. The role of the Core HTA project coordinator is major here, and the project requires a predefined project plan including timeline and relevant check points or each domain separately.

Online:
The Online Tool Phase 3 contains some templates and further technical instructions for conducting the research and collecting the results, as well as handling references to other studies.

2.2.4 Phase 4: Entering the results

In this phase the results of the assessment are included in the electronic database. Each protocol in the database is associated in this phase with a collection of (i.e. an assessment element and the answer to the question(s) defined by the element) and a Core HTA *frame* that puts the cards into context. Each Core HTA consists of the following parts:

- General Introduction (for the whole Core HTA)
- Domain-specific sections (one for each domain)
    - Introduction of domain

- Domain methodology
- Assessment elements within domain (each element contains the following sections)
  - Methods
  - Results (answer to the research question)
  - Comment (optional)
- Discussion of findings within domain
- References of domain
- Appendices of domain
- Assessment elements table of domain

- Summary of findings for the whole Core HTA

Results can be entered only for a locked protocol. Notice that information within a Core HTA is divided between three levels: a) the whole Core HTA, b) individual domains, and c) individual assessment elements.

Results on each level need to be marked separately "completed". Once all content is marked completed, you can proceed to peer-review and publishing the results.

Online:
Choose the project from your personal home page and select Results from the left margin.
Enter, edit and view content of the Core HTA through selecting "Edit/Edit answer" and "Show/Hide" and writing in the text boxes. Basic text formatting tools are available within each text box. Once you have saved the text, you may also add figures by clicking the "Add a figure to this text" link above the textbox. Remember to save each page between entering or editing content.
Mark each content entry "completed" after it is in its final format through marking respective checkboxes at the bottom of the page (assessment elements and whole Core HTA) or selecting the button at the top of page (domains).

2.2.5 Phase 5: Review and publishing

This phase includes a peer review and publication process, after which your Core HTA is available for use by others. It requires further definition of a set of policies that will be developed within EUnetHTA.

Online:
Open a project and select "Review and publishing" from the left margin. The Core HTA you have produced opens. Select results publishing button from the top of page. Press "Submit for publication" to send your Core HTA for peer review and publishing process (not yet functional - to be defined in more detail later).

2.3 Policies

2.3.1 Creating a new Core HTA

To be defined within EUnetHTA Join Action 2010-2012.

2.3.2 Updating an existing Core HTA

To be defined within EUnetHTA Join Action 2010-2012.

2.3.3 Authorship of a Core HTA

General international standards are used when defining authorship of Core HTAs and the assessment elements within them, particularly the *Uniform Requirements for Manuscripts Submitted to Biomedical*

Journals: Writing and Editing for Biomedical Publication available at http://www.icmje.org/.

More detailed policy to be defined within EUnetHTA Join Action 2010-2012.

2.3.4 Consensus on the content

The research team working on each domain should reach a consensus on the contents of their section of the final Core HTA. Within the unpublished draft phase one can also include tentative content and mark it with a question mark or other means.

More specific instructions regarding internal and external peer review will be agreed on in the future EUnetHTA Collaboration.

2.3.5 Content from other sources

Authors of any content of a Core HTA should ensure that appropriate permissions have been acquired for any images, graphs or tables that are originally made or published by someone else. A written permission is typically needed.

3 Methodological guidance

IMPORTANT NOTE ON THIS SECTION:

The online version of the Handbook contains also links to detailed guidance from the actual HTA Core Model and its applications.

3.1 Health Problem and Current Use of the Technology

3.1.1 Description

Health problem and current use of technology domain describes the health problem and target population to be intervened with the technology under assessment; the epidemiology and the burden of disease on individuals and the society. It describes the availability, patterns of use, life cycle, and regulatory status, as well as the alternatives to the technology. It is essential background information for Core HTA investigators in other domains as well as for readers and implementers of a Core HTA.

3.1.2 Methodology

Health problem and current use domain uses published epidemiological, prognostic and qualitative research, and statistics and registers as sources of information. Guideline producers' and technology developers' web sites are often relevant, as well as databases on horizon scanning and ongoing research. Both National and EU-wide information can be valuable.

3.1.3 Assessment elements

3.2 Description and technical characteristics of technology

3.2.1 Description

Descriptions and technical characteristics of the technology domain gives the an overview of what the technology is, when it was developed and for what purposes, who will be using the technology, in what manner, and at which level of health care. The material requirements, premises, equipment and staff, are

described, as well as the training and information needs the new technology brings along.

3.2.2 Methodology

Information for the Description and technical characteristics of the technology are sought in review articles and textbooks. Technical reports from governmental agencies or scientific research groups, and manufacturers' web sites are valuable sources as well. A systematic review is not always needed. However, for the transparency of HTA, the approaches and sources of information should be explicitly documented.

3.2.3 Assessment elements

3.3 Description and technical characteristics of the technology

3.3.1 Description

3.3.2 Methodology

3.3.3 Assessment elements

3.4 Safety

3.4.1 Description

Safety domain describes the direct and indirect harms of a technology for patients, staff and environment, and how to reduce the risk of harms. There is usually a spectrum of known and unknown harms, which can be intended or unintended, of different seriousness, and dose or time dependent. Authors of a Core HTA select the safety issues that are significant for patients, or most likely to be important in guiding the decision of health care providers and policy makers.

3.4.2 Methodology

Core HTA producers should focus their review and predefine the safety issues and outcome measures they wish to work on in their assessment. Harms are not always well-reported in randomised trials. Terms for specified adverse effects have to be defined and added in the search strategy. Information about new, serious, rare or long-term adverse effects are typically found in observational studies (cohort, case-control, nested case-control, and cross-sectional studies).

3.4.3 Assessment elements

3.5 Clinical Effectiveness

3.5.1 Description

Clinical Effectiveness domain describes the spectrum and amount of beneficial health effects and quality of life that is exptected through the implementation of the technology. In diagnostic technologies the test accuracy and beneficial changes in management are considered as outcomes of indirect effectiveness as well. Proven effectiveness and safety of a technology is fundamental, considering further assessment and the potential use of the technology.

3.5.2 Methodology

The gold standard for intervention effectiveness research is randomised controlled trial (RCT). Inferences

regarding the effectiveness of diagnostic technologies are often made based on linked evidence from studies on accuracy, change-in-management and treatment effectiveness, because test-treatment RCTs are rare.

3.5.3 Assessment elements

3.6 Costs and economic evaluation

3.6.1 Description

Costs and economic evaluation domain identifies, measures, values and compares the costs and outcomes of technologies being considered to inform value-for-money judgments about the intervention and priority-setting between different health technologies. The issues deal with resource utilization, unit costs, indirect costs, outcomes/consequences, and incremental cost-effectiveness of the technology.

3.6.2 Methodology

An economic analysis requires careful framing. Type of economic analysis (Cost-effectiveness, Cost-minimisation, Cost-utility or Costs-benefit analysis) depends on the research question and data available. Modelling is useful e.g. when economical and clinical data is missing. Sensitivity analysis shows the decision maker how robust the conclusions of an economic analysis are. Ideally the analysis is conducted from the broad societal perspective instead of e.g. hospital or patient perspective.

3.6.3 Assessment elements

3.7 Ethical analysis

3.7.1 Description

Ethical analysis domain considers prevalent social and moral norms and values relevant for the technology in question. Ethical questions are addressed both with regard to the technology itself and with regard to the consequences of implementing or not implementing a health technology. In addition, the moral and ethical issues inherent in the entire HTA process are identified and evaluated.

3.7.2 Methodology

An ethical analysis is an ongoing process that lasts throughout the HTA project. It is done together with content experts; it should never be a purely philosophical add-on input by an ethicists. The method of analysis is tailored to suit the topic under study, local culture, health care system, and the HTA organisation itself. The various approaches include the Casuistry, Coherence analysis, Interactive, participatory HTA approach, Principalism, Social shaping of technology, and Wide reflective equilibrium methodologies.

3.7.3 Assessment elements

3.8 Organisational aspects

3.8.1 Description

Organisational domain focuses on the delivery models of the technology, analysing processes, resources, management and cultural issues within variety of stakeholders, in the intra- and inter-organisational and health care system level. Understanding organisational aspects may reveal essential challenges and barriers in implementing health technologies.

3.8.2 Methodology

In an organisational analysis both qualitative and quantitative research data are required. Registers and routine collected statistics are often useful. Comparing the results from two or more data collection methods, e.g. interview and observation, is a way to reduce bias. At least two different views on causality and transferability are used in organisational research: the diffusion model and the translation model. The assessment of the organisational issues is in many cases context-dependent.

3.8.3 Assessment elements

3.9 Social aspects

3.9.1 Description

Social domain focuses on the patients' and his or her significant others' considerations, worries and experiences before, during and after the implementation of the technology. It describes how the technology moulds and is moulded in diverse social arenas where the patients use it (hospitals, general practitioner, everyday life, homes, schools, and workplace), and what specific meanings people give to the technology.

3.9.2 Methodology

Relevant social issues could be identified together with organisational and ethical issues. Qualitative studies are highly relevant, along with quantitative studies with various observational designs. If no relevant studies are found, a primary study, e.g. interview, survey, or participant observation, should be considered. A thematic synthesis, a thorough description of relevant themes and sub-themes identified in literature or interviews (the thematic mapping), is more important than finding every single study or opinion.

3.9.3 Assessment elements

3.10 Legal aspects

3.10.1 Description

Legal domain includes questions on basic rights of patients, such as autonomy, informed consent, privacy and confidentiality, and legal requirements, such as authorisation, guarantee, and regulation of market. European Union is producing ever more health technology related legislation. Harmonisation of national legislation is likely to occur in the health care sector, as the patients and professionals are allowed free movement within Europe. Proper knowledge of relevant legal questions has often relevant legal consequences in decision making.

3.10.2 Methodology

Compulsory legal sources form the basic regulatory framework for any given question. These are international laws, European Union laws and national legislation. These sources are often complemented by various so called soft law instruments, agreements and documentation by the technology supplier, and legal scientific literature.

3.10.3 Assessment elements

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

HTA Core Model for screening technologies

Second public draft March 2012

Developed by
Work Package 4 Core HTA
EUnetHTA Joint Action 2010 - 2012

WP4 Lead Partner:
Finnish Office for HTA (FINOHTA),
in the National Institute for Health and Welfare (THL),
Finland

Contents

Glossary

Application of the HTA Core Model: Different kinds of technologies (e.g. surgical interventions or pharmaceuticals) may require different questions to be asked in an assessment and the answers to the questions may require different research methods. An application of the HTA Core Model is built for assessing a specific kind of health technology. Different applications all draw from the same pool of assessment elements, but not all elements are used in all applications. Currently there are two existing applications, one for medical and surgical interventions and another for diagnostic technologies. This document presents the draft version of the third application: HTA Core Model for screening technologies.

Assessment element: The basic unit of the model. Defines a piece of information that describes the technology or the consequences of implications of its use, or any other implication that is relevant for the assessment, such as the patients and the disease for which it is applied. Each assessment element contains an "issue", which is a question that should be answered in an HTA. Not all issues, however, are relevant to all technologies/settings, and hence their relevance is considered separately for each assessment. Elements are defined through a combination of domain, topic and issue.

Core HTA: An actual assessment that a) has been conducted using the HTA Core Model and b) has considered all core elements of all 9 domains. (Note: through this consideration some elements may be defined as irrelevant, but that should be documented). A Core HTA contains a chapter that draws together key findings of various domains, but does not make recommendations regarding the use of technology. Through the wide scope, focus on core elements and the summary chapter, a Core HTA gives an overview of a technology that is likely to be useful in the European context. A Core HTA can be used as a basis for producing local HTA reports that take into account local circumstances (e.g. epidemiology, organisation, resources, and values).

Core HTA information: Any information on a technology that has been produced through answering the issue defined in a core element, or a collection of such information. This information is very likely to be useful in the European context (i.e. also in another country) due to its importance and/or transferability.

Domain: A wide framework within which technology is considered. It provides an angle of viewing the use, consequences and implications of technology. A standard set of domains is used in the HTA Core Model.

Element card: Each assessment element is connected to an element card, which provides tangible information on the element and its relations to other elements. A card may provide advice on how to answer the question defined by the element. Two characteristics within a card (importance and transferability) define whether an element is a "core element" or "non-core element". While assessment elements are generic (i.e. one element can belong to several applications of the HTA Core Model), element cards are application-specific (i.e. the cards describing an element within different applications may be different).

HTA Core Model: A structured manner of creating and presenting HTA information as assessment elements. Some elements are prioritized over others to support European collaboration through defining them as "core elements".

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 always expressed as a question that can be answered through answering one or more research questions.

Screening technology: In this document a full population screening program with the following components:

- It involves a test or an examination or a series of tests or examinations, AND
- is provided either systematically to the whole target population (i.e. in a screening program) , or unsystematically for asymptomatic people, e.g. in the form of locally provided health promotion or case finding programs, AND
- is done in order to make a statement regarding the possibility of having a certain disease or risk factor, AND

aims at improved prognosis, or an improvement of the management or coping with the disease (excludes technologies which aim at surveying the prevalence or spread of a certain disease, risk factor, or exposure only).

Structured HTA information: Information on any aspect of health technology that has been created through answering the issues defined in the assessment elements of the HTA Core Model.

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

Updated glossary in the HTA Core Model Handbook, available at http://www.corehta.info

Introduction

Objective of the document

HTA Core Model for screening technologies is a document that describes a model for assessing screening technologies. It presents the questions that should be considered when assessing screening programs, and the methods needed to answer these questions. It is the third in a series of Core Model applications, prepared by EUnetHTA, and designed for assessment of different types of health technologies; the previous two are on medical and surgical interventions, and on diagnostic technologies. The model enables production of structured HTA information which can be shared by HTA agencies and adapted into local settings.

The development of this report was conducted as a part of the EUnetHTA project. It was produced by 68 individuals from 23 HTA agencies in 16 European countries. Responsible organisation and the lead partner of Work Package 4 of EUnetHTA Joint Action was FINOHTA (Finnish office for health technology assessment at THL).

About EUnetHTA

The EUnetHTA Joint Action (JA) 2010-2012 (www.eunethta.net).is a response to the request by the EU Commission and EU Member States, in the Work Plan 2009 of the Health Programme, to continue fostering the development of HTA in Europe. The main objective of the JA is to put into practice an effective and sustainable HTA collaboration in Europe that brings added value at the European, national and regional level. The EUnetHTA JA focuses on HTA in Europe to; facilitate the efficient use of resources available for HTA, to create a sustainable system of HTA knowledge sharing, and to promote good practice in HTA methods and processes. The EUnetHTA JA builds on the methods and tools developed by the EUnetHTA project (2006-2008) and the work done in the Working group on Relative Effectiveness of the High Level Pharmaceutical Forum. The EUnetHTA JA involves a total of 35 government appointed organisations from 24 EU Member States, Norway and Croatia and a large number of relevant regional agencies and non-for-profit organisations that produce or contribute to HTA. The EUnetHTA JA work is organised in eight Work Packages (WPs), three horizontal WPs and five core WPs. The objective of WP4 Core HTA, was to develop principles, methodological guidance, tools and policies for producing, publishing, storing and retrieving structured HTA information, and to test them in actual Core HTA projects.

EUnetHTA JA is supported by a grant from the European Commission. The sole responsibility for the content of this article (publication, presentation, etc) lies with the authors and the European Commission is not responsible for any use that may be made of the information contained therein."

About the HTA Core Model®

Any health technology assessment (HTA) contains a vast amount of information. The content, focus, quality and reporting of HTAs vary a lot; this makes finding and transferring the information into local context difficult. *The HTA Core Model* tackles particularly this problem. The Model defines the content elements to be considered in an HTA and enables standardized reporting. The aim is to improve the applicability of an HTA in other national HTA projects, and enable actual collaboration between HTA agencies by providing a common framework for HTA production.

The HTA Core Model divides HTA information into standardized pieces referred to as assessment elements. An assessment element defines a piece of information that is relevant for the HTA. .The elements that are most likely to be useful for international sharing of information are defined as core elements. Each assessment element contains a question that one should consider including and answering for a specific technology. The Model provides methodological guidance to assist the answering of these questions, and a reporting tool (Fig 1). There is also a storage function for the question-answer pairs referred to as *pool of structured HTA information*.

The HTA Core Model, and the electronic tool supporting it *the HTA Core Model Online*, is used to produce the structured Core HTA information. A *Core HTA* is a project which provides the answers for all relevant core elements for a specific technology, considers the findings per domain in "domain discussions", and summarizes the most important findings. The model serves also those who wish to pick a free selection of elements to be answered. E.g. one could consider sharing certain pieces of information from a national HTA project by sharing them in the pool of structured HTA information with other European HTA agencies.

The HTA Core Model builds on earlier work of projects EUR-ASSESS1, HTA Europe and ECHTA/ECAHI as well as on other theoretical guidance (refs). It is loyal to the definitions of HTA that emphasize the multidisciplinary nature of assessments. It employs the nine domains that were originally identified in the EUR-ASSESS project (Table 1). Two first applications of the HTA Core Model, one for medical and surgical interventions (EUnetHTA 2008d) and the other for diagnostic technologies (EUnetHTA 2008c), were created during the EUnetHTA Project 2006-08.

Figure 1

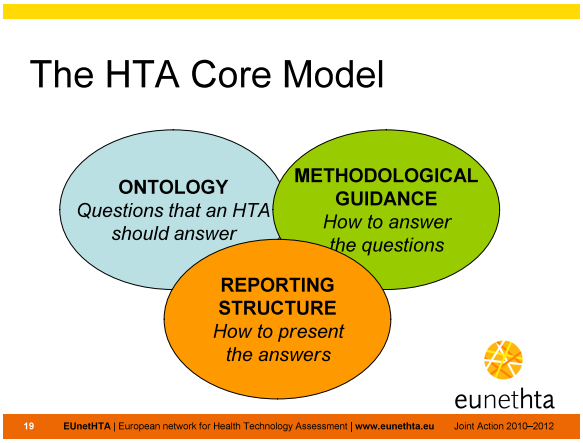

Table 1. Domains of an HTA

1. Health problem and current use of the technology
2. Description and technical characteristics of technology
3. Safety
4. Clinical effectiveness
5. Costs and economic evaluation
6. Ethical aspects
7. Organisational aspects
8. Social aspects
9. Legal aspects

Ontology – the assessment element structure

In philosophy, 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 in contexts where the aim has been to assign meanings to information and to describe the relations between concepts. Ontologies typically make it easier for both humans and computers to understand information and its context. Within HTA increased standardisation of the way of searching, handling, and presenting of information may lead to better use of information. The use of other 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.

The HTA Core Model structures the information of an HTA first by dividing it into nine *Domains* (Table 1). Each Domain is divided into three or more *Topics*, and further, each Topic is divided into several *Issues*. The Issues are the generic questions that should be considered when doing a Core HTA. The combination of Domain, Topic and Issue defines an Assessment element (Fig 2).

Assessment elements are the standardized pieces of a Core HTA. Each assessment element is connected to an "element card", which provides tangible information on the element and its relations to other elements. A card may provide advice on how to answer the question defined by the element. Two characteristics within a card (importance and transferability) define whether an element is a "core element" or "non-core element". The answers to questions defined by the element cards are recorded as structured pieces of information in respective "result cards". These are associated with relevant metadata to enable their effective use in the database of HTA information that is being built within EUnetHTA Joint Action WP4.

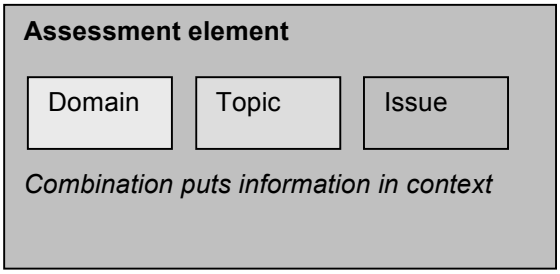

Figure 2. An assessment element

Being in Core

The inclusion of an element in the core is a function of two basic characteristics of the element: its importance and transferability. If the information is fully or partly transferable, it may provide valuable input beyond its original production location. Transferability is low for information that is very specific to a particular context (e.g. region, country, health care system) and is most likely not useful as such in other settings. On the other hand even non-transferable information may be useful; e.g. Italian incidence data on cardiovascular mortality is applicable to all Italian HTAs assessing cardiovascular technologies or, Swedish data on current use of the technology may suggest over- or underuse of the technology in one's own country.

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.

We are aware of the various definitions for transferability and generalizability. These terms need to be clearly defined in future updates of the Model. For this document transferability is defined as an estimate about the transferability of data or other findings from one context to another (3=complete, 2=partial, 1=not). Likewise

importance in this document defines how important it is to consider the particular issue when conducting HTA (3=critical, 2=important, 3=optional). This is not always the same as "relevance" in a particular policy context.

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

CORE MATRIX		**Importance**		
		1 Optional	*2 Important*	*3 Critical*
Transferability	*3 Complete*	Not core	Core	Core
	2 Partially	Not core	Core	Core
	1 Not	Not core	Not core	Core

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 of 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 piloting will provide more accurate values.

Generic Model and its applications

Different types of technology - such as drugs, devices or procedures - may require different kinds of assessment. Therefore it has been decided that within one HTA Core Model there are different applications for the assessment of different types of technologies. There are two earlier HTA Core Model applications created during the EUnetHTA Project 2006-2008: one for **medical and surgical interventions** and the other for **diagnostic technologies** (EUnetHTA 2008 b and a). During the EUnetHTA Joint Action 2010-12 there will be two further Model applications designed: one for **screening technologies** (which is described in this document) and the other for the **relative effectiveness assessment of pharmaceuticals** (WP5 of EUnetHTA JA) which includes additional modification called “rapid model”.

When creating a new HTA Core Model application, or updating an existing one, the aim is to keep most of the Model generic, i.e. identical across various applications. Additional to the generic main part, the applications contain assessment elements and methodological guidance which are specific for thy type of technologies the application covers. When updating the HTA Core Model, all changes in the generic part of the Model will be transformed automatically to all applications. Application-specific amendments need to be updated separately.

HTA Core Model Online Tool and Handbook

A pilot version of the HTA Core Model Online, at http://www.corehta.info, was opened to EUnetHTA JA partners in March 2011. The tool contains a Handbook which guides the users of the tool in five phases. The project and its participants are defined in phase 1 and the assessment protocol designed in phases 2 and 3. After finding answers to the study questions the process continues in submitting the results of the research in the online database (phase 4) and publishing the results (phase 5). An editorial process

precedes the final publication. The HTA Core Model is subject to Terms of Use, available through www.eunethta.net.

Work process of HTA Core Model on Screening Technologies

The HTA Core Model was built by several working groups called *Domain teams* (see pages 14 - 16). Each team focused on one domain. The roles were divided into *investigators* and *reviewers*. The work of investigators within each domain team was coordinated by a *primary investigator*. The investigators used the existing two HTA Core Model applications (EUnetHTA 2008 a and b) as base text, which they updated and adjusted to screening technologies. Reviewers commented on the draft versions of the investigators' work. The primary investigators from each domain formed the *Coordination and editing team* (CET) which task was to prepare documents with common interest across domains: e.g. the **communication protocol** (Box 1) and **definition of screening (see below)**.

The task of the Domain teams was divided into three sections:

- Updating the *Domain description,*
- updating the *Assessment elements table, and*
- updating the *Domain methodologies.*

1) Updating the Domain description

The investigators' task was to modify the base text so that it remains generic, i.e. is applicable to all types of technologies; medical & surgical interventions, diagnostic, and screening technologies. If there was a need to amend information that is specific for screening technology only, it should be placed under separate subheading.

The domain descriptions in the earlier Model applications were heterogeneous; they differed in length, content and style. Therefore new subheadings were introduced to harmonize the texts. They are:

- What is this domain about? (including concepts)
- Why is this domain important?
- Relations to other domains
- Specific features in finding and interpreting information for this domain
- Issues specific for screening technologies

2) Updating the Assessment elements table

The investigators went through the topics and issues in the assessment element tables of the earlier model applications considering inclusion and modification for this model. They were encouraged to comment the hierarchy and relations of the elements and to suggest new elements if needed.

3) Updating the Domain Methodologies section

The task and the problems were here the same as in domain description. The investigators should combine and harmonize the original texts that were lengthy and heterogeneous. New subheading to harmonize the content were

- Where to find information for this domain?
    - Databases and search strategies
    - Useful other sources and links
- What kind of information is required?
    - Study types: including design, outcome measures
    - Critical appraisal tools

- How to collect information?
    - Systematically vs other
    - Data extraction template
- Own research/evidence generation
- Analysing and synthesizing evidence
    - Biases, confounding factors, level of evidence
    - Evidence tables
    - Meta-analysis
    - Qualitative synthesis
- Reporting and interpreting

The task of keeping generic items separate from screening technology specific methodology items was a challenge. Additionally, the authors were encouraged to identify text that was not directly specific for their domain. The methodological guidance that is applicable in several, or even in all domains, was moved to the "Shared methodologies" section in Appendix 3.

It was made explicit that the style should not be a text book, neither a methodological article. Instead of lengthy descriptions, the investigators were encouraged to write brief sentences and use lists and links to useful sources and tools.

Box 1 Communication protocol

This is a shortened version of the original project communication protocol which included also rules for internal communication and practical guidance on e.g. e-meetings.

External communication and feedback

Communicating about the project is in general encouraged. Anyhow, all project participants shall keep the project coordinator informed about any occasion where the aims or results of this project are presented; be it interview, poster, speech or article. We also wish to gather success stories (or failures), and all kind of feedback of the HTA Core Model and the screening application. All participants are encouraged to inform the coordinator of any comments and feedback they have encountered. EUnetHTA Joint Action secretariat will be kept informed about the external communication and feedback.

"*Restricted authorship*"

In this project we are working on two earlier applications of the Core Model. The aim is not to rewrite the text in them, but rather to keep it as unchanged as possible and do only the necessary updates and adjustments. We deal with text that has several earlier authors and add our own intellectual input on top of the earlier work. It is similar as writing an article in Wikipedia. We are authors but will less power than when writing a traditional original article. Careful consideration and full transparency and recognition of all original authors are needed if someone wants to present or publish an article about the work done in this project.

Defining what is screening technology

Depending on background and training, people give different meaning to the word "screening". The following observations and definitions were agreed for this project.

Why do we need a dedicated Model application for screening technologies?
Screening involves testing to identify people at high risk of having a specific disease (diagnosis). As there is already a HTA Core Model application for diagnostic technologies that covers testing procedures, why do we need additional application for screening? The following properties of screening were identified that justify the need of a dedicated application of the HTA Core Model.

- As preventive or early diagnostic intervention, screening is targeted to a large number of healthy or asymptomatic people – in contrast to diagnostics where people typically already have some symptoms or signs of illness.
- Screening tests are usually applied in a population with low disease prevalence; mostly healthy people. Therefore, the diagnostic tools often perform very differently from clinical settings (i.e. very low positive predictive value). The same technology has different performance when used in diagnosis than in screening.
- Effectiveness depends on participation rate of the target population.
- Screening usually requires careful ethical and legal considerations, due to the risk of false positives and false negatives, the consequences related to the under- or over-diagnosis and -treatment, and earlier diagnosis in cases where prognosis improvement is neglible. Equity of access is always an issue in screening programs.
- There are several organizational issues specific for screening as it
    - involves active contact of the target population by the health service
    - is multidisciplinary and involves multiple providers
    - requires quality control and a continuous monitoring system.
- There are many specific characteristics and methodological issues which have to be taken into account when evaluating economic impact of a screening program. For example, most of the costs of a screening program are incurred within a relatively short time period and the benefits (e.g. life years gained) further in the future. This means that decisions about whether to discount the future costs and effects or not, and which discount rate(s) to use, need to be carefully considered.

Multitude of definitions for screening
There are **two main streams** of considering screening as a public health intervention.

- The first, mostly adopted in Europe, considers screening as a program in which
    - the target population and adequate screening interval are determined in advance;
    - all individuals in a certain category (e.g. all women of a certain age) are involved;
    - the health services contact systematically and actively the target population; and
    - a standard process is determined for further diagnostic examinations subsequent to the screening test, as well as for treatming those with the diagnosed condition.
    - This approach is also called universal screening, mass screening, population screening, or community screening.
- The second stream, mostly adopted in the USA, considers screening to be spontaneous, or so called opportunistic screening, in which the practitioners recommend the test to their (asymptomatic) patients more or less systematically and according to their attitudes and knowledge. This kind of screening lacks systematic identification and contacting of the target population. Instead it is dependent on the activity of the individuals themselves, their health service providers, and funding arrangements (health insurance package).The process for further examinations and treatment is not standardized.

There are **additional uses** of the word screening in medicine

- "Screening" may be performed during a regular patient visit, on an asymptomatic patient, to exclude or confirm diagnosis (e.g. bone density measurement).
- Surveillance screening involves testing of a sample of the population to survey the prevalence of a disease or an exposure, without the aim of improving prognosis in diseased individuals.
- Toxicological screening involves testing of environmental or clinical samples to identify toxic substances.
- Molecular screening is a phase in the selection of active molecules in pharmacology.

More **related concepts**

- Case finding: Involves a smaller group of people based on the presence of risk factors (e.g. when a family member has been diagnosed with a hereditary or communicable disease). "Case finding" is also used in the context of screening a single patient who consults the doctor on a problem not directly related to the disease being screened . An example of this is cervical cancer screening during a consultation for other gynecological problem.
- Routine safety checks (e.g. related to anaesthesia)
- Baseline value assessment (e.g. liver enzymes before medication)
- Check-up, periodic health examinations often involve a number of screening elements

Solution: What is meant by 'screening technology' in the context of this Core Model application?

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

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

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

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

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

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Team list

The work has been done as a collaborative effort of Domain teams. Each domain team consisted of investigators that were responsible for writing the sections of the report and reviewers who provided support and feedback to investigators.

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Table of all who have made major contribution to the text in this document (including the investigators from previous model applications)

DOMAIN	Investigators (**primary investigator bolded**)		
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Health problem and current use of the technology

Domain description

What is this domain about?

This domain describes the target conditions, target groups and the availability and patterns of use of the technology in question. Some of the topics considered relevant for this domain have generally been called “Background Information” in previous European projects or recommendations for conducting assessments (Burls 2000, Busse 2002, Liberati 1997).

The qualitative description of the **target condition**, including the underlying mechanism (pathophysiology), natural history (i.e. course of disease), diagnosis and prognosis, the risk population and risk factors for acquiring the condition as well as available treatments are described in this domain. A description of subgroups or special indications should be included especially when the technology does not target the whole population.

Current management patterns are described, and whether the technology is intended to replace, add or triage another technology in the management chain. Anticipated problems in the use, e.g. inappropriate extension of indications, participation rate, over-diagnosis, misuse, and acceptability by the population, are to be discussed, as well as the alternatives to the technology and agreed policies on whom to treat as patients or target group.

Why is this domain important?

The information produced in this domain provides baseline knowledge which is needed when the results from other domains of the assessment are put into context in a particular geographical or organisational setting. If health problem and the target population cannot be clearly defined, the appropriate use of the technology may be rightfully challenged. If the current management practice is not in accordance with evidence-based guidelines, the public might get the impression that a need for a new technology exists. A new technology could be costly and not necessarily more effective than existing ones. In that case it could be more appropriate to improve the compliance to guidelines than to add a new technology with a similar effectiveness and/or higher costs.

National decision-makers are interested in the extent of utilization of technology in their own country, and if there is regional variation. On the other hand, international benchmarking may have a great impact on decision-making process (Zentner 2004). Particularly important it may be when the estimation of the harm-benefit-costs equation is inconclusive. It might be important to be aware of the variation in the management patterns and current use of the technology in Europe; this often reflects country-specific epidemiology and priorities, but can also be an indication of under- or overuse of the technology. In Europe, great variation in approval status of technologies is seldom expected; therefore it may be of interest to compare the status with non-European countries.

Relations to other domains

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

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

Issues specific for screening technologies

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

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

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

Assessment elements

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
A0001	Health Problem and Current Use of the Technology	**Target Condition**	Which disease/health problem/potential health problem will the technology be used for?	Definition (naming) of the condition, health problem, disease for which the technology is intended.	3	3	Medical literature, narrative reviews, book chapters	Burls 2000, Busse 2002, Liberati 1997 Imaz-Iglesia 1998, Kristensen 2009	
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 allows a precise diagnostic and differentiation of the indication for the use of the technology.Subgroups or indications are considered under the Domain Clinical Effectiveness	3	3	WHO	Burls 2000, Busse 2002, Liberati 1997 Imaz-Iglesia 1998, Kristensen 2009	Clinical Effectiveness Domain
A0003	Health Problem and Current Use of the Technology	Target Condition	Which are the known risk factors for acquiring the condition?	The prevalence of different risk factors might be different in different geographic areas and among different groups of population. This element clarifies the identification of alternative (also preventive) management approaches.	3	2	Narrative and systematic reviews, book chapters	Burls 2000, Busse 2002, Liberati 1997 Imaz-Iglesia 1998, Kristensen 2009	Clinical Effectiveness Domain
A0004	Health Problem and Current Use of the Technology	Target Condition	What is the natural course of the condition?	Description of underlying mechanisms or pathophysiology. Possible relation between early diagnosis and better prognosis?	3	3	Registries	Burls 2000, Busse 2002, Liberati 1997 Imaz-Iglesia 1998, Kristensen 2009	Clinical Effectiveness and Costs Domains

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
A0005	Health Problem and Current Use of the Technology	Target Condition	What are the symptoms at different stages of the disease?	Symptoms by stage might give an idea of possible improvements, and provide proxy outcomes for effectiveness assessment.	2	3	Registries, quality of life studies, narrative and systematic reviews, book chapters	Burls 2000, Busse 2002, Liberati 1997 Imaz-Iglesia 1998, Kristensen 2009	Clinical Effectiveness Domain
A0006	Health Problem and Current Use of the Technology	Target Condition	What is the burden of the condition?	Prevalence or incidence of disease specific mortality, life years lost, disability	3	2	Registries and national statistics	Burls 2000, Busse 2002, Liberati 1997 Imaz-Iglesia 1998, Kristensen 2009	Clinical Effectiveness, Social and Costs Domains
A0009	Health Problem and Current Use of the Technology	Target Condition	What aspects of the burden of disease are targeted by the technology?	The technology can affect only some aspects (e.g. mortality) and leave other aspects (e.g. quality of life) untouched. Screening may increase disease incidence due to early diagnosis and over diagnosis.	3	3	Deductive models (based on the natural history of the disease, test target and treatment target; epidemiological studies (if sufficient testing has been done)		Clinical Effectiveness, Social and Costs Domains
A0007	Health Problem and Current Use of the Technology	Target Population	What is the target population of the technology?	The technology may be used for all patients having the condition, or only those in early stages, or certain severity level, or people with moderate risk of having the condition. In screening and other preventive interventions the target population represent a defined subgroup of healthy or asymptomatic individuals. Who have defined the selected subgroup(s) and for which reasons?	3	2	Medical literature, narrative reviews, commentaries, editorials of scientific associations, guidelines, recommendations		Clinical Effectiveness Domain
A0023	Health Problem and Current Use of the Technology	Target Population	How many people belong to the target population?		3	1	National registries, statistics, systematic reviews		

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
A0011	Health Problem and Current Use of the Technology	**Utilisation**	How much is the technology being used?	Provide EU level and national information about the extent of implementation of the technology. Information is usually available when (re-)evaluating established or obsolete technologies. For new technologies, information from other countries may be useful. Factors that modify the actual use of the implemented technology, and thus affect the interpretation of the statistics should be mentioned; e.g. such as acceptance and adherence (of both service providers and patients).	3	1	National statistics, surveys, disease management studies, manufacturer sales data	Burls 2000, Busse 2002, Liberati 1997 Imaz-Iglesia 1998, Kristensen 2009	Costs and Organisational Domains
A0012	Health Problem and Current Use of the Technology	Utilisation	What kind of variations in use are there across countries/regions/settings?	Variation in use should be examined (or interpreted) in the light of information from e.g. organisational, ethical and legal domains.	2	2	National statistics, surveys, disease management studies, manufacturer sales data	Burls 2000, Busse 2002, Liberati 1997 Imaz-Iglesia 1998, Kristensen 2009	
A0013	Health Problem and Current Use of the Technology	**Current Management of the Condition**	How is the disease/health condition currently diagnosed or screened?	Properties of diagnostic or screening tests affect patient spectrum and thus the effectiveness of subsequent interventions. Different tests are applied by different professional groups. This information is needed e.g. in cost-effectiveness models.	3	1	Surveys, utilisation reviews. If such information is lacking: Expert surveys / expert interviews, web search	Burls 2000, Busse 2002, Liberati 1997 Imaz-Iglesia 1998, Kristensen 2009	Clinical Effectiveness, Costs and Organisational Domains

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
A0014	Health Problem and Current Use of the Technology	Current Management of the Condition	How should the condition be diagnosed or screened according to published algorithms/guidelines?		2	2	Guidelines	Burls 2000, Busse 2002, Liberati 1997 Imaz-Iglesia 1998, Kristensen 2009	Clinical Effectiveness, Costs and Organisational Domains
A0015	Health Problem and Current Use of the Technology	Current Management of the Condition	How is the condition currently managed?	Deviation from eb-guidelines may hint over/under use of the technology and it may increase the burden of disease.Identification of practice variations may point out differences in the quality of health care.	2	1	Surveys, utilisation reviews. If such information is lacking: Expert surveys / expert interviews, audits		Clinical Effectiveness, Costs and Organisational Domains
A0016	Health Problem and Current Use of the Technology	Current Management of the Condition	How should the condition be managed according to published algorithms/guidelines?	An assessment of the main differences between guidelines and actual practice allows conclusions to be drawn on how optimal the current management is.	3	2	Review of clinical guidelines, recommendation. If such information is lacking: Expert surveys / expert interviews, textbooks		Clinical Effectiveness, Costs and Organisational Domains
A0017	Health Problem and Current Use of the Technology	Current Management of the Condition	What are the differences in the management for different stages of disease?		2	2	Surveys, utilisation reviews, clinical guidelines, recommendations. If such information is lacking: expert surveys / expert interviews		Organisational and Social Domains

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
A0018	Health Problem and Current Use of the Technology	Current Management of the Condition	What are the other evidence-based alternatives to the current technology?		3	2	Clinical guidelines, recommendations, systematic reviews	Burls 2000, Busse 2002, Liberati 1997 Imaz-Iglesia 1998, Kristensen 2009	Clinical Effectiveness, Costs and Organisational Domains
A0019	Health Problem and Current Use of the Technology	**Life-Cycle**	In which phase is the development of the technology?	It can be experimental, emerging, or routine use? Usually a new test for primary screening needs studies with very long follow up. Consequently new screening putative tests are usually very old tests. On the other hand a new triage test, therapy for positive individuals may be experimental. Finally we may have a new version of an old primary test, in this case it may be experimental.	3	2	Horizon scanning databases, ongoing research databases, information from manufacturers.	Burls 2000, Busse 2002, Liberati 1997 Imaz-Iglesia 1998, Kristensen 2009	Safety, Clinical Effectiveness, Ethical, Social and Legal Domains
A0020	Health Problem and Current Use of the Technology	**Regulatory Status**	Which market authorization status has the technology in other countries, or international authorities?	Imaging devices may require approval. Substances needed for obtaining images may require additional approval (e.g. radiotracers). In some cases the approval for primary screening is different to that for clinical use (FDA recently licensed tests explicitly for screening), but in most cases approval is obtained for diagnostic use and the test is proposed for screening without any other formal approval.	3	3	e.g. CE-Approval, EMEA, national authorities. Manufacturers should be contacted in order to identify which steps have they taken/ are they planning to take concerning market approval	Burls 2000, Busse 2002, Liberati 1997 Imaz-Iglesia 1998, Kristensen 2009	Legal Domain

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
A0021	Health Problem and Current Use of the Technology	Regulatory Status	What is the reimbursement status of the technology across countries?	Overview of how the technology is reimbursed in other European countries is useful information for national decision makers. Reimbursement status may be different for different purposes: e.g treatment vs prevention, diagnosing vs screening or monitoring. Information of full-coverage, co-payments, coverage under special circumstances and conditional coverage is useful.	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 2000, Busse 2002, Liberati 1997 Imaz-Iglesia 1998, Kristensen 2009	Organisational and Legal Domains

Methodology

Where to find information?

Databases and search strategies

- The EUnetHTA pool of structured HTA information will be a pertinent source of information on e.g. disease incidence.
- HTAs, systematic reviews and original research can be found in reference databases: e.g. CLIB, CRD DARE,Medline, Embase, Cinahl, PsychInfo.
- Evidence based guidelines can be found in reference databases, guidelines producers' web sites and in Guidelines international network's (GIN) web site.
- Textbooks are valuable source of descriptive information, for example for information on disease mechanism.

Useful other sources

- Registers and statistics
    - Technology and procedure registers ([100] in Appendix 1)
    - Disease registers ([105] in Appendix 1)
    - Routinely collected statistics and administrative data (e.g. DRG, discharge databases, reimbursement claims databases)
- Horizon scanning databases and web sites
- Ongoing research databases
- Scientific specialist associations' web sites
- Patient associations' web sites
- Market approval and other regulatory institutions' web sites ([109] in Appendix 1)
- National health services' web sites
- Regional/local governments' health departments' web sites
- Benefits and sickness funds' web sites
- Technology developers and manufacturers web sites
- Various sources through using internet search engines
- There are some issues, e.g. the coverage status of a technology (inclusion in the benefit catalogue, levels of co-payment, etc.), where information is not easy to retrieve. It requires local knowledge of the health-care system to identify adequate and usable information sources (Velasco-Garrido 2006).

Own research and evidence generation

- Own qualitative research might be the only way to assess real practice use and misuse. However, these studies are not frequently undertaken since they are resource consuming.
- Discussions with experts or officials
- Expert surveys or interviews
- Own register based research

What kind of information is required?

Study types, design, outcome measures

There is no single methodological approach which can be applied to all issues in this domain (See Table 1). The epidemiology of the target health condition and its consequences are usually described in terms of prevalence and incidence (e.g. mortality, disability, sickness leave, retirement).

Specific for screening technologies

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

Table 1. Types of information required in this domain

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

Tools for critical appraisal

The validity of the information may differ considerably depending on the source and type of information requested (see Table 1). For example, it might be difficult to find up-to-date information on the approval status of a technology by doing a review of published literature. Even if there are scientific publications on the issue (i.e. policy studies) they are likely to be rapidly outdated. The information obtained by directly inquiring (e.g. via telephone query) the relevant approval agencies will be more reliable and practical. Quality assessment of the information retrieved may be difficult, as there is often no standard way of doing it.

Quality assessment of epidemiologic studies

Newcastle Ottawa scale (see Appendix 3) may not be appropriate in the quality assessment of studies examining disease prevalence or burden of disease. It is more appropriate for studies assessing the link between diseases and risk factors. STROBE check list can be used as a check list for study quality, although it is an instrument meant for assessing the quality of reporting (see Appendix 3).

Quality assessment of registers and statistics

Several national and international sources of statistics exist which can be used to assess the incidence, prevalence, mortality, or burden of disease. These statistics are usually available in aggregated form and increasingly through the internet. 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. However, when there is a quality assured register, as in the case of many organized screening programs, the information can be highly reliable.

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

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

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

Quality assessment of routinely collected statistics and administrative data

Routinely collected administrative data (e.g. DRGs, discharge databases, reimbursement claims databases) can be useful too, when available. For example sickness funds collect great amounts of information which could be used to analyse utilisation of technology. By definition, these data have been collected for other purposes than research and they cannot be used to answer scientific questions without previous processing. Analysis of this kind of data might be very time consuming, since data need to be “prepared” before analysis. This might not be feasible in the context of an HTA project, due to resource constraints.

The use of routinely collected statistics has several limitations. The reliability of the diagnosis varies and usually it is not possible to differentiate between different stages of the disease. Even the validity of the coding of causes of death may be variable, and in some countries it is known to be very limited. Own analysis of administrative data often requires authorization from the data owner, which in some countries might be difficult to obtain due to issues of privacy protection and confidentiality.

Quality assessment of manufacturer data

The information provided by manufacturers 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. Scientific information provided by manufacturers needs to be evaluated for validity and applicability.

Analysing and synthesizing evidence

There are several issues, particularly in this domain, where systematic data retrieval is not necessary (see Table 1). Unsystematic gathering of information from books, introduction sections of reviews and articles, registers and internet until saturation is reached, may be enough. However, one should consider the risk of selection bias due to insufficient or selective inclusion of information sources and data.

Reporting and interpreting

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

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

Overview of guidelines synthesizing the main recommendations on management practises would be illustrative. Flowchart of the current management pathway is particularly illustrative in diagnostic technologies. It helps the reader to understand what is the intended role of the new technology in the current management chain (add-on, replacement or triage).

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Description and technical characteristics of the technology

Domain description

What is this domain about?

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

The issues in this domain need to be described in sufficient detail to differentiate the technology from its comparators. Such terms and concepts should be used that allow those unfamiliar with the technology to get an overall understanding of how it functions. It is important to distinguish between scientifically proven versus suspected mechanisms of action. Important terms should be defined, and a glossary or a list of product names provided. The section may include pictures, diagrams, videos, or other visual material, in order to facilitate understanding.

Why is this domain important?

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

Relations to other domains

There is a considerable overlap with the current use, organisational and legal Domains. The authors should co-operate with the authors of those domains to avoid duplication of work.

Assessment elements

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
B0001	Description and technical characteristics of the technology	**Features of the technology**	What is this technology?	Type of device, operation, imaging, etc. Biological rationale and mechanism of action of the technology. Technology may include a single device, a questionnaire, imaging or sequence of technologies. The HTA may address one or several similar technologies. Minor modifications between manufacturers/products need to be accounted for as these may affect performance.	3	2	Manufacturers´ sites, published literature including reviews, introduction sections of research articles.		
B0002	Description and technical characteristics of the 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 over previous / existing technologies used for the same health problem?	2	3	Manufacturers´ sites, published literature including reviews, introduction sections of research articles, grey literature, hand-searches and conference proceedings.		A0009, A0018, D1019, C0008
B0004	Description and technical characteristics of the technology	Features of the technology	Who will apply this technology?	Which professionals (nurses, doctors, other professionals) use the technology?	3	2	Manufacturers´ sites, published literature including reviews, textbooks, handbooks, introduction sections of research articles, interviews with specialists, as well as grey literature, hand-searches and conference proceedings.		Current Use

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
B0016	Description and technical characteristics of the technology	Features of the technology	In w'hat population(s) will this technology be used?	The technology might behave differently in different patient groups. Define as many subgroups as possible. The technology might behave differently in different patient groups. Define as many relevant subgroups as possible (e.g., 'optimal' age group versus optional age groups). Are there specific populations that should not be recipients of the technology because of technical difficulties, inaccuracy, inconclusive results or because of safety issues? Does the population need to use the technology more than once? In that case how many times, and how frequently?	3	2	Manufacturers´ sites, published literature including reviews, textbooks, handbooks, introduction sections of research articles, interviews with specialists, as well as grey literature, hand-searches and conference proceedings.		A0007, C0005
B0003	Description and technical characteristics of the technology	Features of the technology	In what phase of developement is the technology?	When was the technology developed? Is it an innovation or rather a modification of an existing technology? When was the technology introduced into healthcare? Is the technology an already established one, but now used in a different way, for instance for a new indication? Most technologies will be introduced at approximately the same time in several countries. The evidence base (published trials etc) may change rapidly for technologies that are at an earlier stage in their development.	3	2	Manufacturers´ sites, published literature including reviews, introduction sections of research articles, grey literature, hand-searches and conference proceedings.		A0019, A0020, F0001
B0017	Description and technical characteristics of the technology	Features of the technology	Is this technology field changing rapidly?	For end users it is useful to know if new versions or adaptations of the technology are expected in the near future.	2	3	Manufacturers´ sites, published literature including reviews, textbooks, handbooks, introduction sections of research articles, clinical trial sites, interviews with specialists, as well as grey literature, hand-searches and conference proceedings.		

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
B0006	Description and technical characteristics of the technology	Features of the technology	Are there any special features relevant to this technology?	How does this technology differ from its predecessors (other technologies used for similar purposes)? Are there new aspects that may need to be considered when applying it? Is there evidence that the technology works (or is used) outside its current indication area or produces incidental findings that can have consequences relevant to effectiveness, safety, organisational, social and ethical domains.	2	2	Manufacturers´ sites, published literature including reviews, introduction sections of research articles, interviews with specialists, grey literature, hand-searches and conference proceedings.		A0018, C0007, C0060, D0022
B0005	Description and technical characteristics of the technology	Features of the technology	In what place and context is the technology intended to be used?	It can be primary care, secondary care or self care. Its role in the management pathway can be as a replacement, an add-on or for triage.	3	2	Manufacturers´ sites, published literature including reviews, textbooks, handbooks, introduction sections of research articles, interviews with specialists, as well as grey literature, hand-searches and conference proceedings.		Current Use, D1007, G001, G0005
B0018	Description and technical characteristics of the technology	Features of the technology	Are the reference values or cut-off points clearly established?	Are conflicting /varying definitions of an abnormal finding likely to affect the interpretation of the results?	2	3	Manufacturers´ sites, published literature including reviews, textbooks, handbooks, introduction sections of research articles, interviews with specialists, as well as grey literature, hand-searches and conference proceedings.		

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
B0007	Description and technical characteristics of the 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 organisation in order to use the technology. Includes need for back-up investment to cover for breakdowns in use.	2	2	Manufacturers´ sites, published literature including reviews, textbooks, handbooks, introduction sections of research articles, interviews with specialists, as well as grey literature, hand-searches and conference proceedings.		E0001, E0002, G0006
B0008	Description and technical characteristics of the 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 organisations, 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 general statement (e.g. to be used in hospitals only)	2	2	Manufacturers´ sites, approving authority, published literature including reviews, handbooks, textbooks, introduction sections of research articles, interviews with specialists, as well as grey literature, hand-searches and conference proceedings.		Organisational domain
B0009	Description and technical characteristics of the 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, including published literature such as reviews, introduction sections of research articles, interviews with specialists, as well as grey literature, hand-searches and conference proceedings.		E0001, E002

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
B0010	Description and technical characteristics of the technology	Investments and tools required to use the technology	What kind of data and records are needed to monitor the use of 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		G0008
B0011	Description and technical characteristics of the technology	Investments and tools required to use the technology	What kind of registers are needed to monitor the use of the technology?	Are there existing registries that could be used, or should a registry be established to collect the necessary data?	2	1	HTA-reports, local authorities		G0008
B0012	Description and technical characteristics of the technology	**Training and information needed to use the technology**	What kind of qualification, training and quality assurance processes 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. interpreting the results and make treatment decisions. 3. taking 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 or frequent standardisation or quality checks required? E.g. CME points.	3	2	Manufacturers´ sites, approving authority, published literature including handbooks, textbooks, reviews, HTA-reports, interviews with specialists, as well as grey literature, hand-searches and conference proceedings.		G0003, C0020, C0062, C0063
B0013	Description and technical characteristics of the technology	Training and information needed to use the technology	What kind of training is needed for the personnel treating or investigating patients using this technology?	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. If the technology requires a specific skill that is developed over a period of time using the technology (learning curve), an estimate should be provided of the number of patients a professional needs to treat (as a basis or per year) in order to reach an acceptable minimum standard	2	1	Manufacturer, effectiveness studies, observational studies, applicability studies, clinical experts, user information. National or local judgement.		C0062, C0063, D1008, G0003

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
B0014	Description and technical characteristics of the technology	Training and information needed to use the technology	What kind of training and information should be provided for the patient who uses the technology, or for his family/carer?	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 Informed consent regarding the risk / benefits of participation.	2	2	Manufacturer data, effectiveness studies, observational studies, applicability studies, clinical experts, user information, HTA-reports.		C0001, C0003, C0005, C0007, C0062, F0004, F006 G0004, H0003, H0007, H0008, I0002
B0015	Description and technical characteristics of the technology	Training and information needed to use the technology	What information of the technology should be provided for patients outside the target group and the general public?	Information materials: writing and/or translation, other adaptation? Informed consent for participating?	3	2	HTA-reports, manufacturers' sites, interviews, as well as grey literature, hand-searches and conference proceedings..		F0005, F0011, G0004, H0002, H0007, H0008, I0002, I0008

Methodology

Where to find information?

The source of information will depend on the location of a technology within its product life cycle. Review articles and textbooks can be helpful when searching for information about the history and characteristics of established technology. For prototypes and innovative technologies published peer reviewed literature may be limited. It may need to be supplemented by grey literature (includes non-peer reviewed and non-published literature, as well as confidential commercial information) as well as anecdotal information from general web-searches. The use of a systematic search is usually not necessary when gathering information on the descriptive and technical characteristics of a technology.

Databases and search strategies

Published literature may be obtained by searching bibliographic databases such as Pubmed, EMBASE, the Cochrane Library and the Centre for Reviews and Dissemination (CRD). Establishing regular notifications for new results using the alert function on these databases will facilitate easy updating of the literature review to ensure that it is current at the time of completion of the HTA. Electronic searches can be supplemented by hand-searching the reference lists of key papers.

Useful other sources and links

Grey literature (e.g.working papers from research groups or committees, white papers, or preprints), hand-searching of reference lists, as well as conference proceedings may be identified by searching the websites of HTA and related agencies, professional associations. Key information may also be extracted from the life sciences database BIOSIS (http://science.thomsonreuters.com/training/biosis), which includes patents, journals, conferences, books, review articles etc. While selection of the most relevant of these sources to search will largely depend on the technology in question, compilations of potentially relevant sources of information, such as the HTAi IRG Vortal (http://www.htai.org) and Institute of Health Economics (IHE) 'Health technology assessment on the net' report (http://www.ahfmr.ab.ca) can provide a useful starting point (see also other sources in [111] in Appendix 1).

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

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

Reporting and interpreting

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

For diagnostic and monitoring technologies (laboratory tests, imaging, questionnaires etc), it is important to include sufficient information about the technical precision of the technology. This information, which is

different from the accuracy data presented in the clinical effectiveness domain, should be reported in this domain.

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

Safety

Domain description

What is this domain about?

Safety is an umbrella term for any unwanted or harmful effects caused by using a health technology. Safety information, balanced with the effectiveness data, forms the basis for further assessments of the technology on e.g. costs and organisational aspects.

There are several ways to categorize harms:

- A technology may have **direct** harm; mortality, morbidity or disability due to e.g. radiation, toxicity or invasiveness; or it can **indirectly** cause harm due to e.g. insufficient training, experience, maintenance of equipment, or inappropriate patient selection.
- Indirect harms can further be categorized into **operator or setting dependent** and **patient dependent risks.** The former can be modified by changing practices or affecting users´ knowledge, skills and behaviour. Latter means that there are vulnerable patient groups in whom protection is especially required.
- Harms are usually classified according to their **fatality or intensity** into mild, moderate, and serious or severe (Higgins 2008). '**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). The term 'risk' includes both the seriousness and the probability of the harm. Thus, moderate but very rare harm results in low to moderate risk, whereas even a mild harm with high occurrence is seen as a high risk.
- They can be classified according to their **dose-relatedness or time-relatedness**
- Harms do not occur only in **patients** or individuals using the technology. Their **family** and close ones, other patients, health care **professionals**, **public**, and the **environment** can be affected also.

The definitions and the terminology of safety used in HTA have not been standardised. Frequently used terms include: 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 (Ioannidis 2004). 'Harm' defines something once it has occurred, whereas 'risk' includes both the seriousness and probability of the harm. Thus, a moderate harmful effect . The Cochrane Handbook proposes some definitions for safety related terms (Higgins 2008). 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.umc-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 (Medawar 2003).

Why is this domain important?

Reliable information on harms of a technology is particularly difficult to retrieve in practice; it is therefore particularly important share it on a European level.

Assessment of safety issues is especially needed when

- The technology has major risk of harm
- The margin between benefit and harm is narrow

- Several technologies with similar effectiveness can be used for the condition, and they have different safety profiles
- The rate of false positive in a diagnostic test is high and patients may end up with unnecessary potentially harmful investigations or treatments
- Adverse effects or poor tolerability threatens the acceptability and use of the technology (modified from Loke 2007).

Relations to other domains

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

Specific features in finding, interpreting or implementing information

Systematic assessment of all safety issues of a technology can be time consuming. Authors of a Core HTA may need to limit themselves to the safety issues that are significant for patients, or most likely to be important in guiding the decision of health care providers and policy makers (Busse 2002). Severe and serious harms should always be reported. Mild harms should be considered if they can be accumulated or if they influence acceptability or are of importance for patients.

Issues specific for screening technologies

While screening technology is used for large number of healthy persons, the tolerance threshold for risks should be very low (Kristensen 2007). Indirect harms specific to screening technologies are:

- False positive results, which may cause stress, anxiety, and lead to unnecessary, possibly harmful further investigations or treatments.
- False negative results of screening test may have the potential to delay the detection of the illness. The false negative results may have medical, psychological, economic, and legal consequences.
- True negative test result may reduce normal alertness to symptoms of disease and lead to false sense of security.
- Overdiagnosis and overtreatment can be a problem if screening tends to detect and lead to treatment of conditions with good prognosis, even if left untreated. The same occurs if screening detects other conditions than the one it is aimed to detect.

Assessment elements

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
C0001	Safety	**Patient safety**	What kind of harms can use of the technology cause to the patient; what are the incidence, severity and duration of harms?	If the HTA is about test and treatment or a screening program, describe the possible harms for every stage of the management pathway	3	3	Observational research, safety monitoring databases, registers, statistics	Loke 2006, 2007, Ioannidis 2001, 2004, Higgins 2006, Papanikolaou 2006Busse 2002Golder 2006, Mac Mahon 2001	
C0002	Safety	Patient safety	What is the dose relatedness of the harms to patients?	Here one should consider also the accumulated harm due to repeated dosage or testing	3	3	Research articles, manufacturers' product data sheets, safety monitoring databases	Aronson 2003	
C0003	Safety	Patient safety	What is the timing of onset of harms to patients: immediate, early or late?		3	3	Research articles, manufacturers' product data sheets, safety monitoring databases	Aronson 2003	
C0004	Safety	Patient safety	Is the incidence of the harms to patients likely to change over time?	For some technologies the occurrence of harms may change over time and be dependant on the experience or training of the operator?	3	2	Medical literature/ grey literature/ professional societies/ registries		Current use, effectiveness, costs domains

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
C0005	Safety	Patient safety	Are there susceptible patient groups that are more likely to be harmed through use of the technology?		3	3	Research articles, manufacturers' product data sheets, safety monitoring databases	Aronson 2003	Ethical, F0005
C0006	Safety	Patient safety	What are the consequences of false positive, false negative and incidental findings brought about using the technology to the patients from the viewpoint of patient safety?		3	2	Research articles		Effectiveness, Social, Costs, Ethical and Legal domains
C0029	Safety	Patient safety	Does the existence of harms influence tolerability or acceptability of the technology?		2	2	Qualitative research articles, patient associations' web sites, Internet discussion forums		Effectiveness, Social, Ethical and Legal domains
C0007	Safety	Patient safety	What are the special features in using (applying/interpreting/maintaining) the technology that may increase the risk of harmful events?	Is there evidence for operator dependent harms? Is there a 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?	3	2	Research articles, manufacturers' product data sheets, safety monitoring databases		Description and technical characteristics and Organisational domains
C0008	Safety	Patient safety	What is the safety of the technology in comparison to alternative technologies used for the same purpose?		3	2	Research articles, manufacturers' product data sheets, safety monitoring databases		Current use, Clinical Effectiveness and Ethical domains

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
C0020	Safety	**Occupational safety**	What kind of occupational harms can occur when using the technology?		2	3	Research articles, manufacturers' product data sheets, safety monitoring databases		Ethical and Social domains
C0040	Safety	**Environmental safety**	What kind of risks for public and environment may occur when using the technology?		2	2	Research articles, manufacturers' product data sheets, safety monitoring databases		Ethical and Social domains
C0060	Safety	**Safety risk management**	How does the safety profile of the technology vary between different generations, approved versions or products?		3	3	Research articles, manufacturers' product data sheets, safety monitoring databases		Description and Technical Characteristics
C0061	Safety	Safety risk management	Is there evidence that harms increase or decrease in different organizational settings?		3	2	Accuracy and effectiveness research, epidemiological risk research		Current use, Effectiveness, Organisational
C0062	Safety	Safety risk management	How can one reduce safety risks for patients (including technology-, user-, and patient-dependent aspects)?	Technical means, protective equipment, education etc. Including information on what kind of risk communication is needed for patients, citizens and decision makers	3	3	Research articles, manufacturers' product data sheets, safety monitoring databases		Ethical F0006, Description and technical characteristics B0012, B0014, B0015

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
C0063	Safety	Safety risk management	How can one reduce safety risks for professionals (including technology-, user-, and patient-dependent aspects)?	Technical means, protective equipment, education etc. Including information on what kind of risk communication is needed for patients, citizens and decision makers	2	2	Research in occupational health and safety		Organisational and Social Domains
C0064	Safety	Safety risk management	How can one reduce safety risks for environment (including technology-, user-, and patient-dependent aspects)?	Technical means, protective equipment, education etc. Including information on what kind of risk communication is needed for patients, citizens and decision makers	2	2	Research articles, manufacturers' product data sheets.		Social Domain

Methodology

Where to find information?

Databases and search strategies

- EMBASE, MEDLINE, CENTRA, Science Citation Index
- The Cochrane Library http://www.cochrane.org/cochrane-reviews, CRD databases http://www.crd.york.ac.uk/crdweb/
- BIOSIS previews
- PASCAL
- TOXLINE
- TOXICOLOGY (searches 40 different databases) http://library.dialog.com/bluesheets/html/bl0157.html
- Micromedex (Thomson reuters) http://www.thomsonhc.com/home/dispatch
- National or international safety monitoring systems (databases) 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
  - IAEA: Radiological protection of patients http://rpop.iaea.org/RPoP/RPoP/Content/index.htm
  - ICRP: Publications of International Comission of Radiological Protection http://www.icrp.org/
  - TGA (Therapeutic Goods Administration), http://www.tga.gov.au/index.htm
  - The Medical Devices section of the UK Medicines and Healthcare Products Regulatory Agency http://devices.mhra.gov.uk/
  - Canada Vigilance Adverse Reaction Online Database http://www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/index-eng.php
  - Manufacturers product data sheets or applications for a product license

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 (Derry 2001). 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 (Golder 2006). New, previously unrecognised adverse effects remain therefore easily undetected (Golder 2006b). Several study types should be considered for inclusion in the search.

There is no optimal search strategy for specifically identifying reports of adverse effects. There are several highly sensitive (97- 100%) search strategies, but the problem is their low specificity 0.9-2.8%). This precision means that for each retrieved relevant article on adverse effects one have to screen 36-125 other records (Golder 2009). There are suggested search strategies for MEDLINE and EMBASE (Golder 2010 and 2006) and other sources (The InterTASC Information Specialists' Sub-Group, http://www.york.ac.uk/inst/crd/intertasc/adverse.htm).

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 risk in general: e.g. Adverse Effects (subheading), safety, toxicity, drug toxicity, complications
- Subheadings/qualifiers either attached to technology name indexing terms or "floated", i.e. searched without being attached to an indexing term (floating subheadings)
- 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 risk in general: side-effect, adverse effect/event/reaction, complications, poisoning, drug effects, safety management.
- Index terms and text words to capture certain study design, such as cohort studies or case reports.

The approach adopted will lead to different estimates of risk (McIntosh 2004). Therefore, the search strategies for electronic reference databases and study inclusion criteria should be clearly reported. This applies also for information retrieved elsewhere.

Search issues specific for screening technologies

Suggested index terms:
Primary Prevention [Mesh] or Mass Screening [Mesh] or Public Health Practice [Mesh]. Medicalisation, false positive, false negative, over-diagnosis, over-treatment

Example: Suggested search strategy in CURRENT CONTENTS.

- #1 «Primary Prevention» [Mesh] or «Preventive Health Services» [Mesh] or «Mass Screening» [Mesh] or «Public Health Practice» [Mesh]
- #2 «screening»
- #3 «preventive drug»
- #4 «preventive drugs»
- #5 #1 or #2 or #3 or #4
- #6 «Safety Management» [Mesh] or «adverse effects» [Subheading]
- #7 «safety»
- #8 «adverse events»
- #9 «medicalization»
- #10 #6 or #7 or #8 or #9
- #11 #5 and #10

- #1 «screening»
- #2 «false positive»
- #3 «false positives»
- #4 «false negative»
- #5 «false negatives»

- #6 #2 or #3 or #4 or #5
- #7 #1 and #6

Useful other sources of information

- Drug monographs
- Bulletins
- Conference proceedings
- Reference checking
- Hand searching
- Personal communication
- Manufacturers Periodic Safety Update Reports (PSURs)
- National or international safety monitoring systems (databases) of adverse events which may be managed by a national statutory body or by a supra-national body ([110] in Appendix 1).
- Disease ([105] in Appendix 1) or technology registries ([104] in Appendix 1) of patients receiving treatment which may be organised at an international, national or regional level and managed by a government agency, professional body or the manufacturer.
- In some cases routine statistics from hospital, primary care or health system funders may be available and provide suitable information
- Specific enquiries to manufacturers (e.g. industry submissions, product information), regulators or professional bodies
- Information from patient associations may provide valuable patient experiences especially in emerging technologies (Cross 2005).
- Internet discussion forums may provide valuable, but probably unreliable, additional information.

Inclusion of unpublished studies can provide additional adverse effects information and more precise risk estimates. However, there is insufficient evidence to indicate whether inclusion of unpublished studies has a major influence on the pooled risk estimates in meta-analyses of adverse effects (Golder 2010b).

What kind of information is required?

Study types, design, outcome measures

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, safety reporting in randomized trials is heterogeneous and often inadequate (Pitrou 2009, Ioannidis 2001). 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).

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 (Busse 2002). Their information is especially relevant in the assessment of e.g. public preventive programs.

Spontaneous reporting of adverse drug reactions is a standard method to identify safety signals for marketed drugs. Its primary purpose is to provide early warnings of adverse drug reactions not recognized prior to the

marketing. Once a signal has been identified, other methods will be used to quantify the potential risk in order to avoid unnecessary alarms.

The risks are sometimes quantified as a quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs). QALYs are non-disease specific measurement of outcomes that incorporates both quality and duration of life, defined as years of healthy life lived (Drummond 2005). DALYs are defined as years of healthy life lost. DALYs and QALYs are complementary concepts and both approaches multiply the number of years by the quality of those years. In order to reflect the burden of the same states QALYs use “utility” weights of health states, whereas DALYs use “disability weights”. QALYs and DALYs simultaneously capture both positive and negative changes in morbidity and mortality associated with treatment-related benefits and risks, and translate outcomes from different disease states into a comparable common metric that is useful for subsequent quantitative benefit–risk analysis (Arnesen 1999, Rehm 2010)

Results from trials are usually presented as information on the frequency of occurrence, relative risk RR, risk difference (RD), odds ratio (OR), or number needed to harm (NNH). Estimates of risk from case-control studies are presented in exposure odds ratio of cases compared with controls. The unintuitive odds ratios have been used to calculate the additional absolute risk of an adverse event NNTH (number of patients needed to be treated for on additional patient to be harmed) (Bjerre 2000).

For meta-analysis risk ratio (RR) is the most common summary statistic, followed by Peto odds ratio. Risk difference (RD) is rarely used in meta-analyses although it is the most interpretable statistics and is particularly appropriate in examining rare event data (Deeks 2002).

Analysing data based on NNH can be dangerous since this measure can be very sensitive if the point estimate is close to zero (i.e. close to 1 for an OR or RR and close to 0 for a RD) (Vandermeer 2009).

Issues specific for screening technologies

Diagnostic accuracy studies are essential in the assessment of screening technologies in order to assess sensitivity and specificity of the test itself, and the rates of false negative and false positive results and their consequences.

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). The results of the index test(s) are then compared to the results of the reference 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 (Rutjes 2007). Another possibility is to investigate the probability of disease presence as a function of all diagnostic variables simultaneously with multivariable modelling (Moons 1999). 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).

Tools for critical appraisal

There is often a trade-off between the comprehensiveness and quality of the risks 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. There is a lack of a relevant quality assessment tool to risk analysis (Loke 2007). Any available tool should be used cautiously. Comparing evidence from randomised trials and observational studies is useful.

The authors of a 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 risks analysis

Different methods of monitoring risks yield different results, which make comparisons between studies meaningless. Active surveillance and use of checklists yield higher harm frequencies than passive or less-focused methods (Loke 2007). 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).

Systematic reviews of adverse effects have often used inadequate searches to identify studies (Golder 2008).

Trials

Adverse events are variably and sometimes poorly reported in randomised trials (Pitrou 2009), and in systematic reviews of trials (Ernst 2001, Golder 2006b). The definition of a particular risk may vary between studies, as can definitions of severity. They can be measured in different ways and different thresholds can be used. An extension of the CONSORT Statement (Consolidated Standards for reporting Trials) is made for better reporting of harms in randomised trials (Ioannidis 2004).

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 (MacMahon 2001). The analysis of zero events ("no serious adverse effects were seen") needs careful consideration. Before concluding that no adverse effect occurred, reviewers should ask themselves how thorough were the methods used to detect adverse effects in the original studies and how many patients were studied and for how long (Loke 2007)?

Even in cases where adverse events are examined and reported adequately, there is often insufficient evidence for conclusion since most trials are tailored towards optimizing efficacy estimates (Vandermeer 2009).

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 seriousness or 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 risk analysis or, exceptionally, to include it on the assumption that the incidence was zero (Loke 2007).

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 (Ioannidis 2004). Patients in trials and investigators may be more (or less) willing than generally to continue in trial although there are some side effects (Loke 2007).

Observational studies

Trials may report small, fragmented pieces of evidence of risks that are not primary outcomes, whereas observational studies may be primarily devoted to assessing specific risks. Nested case control studies, full cohort analysis, and survival analysis methodologies are the study designs frequently used for risk 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 (MacMahon 2001). 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 (Jefferson 2003). Newcastle Ottawa scale is a tool to assess observational studies, available at 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 (vonElm 2007).

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 (Loke 2006). Some spontaneous reporting systems are inevitably erroneous (Loke 2007).

Issues specific for screening technologies

Aspects of study quality of diagnostic accuracy studies include the selection of a clinical relevant cohort, the consistent use of a single good reference standard, and the blinding of results of experimental and reference test (Deeks 2001). QUADAS tool is a checklist to assess quality of diagnostic accuracy studies.

Quality assessment of diagnostic accuracy studies is subjective and hampered by poor reporting. 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 (Higgins 2008) recommends QUADAS tool with its 11 mandatory and more than 10 facultative items. HTA-authors create an own selection of relevant items presented in the tool. 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. See more about Quadas tool in Appendix 3.

Analysing and synthesizing evidence

A systematic approach is required in the assessment of safety (risks). Core HTA authors, who are not aware of any specific safety problem, usually start with a broad overview of the whole range of adverse effects associated with the use of the technology. They may be confronted with an unstructured mix of lists and texts covering many diverse outcomes due to lack of consistency of reporting harms. A predefined classification of adverse effects could help the authors to approach the data (Loke 2007).

The aim is not necessarily to cover all known and previously unrecognised risks of a technology. Rather, Core HTA preparers should focus their review and predefine the safety issues and outcome measures they wish to work in their assessment (Higgins 2008). The demographic characteristics of the population in which the technology is to be used should be defined for later comparison against the populations in which safety data has been identified.

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

- the five to ten most frequent adverse effects
- all adverse effects that either the patient or the clinician considers to be serious
- 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 (Higgins 2008).

Biases, confounding factors, level of evidence

Harms are frequently insufficiently reported (Pitrou 2009). Poor safety reporting of the original research can lead to misinterpretation and inadequate conclusion of the technology assessed.

Reported harm frequencies 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 (Papanikolaou 2006).

Randomized trials have frequently restrictive inclusion/exclusion criteria which can underestimate harm. Most preliminary trials exclude specific sensitive subgroups because of ethical concerns, or include them in insufficient sample size.

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.

Adverse effects data is usually as well reported in industry funded than in non-industry funded studies. However, there is a risk that interpretations and conclusions of industry funded authors carry potential bias (Golder 2008b).

Evidence tables

A table of included evidence might be a helpful way to make overall assessment for each assessment element. The table could contain 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, trial, systematic review, HTA report, manufacturer report, register data, consensus
- Which harm?
- Intensity: 1=mild, 2=moderate, 3=serious/severe
- Other classification: self reported/objective measure, immediate/delayed etc.
- Number of harm events per study arm
- Quality of information: how was data collected etc
- Comments on generalisability of the evidence

Meta-analysis

Safety estimates usually require larger sample size to detect differences in patient groups in trials. Safety events are usually rare (incidence <5%). Exact methods seem to be superior to the asymptotic Mantel-Haenzel method for rare event data, and to the Peto method when trials are balanced (Bradburn 2007). Asymptotic approximations are known to be imprecise with rare events; still majority of systematic reviews use them.

While asymptotic approximations in dichotomous data require a non-zero event rate, most reviewers add 0.5 to each cell in stead of zero. This approach is inappropriate if the event is rare. Exact methods do not provide a point estimate in a situation where no events are observed in one arm, which is intuitively acceptable too.

Read more about meta-analysis of diagnostic accuracy studies in Appendix 3.

Qualitative synthesis

At this stage authors of a 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.

In many circumstances it is not possible to calculate frequencies, and information about risks 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 risks can be reported congruently, whereas unanticipated risks, that are detected during a trial might be reported in a markedly different ways by different investigators (Papanikolaou 2004).

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 (Jefferson 2003, Wald 2003).

Reporting and interpreting

The interpretation of evidence should clearly state qualitative and quantitative limitations of the sources, searches, data and methods used for the analysis. Presentation through tables is transparent and may be helpful in summarising different data (Busse 2002). The sources of information should be clearly stated.

When discussing the safety of a technology, the way harms were caused should be described. Harm may be device dependent or related to 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.

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). NNH is perceived as the most understandable summary statistic for adverse events, 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 (Papanikolaou 2004). Comment should be made about the generalisability of the findings to the population for whom the HTA may be used.

In RCTs presenting adverse event rates, non-statistically significant differences are associated with low statistical power. A high probability of type II error may lead to erroneous inferences (Ioannidis 2001).

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Clinical effectiveness

Domain description

What is this domain about?

The effectiveness domain in a health technology assessment considers two questions: Can this technology work, and does this technology work in practice? Efficacy is the extent to which an intervention does more good than harm under ideal circumstances. Effectiveness assesses whether an intervention does more good than harm when provided under usual circumstances of health care practice (Haynes 1999). The research questions defined within this domain aim at answering these questions, with emphasis on the second question.

Two or more alternative methods to prevent, diagnose, treat and monitor a clinical condition or to improve the delivery of care are compared in comparative clinical effectiveness research. The two key elements are that effective interventions should be directly compared and studied in patients who are typical of day-to-day health care settings (Sox 2009). The focus is in determining the magnitude of health benefits and harms, and the net benefit (benefits minus harms) that is caused by an intervention, and present the certainty of the evidence (Sawaya 2007). The generally accepted standard for proving the evidence of a causal relationship between intervention and health outcomes is an appropriately designed and conducted randomised controlled trial (RCT), even without a need for a deeper biological theory as to why the intervention works or not (Ashcroft 2002).

The assessment of health benefits should primarily consider patient relevant outcomes such as mortality, morbidity, and quality of life. Intermediate outcomes such as biochemical or physiological markers, or the proportion of early detected cases may be useful and necessary in order to understand how interventions work or as quality assurance benchmarks for health care programmes. If long term clinically important outcomes are not available, surrogate endpoints may be used to indicate or predict clinically important outcomes. To be valid the surrogate must have been shown to correlate with and accurately predict the outcome of interest (CRD 2009).

New diagnostic technologies frequently enter into clinical practice without evidence of improved patient outcomes. Randomised trials of test-and-treatment strategies are not routinely performed, and they are not required for marketing approval. Accuracy studies are far more frequent, but relying on accuracy information only when deciding whether to adopt a new diagnostic test is usually insufficient (Tatsioni 2005).

Why is this domain important?

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

Relations to other domains

- Effectiveness domain requires information from **health problem and current use** domain, as well as **safety** domain in order to specify the appropriate populations, interventions, comparisons and outcomes for the research questions.
- There is a possibility of overlapping with **safety** domain, so co-operation is needed in the protocol phase.

- The **costs and economic evaluation** domain requires information from the effectiveness domain in order to determine the incremental health benefit part of the incremental cost-effectiveness ratio
- Depending on the technology the **ethical** domain may be important for the setting of the framework of the effectiveness analysis. For example value judgements in how patient relevant outcomes are defined may be important. (Strech 2008)
- Effectiveness may sometimes strongly depend on **organisational** aspects.
- Effectiveness may also be related to the **legal** domain, e. g. when there is legal support to a public health programme (mandatory vaccination or mass screening)

Specific features in finding, interpreting or implementing information for this domain

If all trials concerning a technology have been performed under ideal conditions one will have to make assumptions about the magnitude of effectiveness based on the available efficacy data. The challenge is then to examine the reasons why the technology works or wouldn't work in specific circumstances. Long term surveillance information from observational studies usually becomes relevant.

Issues specific for screening technologies

For population based screening programmes the most important determinants of effectiveness are a reduction in disease specific mortality and morbidity and a gain in health related quality of life.
The overall effectiveness of a screening programme is determined by a combination of several factors:

- the prevalence and incidence of a disease
- the natural history of disease and the proportion of subclinical or reversible cases that would not become clinically relevant (potential for overdiagnosis and overtreatment)
- the participation rate as the number of participants divided by the number of eligible individuals in the target screening population
- the screening interval
- the accuracy of the screening test
- the proportion of subjects with positive screening test results which have a diagnostic follow-up
- the test accuracy of the tests used in the diagnostic follow-up
- the impact of the test results on treatment decisions and quality of life
- the effectiveness of the therapies for the cases identified by screening

The evaluation of a screening technology must comprise the whole chain from the screening test with true and false test results, the possibility of adverse effects from the test, the accuracy and potential for adverse effects of the subsequent confirmatory diagnostics, the losses to follow up before the therapeutic intervention is provided, and the effectiveness and adverse events of the therapeutic intervention. (Sawaya et al 2007).

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

Additionally, it is probable that the effectiveness will fall during the early stages of a new screening programme. This occurs as a larger number of cases (both early stage and late stage disease) are likely to be picked up in the first screening round when compared to later rounds. Thus it is desirable to analyse the results of several screening intervals in order to estimate the effectiveness of a screening programme.

Assessment elements

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
D0001	Clinical Effectiveness	Mortality	What is the effect of the intervention on overall mortality?	In screening the technology is seen as the combination of screening test, subsequent diagnostic work-up and treatment.	3	2	Systematic reviews of RCTs (Randomised controlled trials) or CTs (controlled trials); if not available RCTs or CTs itself. If these not available, non-controlled studies and respective systematic reviews. Health care register data. Modelling studies.		
D0002	Clinical Effectiveness	Mortality	What is the effect of the intervention on the mortality caused by the target disease?	A screening test can lead to an earlier diagnosis, thus earlier treatment which might reduce the mortality.	3	2	Systematic reviews of RCTs (Randomised controlled trials) or CTs (controlled trials), if not available RCTs or CTs itself. If these not available, non-controlled studies and respective systematic reviews. Health care register data. Modelling studies.		
D0003	Clinical Effectiveness	Mortality	What is the effect of the intervention on the mortality due to other causes than the target disease?	This may be due to e.g. side effects, accidents, or consequences of interventions after false positive or incidental findings.	3	2	Systematic reviews of RCTs (Randomised controlled trials) or CTs (controlled trials), if not available RCTs or CTs itself. If these not available, non-controlled studies and respective systematic reviews. Health care register data. Modelling studies.		C0001, C0006

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
D0004	Clinical Effectiveness	Mortality	What is the mortality related to the diagnostic test?	In diagnostic and screening technologies it is worthwhile distinguishing the possible mortality risk of the test itself from the mortality outcomes of the whole diagnostic or screening process (D0001-D0003). Inappropriate use of the technology or errors may contribute to this issue.	3	2	Observational research, RCTs, safety monitoring databases, registers, statistics		C0001
D0005	Clinical Effectiveness	**Morbidity**	How does the use of the technology modify the symptoms and findings of the target condition?	Severity, frequency and recurrence of symptoms and findings.	3	2	Trials, observational studies		Social domain
D0006	Clinical Effectiveness	Morbidity	How does the technology modify the progression of the target condition?	E.g. complete cure, alleviation, delay of the onset of the next stage of the disease.	3	2	Trials, prognostic studies		
D0026	Clinical Effectiveness	Morbidity	How does the technology modify the effectiveness of subsequent interventions?	Different tests may detect slightly different subpopulations as test positive. Results from further diagnostic testing and the effectiveness of subsequent interventions can be different in test A positive compared to test B positive. E.g. treatment may work differently in screening-identified cases than in cases that are diagnosed at regular physician's appointment.	2	2	Trials, observational studies, accuracy studies		
D0008	Clinical Effectiveness	Morbidity	What is the morbidity directly related to the technology?	In diagnostic and screening technologies it is worthwhile distinguishing the possible morbidity caused by the test itself from the morbidity outcomes of the whole diagnostic or screening process (D0005-D0006). Inappropriate use of the technology or errors may contribute to this issue.	3	2	Trials reporting adverse events.. Observational studies. Registries		C0003 to C0005

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
D0020	Clinical Effectiveness	**Change-in management**	Does use of the test lead to improved detection of the condition?	Although the test is reliable, the information it provides does not necessarily affect clinical decision making. If it does not change sufficiently the pre-test probability the added value of the information may be low. E.g there may be routine preoperative lab tests that nobody uses in decision making. Moreover, users´ ability to make a correct diagnosis may depend on their knowledge and ability to interpret the results.	2	2	RCT, CT, accuracy studies, before-after studies, interrupted time series, change-in management studies		Organisational domain
D0021	Clinical Effectiveness	Change-in management	How does the use of the test change physicians' management decisions?	There may be technology-related or non-related factors that might influence the physicians' perceptions, ability and attitude to decision making. Management decisions mean both testing and treatment decisions.	2	2	Change-in-management studies, qualitative research		Organisational domain
D0024	Clinical Effectiveness	Change-in management	Is there an effective treatment for the condition the test is detecting?		3	2			Ethical domain
D0022	Clinical Effectiveness	Change-in management	Does the test detect other potential health conditions that can impact the subsequent management decisions?	Management decisions mean both testing and treatment decisions.	2	2	Trials, Descriptive literature		B0006
D0023	Clinical Effectiveness	Change-in management	How does the technology modify the need for other technologies and use of resources?	Some treatments require ongoing monitoring and healthcare visits including hospitalisation. Screening tests may cause further diagnostic testing and different treatment due to detection of disease at an earlier stage.	2	2	RCT, CT, observational studies, statistics		Costs, organisational aspects domain

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
D0011	Clinical Effectiveness	**Function**	What is the effect of the intervention on global function?		3	2	RCT, CT, observational studies		Social domain
D0014	Clinical Effectiveness	Function	What is the effect of the technology on return to work?	Sick leave, retirement and various outcomes describing working ability are relevant outcomes to this issue.	3	2	Trials and other studies with return-to-work or work ability outcomes reported.		Social and costs domain
D0015	Clinical Effectiveness	Function	What is the effect of the technology on return to previous living conditions?	Testing may affect the ability to return to previous living conditions. It may have implications for family members / carers too.	3	2	RCT, CT, observational studies		Social domain
D0016	Clinical Effectiveness	Function	How does use of the technology affect activities of daily living?		3	2	RCT, CT, observational studies		Social domain
D0012	Clinical Effectiveness	**Quality of life**	What is the effect of the technology on generic health-related quality of life?		3	2	RCT, CT, observational studies		Costs, social domain
D0013	Clinical Effectiveness	Quality of life	What is the effect of the technology on disease specific quality of life?		3	2	RCT, CT, observational studies		Costs domain
D0030	Clinical Effectiveness	Quality of life	Does the knowledge of the test result affect the patient's non-health-related quality of life?	It can improve or worsen the quality of life. Test result may alleviate symptoms although there is no effectiveness to the primary outcome. It can also trigger or worsen symptoms.	2	2	Qualitative research, observational studies, trials		Social and ethical domain
D0017	Clinical Effectiveness	**Patient satisfaction**	Was the use of the technology worthwhile?	Patients overall assessment of the worthiness of the intervention.	3	2	Qualitative research, observational studies, trials		Social domain

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
D0018	Clinical Effectiveness	Patient satisfaction	Is the patient willing to use the technology?	Differences in acceptability may predict the overall uptake of the technology and would impact on the overall effectiveness.	2	2	Qualitative research, observational studies, trials		Social domain
D1001	Clinical Effectiveness	**Test accuracy**	What is the accuracy of the test against reference standard?	Accuracy in terms of sensitivity and specificity, and other measures such as likelihood ratios, pre-test probabilities, SDORs, AUC or Q*? In screening programmes one should consider separately the accuracy of the screening test and the accuracy of subsequent diagnostic tests.	2	2	Accuracy studies		
D1003	Clinical Effectiveness	Test accuracy	What is the reference standard and how likely does it classify the target condition correctly?		2	2	Accuracy studies		
D1004	Clinical Effectiveness	Test 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. In screening programs one should consider separately the screening test and the subsequent diagnostic tests.	2	2	Descriptive literature, expert advice, prevalence data, modelling studies, calculations		Ethical aspects domain
D1005	Clinical Effectiveness	Test accuracy	What is the optimal threshold value in this context?	Sensitivity and specificity vary according to the threshold value. Optimal combination of sensitivity and specificity defines optimal threshold value. The optimum depends on the consequences of the test results. E.g. whether it does more harm to overlook a case or to treat someone unnecessarily. In screening programs one should consider separately the screening test and the subsequent diagnostic tests.	2	2	Screening studies with varying thresholds, accuracy studies with varying thresholds, modelling studies		

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
D1006	Clinical Effectiveness	Test accuracy	Does the test reliably rule in or rule out the target condition?	When assessing screening programs one should consider here the combination of the screening test and the subsequent diagnostic tests.	2	2	Accuracy studies, modelling studies		Safety, social, ethical domains
D1007	Clinical Effectiveness	Test 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? This may have implications on how frequently a test needs to be repeated, optimal age range for a screening programme and adjustments in different populations.	2	2	Accuracy studies in different settings, descriptive literature, expert advice		B0004, B0016, B0005, Organisational domain
D1002	Clinical Effectiveness	Test accuracy	How does the test compare to other optional tests in terms of accuracy measures?	Or, how does the technology compare to other development stages of the same technology?	2	2	Accuracy studies		
D1008	Clinical Effectiveness	Test accuracy	What is known about the intra- and inter-observer variation in test interpretation?	This is especially relevant in tests with subjective assessments, such as most imaging tests.	2	2	Accuracy studies, trials, observational studies		
D1019	Clinical Effectiveness	Test accuracy	Is there evidence that the replacing test 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. In screening programs one should consider separately the screening test and the subsequent diagnostic test.	2	2	Accuracy studies, trials, observational studies		Safety domain

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
D0027	Clinical Effectiveness	Test accuracy	What are the negative consequences of further testing and delayed treatment in patients with false negative test result?	In screening programmes one should consider separately the false negative screening test results and the subsequent false negative diagnostic test results.	2	2	Observational studies, trials, qualitative research		Safety domain
D0028	Clinical Effectiveness	Test accuracy	What are the negative consequences of further testing and treatments in patients with false positive test result?	In screening programs one should consider separately the false positive screening test results and the subsequent false positive diagnostic test results.	2	2	Observational studies, trials, qualitative research		C0006, Organizational, costs and ethical domains
D0029	Clinical Effectiveness	**Benefit-harm balance**	What are the overall benefits and harms of the technology in health outcomes?	This question integrates all benefits and harms concerning mortality, morbidity, QoL and further patient relevant outcomes, also considering the amount of false positive and false negative test results. It is the central question about clinical effectiveness. There is no common quantitative summary measure, and even qualitatively a balanced and meaningful presentation is difficult to reach. In diagnostic technologies one should consider also the benefits and harms of subsequent diagnostic testing and treatments in patients with true positive test result in a prior diagnostic or screening test. For true positive cases there is a benefit-harm balance, because diagnostics and treatment can harm. Consequences for true negative cases are identical with the possible harms of the screening test (see D0004, D0008).The integration of some assessment elements of other domains into the benefit-harm-balance is essential and differs between the core model applications. For screening the frequency of disease and coverage of screening are essential AES	3	2	RCT, CT, observational studies, modelling studies		A0007, A0011, C0001, C0003, C0004, C0005, C0006, C0007, C0061, Ethical Domain

Methodology

The specification of the research question using the PICO scheme (Appendix 3) is the first step in performing the evaluation of the clinical effectiveness of a technology. The choice of target population, comparisons and outcomes usually has a strong influence on the results on clinical effectiveness. How to do a systematic search of clinical effectiveness, safety and cost-effectiveness is described elsewhere. The clinical effectiveness results are especially sensitive to flaws in the literature search and study selection when the outcomes of interest are quantitatively pooled in a meta-analysis. Results may be substantially biased if relevant studies are not found or not properly selected.

Specific to screening technologies

Starting with the publication of Wilson and Jungner in 1968 different lists of criteria were developed stating under which conditions the introduction of a screening programme might be useful. (Wilson 1968, NSC 2009, Andermann 2008). Many of these criteria directly relate to the clinical effectiveness of the screening test, diagnostic workup and treatment and stress the linkage between them. They are integrated in the following parts.

Where to find information?

Many different sources of information should be searched, including published and grey literature, searching of journals, contacting experts as well as scanning reference lists of relevant papers.

Databases and search strategies

General medical databases such as
- Medline, Medline in Process,
- Embase

Specialised databases for specific questions such as
- CINAHL,
- PSYCINFO,
- ASSIA, (Applied Social Sciences Index and Abstracts)
- SOCIOLOGICAL ABSTRACTS
- Social Services Abstracts,
- Social Care on line/Caredata and SocINDEX,
- ERIC

Administrative studies: General science publishers'databases such as
- Emerald Library,
- Science Direct and Ebsco Academic Search Elite,
- Pub Med Central (PMC),
- Bio Med Central (BMC),
- ProQuest Health Management

Trial registers such as
- Current Controlled Trials (http://www.controlled-trials.com/)
- Clinical Trials (http://www.clinicaltrials.gov/),
- WHO International Clinical Trials Registries Platform portal

Databases on specific study designs / publication types:
- DARE,
- NHS EED,
- CDSR,
- Cochrane CENTRAL.
- GIN guidelines

Sources and search strategies for test 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. Routine use of methodological search terms is not generally recommended because relevant records may be lost with no significant reduction in the number needed to read (Leeflang 2006, Ritchie 2007).

Over 20% of studies included in diagnostic accuracy reviews were not found in MEDLINE and 6 % were not found by the electronic searches (Whiting 2008). The majority of the studies that were not found in databases were identified by scanning reference lists of included articles.

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

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

Useful other sources

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

Own research and evidence generation

If the data retrieved from the current body of evidence through a systematic review does not provide enough adequate information on the effectiveness of a technology, new primary research may be warranted in the form of register research, modelling, or performing randomised controlled trial. As primary research is often beyond the scope of HTA organisations, the lack of evidence of effectiveness should at least be stated in the discussion.

What kind of information is required?

Study types, design, outcome measures

With a bit of luck one may identify a systematic review on the topic of interest, which is sufficiently comprehensive, satisfies the requirements on methodological quality, and meets the research questions. If the report is judged to be transferable to one's own health care system and the local setting, then the work might end right here. Following the hierarchy of study designs (Guyatt 2006), reviews on efficacy / effectiveness are generally limited to randomised designs. To assess the generalisability to routine clinical practice it might be relevant to distinguish between efficacy (explanatory) and effectiveness (pragmatic) RCT. A set of criteria has been suggested to differentiate between them (Gartlehner 2006). In addition registry data reflecting clinical routine care help judging whether study populations, interventions and

outcomes in RCT are comparable to clinical practice. It may be necessary to broaden the inclusion to other designs, if data from randomised trials are not available or are insufficient (see Appendix 3).

Study types for the assessment of the effectiveness of screening technologies

The most reliable evidence whether screening does more good than harm are well conducted RCTs with a study population representative of those eligible for, and invited to or informed of the screening programme. The control group would be those who are not informed of the screening programme. Otherwise the probability of a cross–over of the control group to screening group would increase and this could result in an underestimation of the screening effect.
Time trend studies which analyse changes in disease frequency such as incidence, the distribution of different severity of disease stages and death can be valuable. But there are many sources of bias such as changes in ascertainment and diagnostic practice or other influences on outcomes such as advances in treatment, or reduction in co-morbidities.
Case-control studies can be useful for a comparison of different screening policies but cannot give a reliable estimate of the difference between screening and no screening because their confounding factors can not be controlled (Raffle 2007).
Modelling studies are especially useful in comparing many different screening options varying in test combinations, screening intervals and treatment options incorporating alternative eligible populations, whereas clinical trials can compare only a limited number of screening options over a short time horizon. When high quality primary data is available, decision analytic modelling can synthesize information from a wide range of sources. Sensitivity analysis can help to show areas in which further research is likely to be most useful (Karnon 2007, Trikalinos 2009)
Often HTA doers need to evaluate the evidence regarding the test characteristics like the diagnostic accuracy – either as additional information or because better evidence is lacking. Therefore we have included in this model the methodological guidance related to diagnostic accuracy studies.

Outcome measures

A number of effect measures are in use for describing the treatment effect. For binary data, common measures are relative effect measures such as risk ratio (= relative risk), odds ratio, and relative risk reduction, or absolute effect measures such as risk difference (= absolute risk reduction), often converted into number needed to treat (NNT) or events per thousand patients to allow for a comparison across studies. Since both relative and absolute effect measures carry important complementary information, recent approaches such as the GRADE profiler {www.gradeworkinggroup.org} encourage a presentation of both measures.

Continuous data are often more difficult to summarize. Commonly used effect measures that allow the summary of treatment effects are “standardised mean difference” or “weighted mean difference”. Unfortunately, both measures are difficult to interpret in a clinical context. A more recent statistic, the ratio of means, reports the percentage reduction for continuous data such as proteinuria. This measure allows a meaningful interpretation to clinicians (Friedrich 2005). For more details about effect measures and their calculations, we refer to the comprehensive, user-friendly description of common measures in the Cochrane handbook.

If there are different outcome measures for benefits and harms it may be difficult to calculate the net benefit quantitatively. For example in prostate cancer screening the benefit might be a reduction in disease specific mortality, on the other hand, both biopsy and surgery may cause sexual dysfunction and incontinence. Therefore summary measures like the QALY or DALY or other multi-criteria models where health states are weighted according to their desirability could be used to create a common measure (EMA 2010).

Study types for the assessment of the effectiveness of diagnostic tests

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

Direct trial evidence

The diagnostic RCT is the most reliable study design. The point in the test-treatment chain at which patients are randomized can vary depending on the study question or other constraints, the most simple design randomizing subjects to receive the new test (strategy) or the routine test (strategy) (Lijmer 2009). 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.

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

Evidence of accuracy can be used to infer effectiveness of the technology when the spectrum of patients, disease, technologies and other conditions are similar enough in diagnostic 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 accurate replacement for an existing diagnostic strategy.

Change-in-management, or therapeutic-impact, or diagnostic before-after-studies measure how often treatment is started, stopped or modified before and after the incorporation of the new diagnostic technology in the management pathway compared to the management pathway without the new diagnostic technology (Guyatt 1986b). 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 (MSAC 2005).

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

diagnoses, 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 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 modelling can be used. Decision analysis allows also the comparison of the test effectiveness in those with a different prevalence of the disease and of multiple test-and-treat strategies of existing tests in clinical practice where it is unfeasible to directly compare all strategies in clinical trials. In fast developing fields completed clinical trials may not be applicable to current practice standards. Modelling can help to assess the trade-offs of a newer test and could also consider potential shifts in the disease spectrum. Modelling can explicitly account for uncertainty in key parameters and assumptions (Trikalinos 2010). 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 (Bossuyt 2000).

Study types for test accuracy studies

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

The design of a basic diagnostic accuracy study is that of a group of patients with the suspected target disease undergoes the test (strategy) under consideration (index test) and the best possible test (strategy) to verify the diagnosis (reference standard, gold standard). Positive and negative results from both tests are shown in a 2x2 table or 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 (Rutjes 2007). Another possibility is to investigate the probability of disease presence as a function of all diagnostic variables simultaneously with multivariable modelling (Moons 1999). Problems may arise for example from the patient spectrum (patient characteristics, patient selection and setting), the non-optimal reference standard, incorporation bias (the index test is part of the reference standard), partial verification (not all patients receive the reference test) or differential verification (patients receive different reference tests).

If a new technology can **replace** an existing one, the accuracy of the new test (index test) and the routine test (comparator test) has to be compared in comparable groups or preferably in the same patients (Irwig 2002). 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 the index test, the comparator test 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 a 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 (Bossuyt 2006). For further options see Lijmer 2009.

In **triage**, the new technology is used before the existing technology and only the patient with a particular result of the test continues the diagnostic pathway. Triage 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, but is a source of bias.

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.

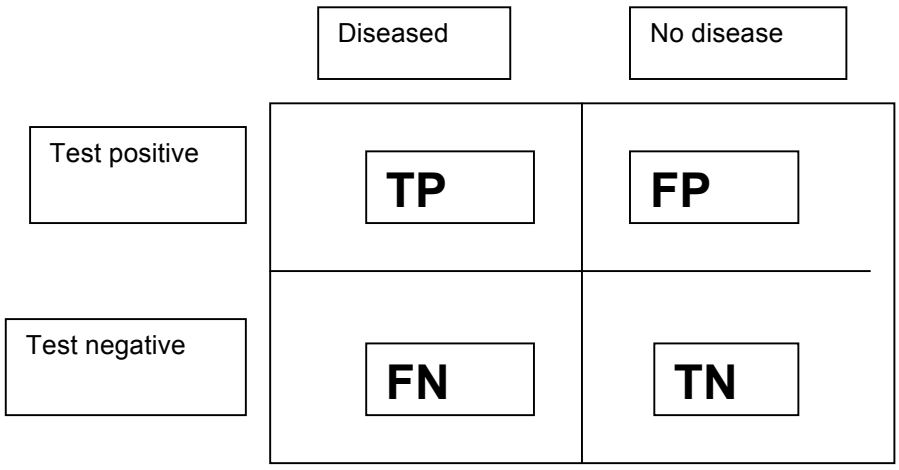
Fully paired or randomised methods are preferred but not always needed in researching add-on tests. Limited designs can be more efficient. E.g. limiting the study to patients who are negative after existing diagnostic pathway, with verification by reference standard only those who test positive on new technology, still allows us to calculate the number of extra true positives and false positives from using the new add-on technology (Bossuyt 2006).

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

Outcome measures for test accuracy studies

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

Figure 2x2 table



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 (Tatsioni 2005)

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	$\frac{(TP/(TP+FN))}{(FP/(TN+FP))}$	Does not depend on prevalence	Applies only to positive test
Negative likelihood ratio	$\frac{(FN/(TP+FN))}{(TN/(TN+FP))}$	Does not depend on prevalence	Applies only to negative test
Diagnostic Odds ratio	TP x TN/FN x 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 draw different conclusions on test positivity.

A 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 (MSAC 2005).

A 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.

A 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 persons 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 high and low DORs occur in different parts of the curve.

The area under the 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. And, if it is below 0.5 the test is misleading because it systematically misclassifies diseased and healthy people, but by a swap of the classification of diseased and healthy it would discriminate better than chance (AUC>0.5). From AUC data alone it is not possible to derive false positive and false negative rates. Because the consequences of false positive and false negative test results may be weighted differently in clinical practice a summary measure like the AUC might be misleading.

Tools for critical appraisal

Sources of bias in studies designed to evaluate the effectiveness of an intervention, or diagnostic test and subsequent interventions, can 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) (Moher 1998, Schulz 1995).

A thorough assessment of the methodological quality of the included studies is crucial to any systematic review. In randomised controlled trials, concealed treatment allocation, blinding of health care provider, patient and outcome assessor to the allocated intervention (experimental or control) and a sufficient rate of follow-up are the minimum items that need to be looked at when assessing the potential for bias of individual studies. Depending on the research question, however, it might be warranted to look at additional features where bias could enter the study design, or where the results might get distorted.

Quality assessment of single studies

The body of checklists for assessing the methodological quality of randomised controlled trials is considerable, most of them are variations (e.g. vanTulder 2003) of the structure suggested in the User's Guides to the Medical Literature (Guyatt 2007), the CONSORT Statement (Altman 2001, Moher 2001, Rennie 1996, Schulz 2010) or the criteria suggested in the Cochrane Handbook.

Agreement on the methodological criteria for non-randomised trials and observational studies are considerably less well developed. However, a methodological HTA-report by John Deeks provides a good overview of available instruments to assess non-randomised intervention studies (Deeks 2003, MacMahon 2001, Radford 2001, Stroup 2000, Equator web site).

Modelling studies

The validity of the results of modelling studies are highly dependent on the model structure, the model assumptions, the validity of the data used as inputs to models, and model validation. There are several checklists for quality assessment for modelling studies available (Weinstein 2003, Philips 2006, Karnon 2007).

Overall quality of the whole body of evidence

Having reviewed the methodological quality of the individual studies, researchers attempt to capture the overall quality of the body of evidence. The concept of the GRADE Working Group captures the currently most comprehensive approach (Atkins 2004, Guyatt 2006). Besides looking at the quality of the individual studies, they also include the consistency or heterogeneity of the results of all included studies and the directness of the comparisons (i.e. how directly does the identified literature address the questions of our HTA-report regarding the population, the intervention and comparators and the selected endpoints, they comment on imprecision of the available data (number of total events and width of the confidence interval) and provide an estimate about the likelihood of the presence of reporting bias. Deficiencies in any of those considerations can lower the methodological quality of the entire body of evidence. On the other hand, the overall judgement about the methodological quality of the evidence can be raised in the presence of strong and plausible associations between intervention and outcome or an obvious dose-response gradient.

Quality assessment of the effectiveness of diagnostic tests

Direct trial evidence

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

Linked evidence

The strengths and limitations of other study types than RCT need to be considered. There are quality check lists for studies of effectiveness in MSAC (MSAC 2005).

Change-in-patient-management studies can be appraised using the same criteria as case series (see list of criteria MSAC page 70) (MSAC 2005). 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 real life situations where the technology is not available. Physicians' subconscious bias may also occur. Change of management is only relevant when it results in a benefit in patient relevant outcomes. Otherwise it can be held only as an surrogate end-point.

Quality assessment of test accuracy studies

Quality assessment of diagnostic accuracy studies is not as straightforward as it is for interventions. It is hampered by poor reporting and the fact that so far there is less methodological and empirical evidence on the importance of the different potential sources of bias. There are many different tools to assess the quality of diagnostic accuracy studies. The Cochrane handbook recommends QUADAS tool with its 11 mandatory and additional items.

QUADAS quality assessment tool (Whiting 2003), QUADAS 2 is in development
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 can adapt QUADAS by dropping irrelevant items. 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.

Issues specific for screening technologies

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

- People taking part in screening are usually healthier than those who do not (healthy screenee bias.
- Less aggressive cases of disease have a longer asymptomatic period and are therefore more likely to be detected by screening. Consequently patients detected by a screening programme tend to have a better prognosis even without therapy (length time bias).
- Survival falsly appears to be longer after diagnosis by screening not because the patients actually live longer but because the diagnosis is known earlier and therefore for a longer period of time (lead-time bias) (Raffle 2007, Gates 2001.)

If a high proportion of participants in the control group (no screening) cross over to screening the effects of screening will be underestimated.
See also shared methodologies in Appendix 3.

Analyzing and synthesizing information

Ideally systematic reviews on randomized controlled trials (RCTs) are the basis of knowledge of effectiveness of an intervention (Khan 2002). The principles on how to conduct a systematic review are nowadays widely agreed upon and most of the methodologies published by different organisations vary only in details (See Appendix 3).

Evidence Tables

A meaningful presentation of the study results is essential for an informative and transparent HTA report. A high degree of reliability and transparency are reqired for the transfer of HTA reports from one setting to another. Comprehensive and informative evidence tables about the methodology and content of the individual studies are the best guarantor for transparency and reliability. They should allow a judgement of the similarities and differences of the included studies and should provide the basis for the conclusions of the review.

The majority of HTA organisations produce tabulated evidence summaries that follow the PICO structure (ideally with an additional cell for comments on issues not captured by the PICO cells but that could have an impact on the results). Although the items reported in each cell will always be driven by the questions of the review, they should follow some core considerations (Malmivaara 2006). A description of the data extraction process including the number of reviewers involved assures objectivity and reliability of the results.

Meta-analysis

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

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

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

Further exploration of the data: Homogeneity and heterogeneity, sensitivity analysis and publication bias

Reviewers need to provide statements about clinical homogeneity or heterogeneity of the studies and their results. While homo-/ heterogeneity in the clinical data is often a matter of judgement, there are statistical tests available to help assessing the presence of statistical heterogeneity (Higgins 2003) which should then be further explored and considered in the discussion. Pre-specified sensitivity analyses based on clinical or methodological issues allow further exploration of the stability of the data. Researchers should always consider publication and reporting bias and explore these either graphically using a funnel plot (provided the number of included studies is large enough) or make a plausible judgement about the likelihood of these biases.

Data extraction from test accuracy studies

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

Pooling and meta-analyzing test accuracy studies

No heterogeneity present

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

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

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

Heterogeneity present

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

Threshold effect only

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

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

Heterogeneity that is more than just threshold effect
If the slope b(the estimated regression coefficient) in the SROC model is statistically significant, the SROC will be asymmetrical and the DOR changes along the threshold. In such cases advanced methods for fitting the SROC is used. Advanced methods to pool are indicated if heterogeneity in the results can be attributed to known sources of variation (see above Chapter Assessing heterogeneity). Otherwise the interpretation of the summary estimate is not possible (Lijmer 2002).

Advanced models enable incorporation of covariates, e.g. population subgroup in the meta-regression analysis. Poor reporting of primary studies may though lead to biased estimates. The two main advanced models are hierarchical SROC and bivariate meta-regression, which are mathematically identical (Harbord 2007). Syntax to run these models in SAS, STATA, WINBUGS, S-PLUS and R is or will be available. Hierarchical SROC (HSROC) produces informative summary measures with confidence ellipses (Reitsma 2005). Model is infrequently used, probably due to the complex fitting.

More reading: Deeks 2001, Deville 2002, Kester 2000, Irwig 1995

The problem of imperfect reference standard in test accuracy studies

If there is an acceptable reference standard test but for various reasons not all patients in the study received it, the researches either impute or adjust for the missing data (Rutjes 2007). 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 (Rutjes 2007). These correction methods can be useful if there is evidence from previous studies about the extent of imperfection of the reference standard and about the correlation of the errors between the index test and the reference standard. Another way to deal with the problem of imperfect reference standard is a sensitivity analysis to demonstrate the effect of imperfect reference test to the accuracy of the index test.

Assessing heterogeneity across test accuracy studies

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

Sources of heterogeneity are

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

If differences in the results can not be attributed to these known sources of heterogeneity, then pooling of results to one summary estimate should not be attempted, because its interpretation will be impossible (Lijmer 2002).

Methods to test for heterogeneity (MSAC 2005):

1. Plot the sensitivity and specificity from each study with their 95% confidence interval in a table and/or forest plot to illustrate the range of estimates and identify outliers.
2. If sufficient data are available, plot the paired sensitivity and 1-specificity results for each study on the ROC plane to detect heterogeneity and identify outliers. A small number of studies will limit the power of regression to detect heterogeneity.

3. Use a chi-square test for heterogeneity (Cochran's Q test) or Fischer's exact test for small studies to test the hypothesis that there is no statistically significant difference in the sensitivity and specificity reported.

Assessing threshold effect in test accuracy studies

Paired estimates of sensitivity and 1 - specificity in original studies are plotted in a ROC plane. Regression model is used to fit the SROC curve (Moses 1993). If the SROC curve is symmetrical around the line where sensitivity equals specificity, the studies share one common DOR, and any variability is due to differences in the test threshold. In statistical terms, if in the model the slope b (estimated regression coefficient) is not statistically significant and approaches zero, The SROC will be symmetrical.

Issues specific for screening technologies

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

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

Reporting and interpreting

Which steps are required?

- Rating the body of evidence as being of high / moderate / low quality (following the GRADE methodology) clarifying (e.g. in footnotes) the reasons for up-/downgrading.
- Interpreting the clinical relevance of the findings:
  - Considering the importance of the outcomes for clinical decision making (distinguishing between a critical and an important outcome as done when formulating the question)
  - Deciding what would be the minimal clinically important effect size for each outcome (independent of its statistical significance):
- Identifying knowledge gaps by comparing the research questions (including the predefined outcome) with the available evidence.

It is possible to make only a preliminary interpretation of the results based on effectiveness data only. A global and balanced interpretation of the benefits and harms of a technology requires also the results of other relevant domains. Evidence about benefits and harms can be combined using e.g. decision analytic methods (Trikalinos 2009).

Interpreting and reporting test accuracy studies

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 clinically informative measures of the accuracy of a diagnostic test, but must be considered in relation to the prevalence of the disease.

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 than10 for a test to be useful (MSAC 2005), although this is very seldom the case.

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. (MSAC 2005).

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.

Additional 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.

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Costs and economic evaluation

Domain description

What is this domain about?

The main aim of the costs and economic evaluation domain is to provide information about the relative costs and cost-effectiveness of health care technologies. It is intended to support decision-making regarding resource allocation for health technologies in the health care sector, to include emerging, new and existing technologies (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, 2006).

Central to this area of economics are the concepts of opportunity cost and incremental change. In publicly-funded health care systems, finite resources mean that not all interventions can be provided in every situation for all who need or want it. Choices must be made between effective health care interventions; the decision to fund one intervention may mean that others cannot be funded (Guidelines for the Economic Evaluation of Health Technologies, 2006). Economic evaluations of health interventions focus on technical efficiency in the production of health, meaning that it indicates how resources should be allocated for maximizing health. Although other societal objectives, such as equity, are typically part of a full HTA report, they are usually not incorporated in economic evaluations and have to be considered separately by decision makers (Cleemput, 2011).

Why is this domain important?

Economic evaluation is an important part of health technology assessment. Over the last two decades, the rate of increase in health-care costs has accelerated, placing increasing pressure on the finite resources available to fund them. This growth in costs has been fuelled in part by the rate of technological development. Increasingly, there is a conflict between what is technologically possible and what is economically feasible. Clinical investigators have begun to recognise the importance of performing economic evaluations alongside RCTs. In evaluating a new technology, it is not sufficient to consider evidence of its efficacy and effectiveness; data on its costs and other outcomes are also needed.

Relation to other domains

Costs Domain requires information from Health problem and current use, Effectiveness, Safety and Organisational Domains.

Specific features in finding, interpreting or implementing information for this domain

An economic evaluation should provide decision makers with information that is useful, relevant, and timely. The economic evaluation component of an 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). Either societal, health care payer's, or hospital perspective can be used depending on the type of HTA.

It is important to provide a detailed description of the alternatives and to justify their choice, so that study users can assess their relevance to their own setting. What represents 'current practice' may vary over time

and between countries. There may also be regional variation in the importance of other elements for the economic evaluation. Therefore, transparency in reporting of economic evaluations is critical to allow the applicability and relevance to economic evaluations performed as part of an HTA to be assessed for different settings.

Issues specific for screening technologies

The overall costs and benefits (effects) of a screening programme should be assessed prior to its implementation (organisation in real life). The economic evaluation of a screening programme differs in a number of respects to that of other health care interventions. In general, the total costs of screening programmes are relatively high. It encompasses the costs of the screening procedure itself in a usually large number of people, the costs of follow-up procedures in people with a positive screening result, as well as the costs of implementing the programme. Screening is rarely limited to a single screening test, but may include confirmatory tests and interventions for those with a positive result; the evaluation of a screening programme therefore needs to incorporate other health care interventions in the analysis. The interventions chosen, the rationale for their inclusion and the measurement of the resources consumed should be clearly described. A decision to implement a programme should take into account the sensitivity and specificity of the screening technology, the number of positive and negative results (true and false, ie. positive predictive value PPV and negative predictive value NPV) and the implications of false-positive and false-negative results. Potential benefits of screening include a more timely diagnosis, allowing more timely treatment with associated reductions in morbidity and, or mortality.

Evidence is often not available from direct test-treatment RCTs but has to be evaluated from "linked evidence". The generalisability of clinical trial data may be limited due to the range of choices for the screening test, screening interval, the eligible population and the organisation of the screening programme. There may also be difficulties in extrapolating benefits from clinical trial data due to the long time interval between screening and the development or progression of the condition of interest (Karnon et al. 2007).

The long time horizon has particular implications for discounting. A decision to discount costs or outcomes, or both, and the choice of the discount rate(s) may have a significant impact on the cost-effectiveness of the intervention and needs to be carefully considered. Most of the costs of a screening programme are incurred within a relatively short time period, whereas the benefits (e.g. life years gained) may not be accrued for many years; for many curative interventions both the costs and the effects occur immediately. The decisions regarding discounting should be made explicit and according to available, e.g. country-specific, guidelines.

Another issue to be considered is the incorporation of utilities in the analyses. Screening programmes profoundly differ from the situation where a patient seeks care due to symptoms, as screening targets populations who are mostly healthy. “Healthy” people may become patients due to their screening result and thus the effect of screening on their utility may be significant. Economic evaluations of screening programmes should in principle take the reduction in utility associated with a positive screening result as well as the increase in utility associated with a negative result –e.g. due to relief, justified or unjustified (in case of a false negative screening result)- into account. Data on the impact of screening results on utility values is, however, limited (Karnon et al 2007). Furthermore, false positive and false negative test results may have impact on peoples’ behaviour, and this in turn, may change the results of the analysis. The data on these issues are limited, some implications exist that false negative test result might lead to more risk-taking behaviour, e.g. a person gets a low cholesterol reading chooses a less healthy diet. The researchers should consider such possible effects and try to assess their impact (e.g. how would the ICER change if false negative screens changes peoples’ behaviour in a specific direction).

Assessment elements

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
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 or whether the costs are born inside or outside the health care sector. If a health care provider perspective is applied, then resource utilization paid for by the patient is not relevant and if a health care payer perspective is applied, non-health care costs should not be taken into account. In identifying the resource use of a screening programme, the screening test, further examinations and treatments, as well as administration and organisation of the screening programme need to be taken into account.	3	2	Health care registers and databases, RCT's with resource utilization data, reimbursement databases, micro-level costing studies/ABC-costing studies	Guidelines for economic evaluation of Health Technologies: Canada, 3rd edition, 2006, Guidelines for Pharmacoeconomic Evaluations in Belgium, 2008	A0011, A0013, A0014, A0015, A0016, A0017, A0018) G0001, G0003, G0004, G0005, G0006, G0007, G0010, B0007, B0008, B0009
E0002	Costs and economic evaluation	Resource utilization	What amounts of resources are used when delivering the assessed technology and its comparators (resource use measurement)?	After identifying the types of resources used, also the quantities of resources must be measured, for all types of resource utilization of implementing the technology and its comparators. Resource use data may be collected prospectively (e.g. alongside a clinical trial) or estimated retrospectively by reviewing patient registries, hospital or reimbursement databases, or other routine data collection.	3	2	Health care registers and databases, RCT's with resource utilization data, reimbursement databases, micro-level costing studies/ABC-costing studies	Guidelines for economic evaluation of Health Technologies: Canada, 3rd edition, 2006, Guidelines for Pharmacoeconomic Evaluations in Belgium, 2008	Organisational, Health Problem and Current Use, B0007, B0008, B0009

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
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 value of 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 or shadow prices (e.g. for voluntary work) are often used as proxies for opportunity costs. Also costs caused by a false negative or false positive screening test result should be included.	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, 3rd edition, 2006, Guidelines for Pharmacoeconomic Evaluations in Belgium, 2008	
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 examinations, treatments, or illness; reduced working capacity due to illness and disablement; or lost production due to an early death. Depending on the perspective of analysis, also indirect costs related to patients and relatives (e.g. income loss, transportation costs) should be examined.	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	D0014, Social

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
E0005	Costs and economic evaluation	**Outcomes**	What are the incremental effects of the technology relative to its comparator(s)?	The calculation of an incremental cost-effectiveness ratio (ICER) requires the estimation of the incremental effectiveness/utility/benefit of an intervention relative to its comparator(s). Estimation of utility related to screening differs from many curative interventions, since the target population of screening is healthy or at least asymptomatic, who might become patients due to the screening. Benefits of screening include improved diagnosis, timely and appropriate treatment and reduction in mortality and morbidity. Also the number of detected positives and false positives (specificity and sensitivity) are important aspects in evaluation of effects of the assessed screening programme.	3	2	Estimation of the incremental effects can be based on 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.	Guidelines for economic evaluation of Health Technologies: Canada, 3rd edition, 2006, Guidelines for Pharmacoeconomic Evaluations in Belgium, 2008	A0004, A0005, A0006, A0009, A0023) D0001, D0002, D0003, D0004, D0005, D0006, D0008, D0011, D0012, D0013, D0023, D0030, C0001, C0002, C0003, C0004, C0006, C0008
E0008	Costs and economic evaluation	**Cost-effectiveness**	What is the method of analysis?	Clinical trials usually compare a limited number of screening options over a relatively short time horizon and it is unlikely that trial data will inform all relevant aspects of a screening programme. Decision analytic models provide a structure for synthesizing information from various sources as well as analysing how the uncertainty affects the results.	3	2		Guidelines for economic evaluation of Health Technologies: Canada, 3rd edition, 2006, Guidelines for Pharmacoeconomic Evaluations in Belgium, 2008	

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
E0007	Costs and economic evaluation	Cost-effectiveness	What is the appropriate time horizon?	Both costs and effects should be modelled over an appropriate time horizon. In most curative interventions both costs and effects occur in a relatively short time period, while in screening the effects occur later in the future. Effectiveness data is rarely available for the whole appropriate time horizon and economic evaluation needs to link intermediate endpoints to final endpoints and/or extrapolate the effectiveness. Thus it is often argued that the effects are penalized by discounting and there is controversy on this issue. One needs to take into account any relevant official guidance when choosing specific discount rate for analysis. After that it is important to decide whether to discount both costs and effects, and whether to use uniform discount rate.	3	2		Guidelines for economic evaluation of Health Technologies: Canada, 3rd edition, 2006, Guidelines for Pharmacoeconomic Evaluations in Belgium, 2008	Effectiveness domain (effectiveness data may need extrapolation)
E0006	Costs and economic evaluation	Cost-effectiveness	What is the incremental cost-effectiveness ratio?	The result of the economic evaluation can be expressed as an incremental cost-effectiveness ratio eg. costs/QALY or cost/Life Year Gained. 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 an intervention against the costs. The concept of a cost-effectiveness threshold is one way of expressing decision-makers willingness-to-pay for health benefits. If other type 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.	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.	Guidelines for economic evaluation of Health Technologies: Canada, 3rd edition, 2006, Guidelines for Pharmacoeconomic Evaluations in Belgium, 2008	Safety, Effectiveness

Methodology

Where to find information?

Databases and search strategies

There are two main purposes for searching for information in economic evaluation. First, when planning and scoping an economic evaluation on any topic, it is useful to search for what is already published on that topic elsewhere. A systematic review of previously published economic evaluations may be done. Furthermore, relevant literature and other data sources may be searched in order to find information on different aspects (e.g. clinical effectiveness, quality of life, resource use, costs) to be combined in a modelling study.

The key sources for published economic evaluations are MEDLINE, EMBASE, CRD-databases, especially NHS Economic Evaluation Database (NHS-EED). Additional sources: EconLit.

InterTASC Information Specialists' Sub-Group Search Filter Resource developes search strategies to improve retrieval of published studies from large databases. The Hedges Project at McMaster University in Canada is another project. Examples of search strategies for cost and economic studies from MEDLINE are available:
http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx#Costs
http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx#Economics

Useful other sources

- Registries (e.g. national screening registries),
- international, national and regional statistics,
- national and regional guidelines,
- hospital databases (costs, resource use data),
- patient reported outcome and quality of life instruments database (http://www.proqolid.org),
- expert opinions and
- manufacturers' handbooks.

What kind of information is required?

Study types, design, outcomes measures

Four main types of economic evaluation can be part of HTA; cost-minimisation, cost-effectiveness, cost-utility and cost-benefit analyses (Table 1, Modification from Drummond 2005). 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.

The objective of economic evaluations -the main types of which are described in Table 1- is different from the objective of a budget impact analysis (BIA). While economic evaluations attempt to inform policy makers about the most efficient way to allocate the available health care resources, given the objective to optimize health outcomes of the population, BIA estimates the financial consequences of adopting a new intervention in health care without taking the health consequences into account. In the Core Model, BIA is included in the Organisational Domain.

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; and/or 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); or only one technology is assessed (net benefit); or there is a wish that individual life's are valued in monetary units; or 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?

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.

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 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.

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 resource use has to be measured and finally these volumes have to be valuated. An important consideration is also the choice of time period, i.e. the choice for how long the resource use should be tracked and measured. The length of time period depends on what is relevant to the topic of evaluation, which in some cases may include lifetime.

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). A broad agreement exists that all costs related to the disease or technology in question should be included in the analysis. A more debated issue is whether to include the unrelated future health care costs or not, such as health care costs of other diseases which people experience when they live longer thanks to a certain treatment or screening. Whether related or unrelated, future costs should be discounted according to national guidelines, if such exist.

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. Inclusion of transfer payments depends on the perspective of the analysis; they are a cost to the paying organisation (e.g. government), a gain to the recipient, but from a societal point of view, not a cost nor a gain.

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.

All costs should be adjusted to a common price level (usually the year of analysis).

Issues specific for screening technologies

When identifying the costs of screening, all the costs associated to the screening programme should be included. This means, that in addition to the costs of screening test itself, also costs of the screening organisation, invitations to screening, further examinations as well as possible treatment costs need to be included. Also, travel costs to and from the screening facility, if relevant, should also be taken into account when identifying the costs.

Population on screening programmes can be considered as healthy people not unable to work because of any health related condition. In that sense, the lost time as a consequence of undergoing the screening programme should be considered as lost productivity and be included as a cost in the economic evaluation.

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) could 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. Single index HRQoL instruments combine the answers of individual questions into a single index number (usually ranging between 0 and 1, although negative values for states worse than death are possible). Generic instruments providing a single index number suitable for the calculation of QALYs include AQoL (Assessment of Quality of Life), EQ-5D (EuroQol), 15D, HUI (Health Utilities Index Mark II/Mark III), QWB (Quality-of-Well Being Scale), Rosser-Kind and SF-6D (based on RAND-36/SF-36).

Future outcomes should be discounted according to national guidelines, if such exist.

Issues specific for screening technologies

In assessment of outcomes, the definition of the intervention and comparator is critical. With regards to screening, it is critical to define the entire care pathway following the screening test (as well as following the comparator).

Screening programmes profoundly differ from the situation where a patient seeks care due to symptoms, as screening is usually targeted to populations who are mostly healthy. This implies that these “healthy” people may become patients due to the screening results and thus the effect of screening on their utility may be significant though data on this is fairly limited (Karnon et al 2007). Also the screening may cause anxiety and concern, especially in the case of false positive test result. The effects on the patients' utility or HRQoL are still fairly unknown, yet some qualitative evidence exists from cancer screenings that abnormal and false-positive screening results have a negative impact on certain psychosocial domains (Brodersen et al 2007).

Tools for critical appraisal

There are several methodological characteristics to consider, when assessing the quality of an economic evaluation. A report of an analysis should inform the reader about all the important aspects of an analysis. Several checklists have been published, in order to use when reporting an economic evaluation, but also to help in identifying the strengths and weaknesses of different studies (e.g. Siegel et al 1996; Drummond et al 2005; BMJ guidelines for authors and peer reviewers of economic submissions to BMJ). Below is presented an example, a summary of a checklist by Drummond et al (2005):

1. Was a well-defined question posed in answerable form?
2. Was a comprehensive description of the competing alternatives given?
3. Was the effectiveness of the programmes or services established?
4. Were all the important and relevant costs and consequences for each alternative identified?
5. Were costs and consequences measured accurately in appropriate physical units?
6. Were costs and consequences valued credibly?
7. Were costs and consequences adjusted for differential timing?
8. Was an incremental analysis of costs and consequences of alternatives performed?
9. Was allowance made for uncertainty in the estimates of costs and consequences?
10. Did the presentation and discussion of study results include all issues of concern to users?

Analysing and synthesizing evidence

As all relevant evidence is rarely available from a single source, the mostly used approach in economic evaluation is modelling: collecting the best available evidence from various sources and synthesising it using appropriate modelling techniques.

Study frame and scoping of the economic evaluation of screening technologies

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 group of people at risk of a disease that the screening is aimed at
Intervention	The screening technology being studied
Comparators	The alternative technologies that the screening is being compared to (often including, but not limited to, current practice or "no systematic screening")
	With respect to evaluation of screening, two main types exist: comparison of screening vs. no screening, and comparison of different screening tests within one screening (e.g. faecal occult blood test vs. colonoscopy in colorectal cancer screening).
Outcomes	The positive or negative health outcomes that are included in the analysis.
	Specific to screening are the outcomes caused by screening to people who would not have been examined or treated in absence of screening.
Costs	The costs of the compared screening technologies and further examinations and treatments
	Organisational and management costs
Time horizon	The time frame during which cost and outcomes are assessed
Perspective	The perspective from which costs and outcomes are assessed
Evaluation type	The chosen type of economic evaluation (e.g. cost-effectiveness, cost-utility, cost-benefit analysis)
Analysis methods and modelling	The statistical tests/models for analyzing the data
Discounting	Rate at which future costs and outcomes are discounted
Sensitivity analysis	The chosen type of sensitivity analysis (e.g. one-way SA, probabilistic SA)
	The chosen variables whose values are uncertain are subjected to a sensitivity analysis

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, but also other approaches are used (e.g. discrete-event simulation, micro simulation).

Useful links:

International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has published guidelines for conducting and reporting modelling studies (Weinstein et al 2003) at http://www.ispor.org/workpaper/healthscience/TFModeling.asp

More detailed guidelines are in development for e.g.

- state-transition http://www.ispor.org/workpaper/modeling_methods/state-based-modeling.asp
- discrete event http://www.ispor.org/workpaper/modeling_methods/Modeling-discrete-event-simulation.asp
- dynamic transmission modelling http://www.ispor.org/workpaper/modeling_methods/Dynamic-transmission-modeling.asp .

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.

Issues specific to screening

Most of the costs of a screening programme incur within a relatively short time period and typically the benefits (e.g. life years gained or quality-adjusted life years gained) incur after a longer time period, while in many curative interventions both the costs and the effects occur immediately. .The consequences of discounting in cost effectiveness analysis are often substantial This means that the questions related to discounting need to be carefully examined. By attaching a lower weight to future health makes preventive health care seem less cost effective because such interventions typically involve current costs and future effects. The decisions to be made are; whether to discount both costs and effect or not, which discount rate to use, and should both, costs and effects, be discounted using the same discount rate? On this issue, please refer to possible national guidelines.

Meta-analysis

Theoretically, it is possible to conduct meta-analysis of economic evaluations, but is not generally used. The existing heterogeneity between studies would demand a great deal of adjustments, which are often not possible. Not only the methods used in economic evaluations vary across studies, but also more profound elements of the research questions, comparators, perspectives, health care systems, clinical guidelines, resource use and time horizon differ significantly (CRD, 2009).

Synthesis

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)

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

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. Presenting ICER alone, however, is not sufficient and it should be presented along with other separate relevant outputs of the economic analysis (absolute health benefits, number of patients, etc). ICER is one of the decision elements, alongside others. 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).

Cost-Effectiveness Plane and CEAC

Incremental Cost-Effectiveness Plane

The incremental cost and incremental effect can be represented visually using the incremental cost-effectiveness plane (Black 1990), which is divided into four quadrants through the origin. The horizontal axis

divides the plane according to incremental cost (positive above, negative below) and the vertical axis divides the plane according to incremental effect (positive to the right, negative to the left).

Cost-Effectiveness Acceptability Curve

Cost-effectiveness acceptability curve is a method of summarizing the information about uncertainty in cost-effectiveness. The CEAC shows the probability that an intervention is cost-effective at each ceiling ratio (or willingness-to-pay threshold), according to the available data. More detailed information about CEAC can be found in, for example, Briggs et al 2006; Fenwick et al 2006.

Reporting and interpreting

A common reporting format increases transparency of studies and facilitates comparison between studies. Several guidelines for economic evaluation have also suggested reporting formats and most of them include at least following items (Drummond & Jefferson 1996; Drummond 2005; CADTH guidelines 2006):

- Costs (direct and indirect costs) and effectiveness (life years gained, quality-adjusted life years gained, etc.) should be reported both in disaggregated and aggregated form. Also undiscounted values should be reported.
- An incremental analysis (ICER, ICUR), comparing the relevant alternatives.
- Conclusion drawn from the analysis, answering the original question of the study. Strengths and limitations of the study should also be reported.

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 an HTA in another country.

Table 3 Transferability of resource utilization and unit cost elements

Data Element	Transferability
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.

Health-economic data can be collected alongside a randomized clinical trial, so called piggyback evaluation. Advantages of this are the internal validity by trial design and practicality in collection of data on resource use and effectiveness simultaneously. The aims of clinical trials and economic evaluations, however, differ in significant ways, which can lead to disagreements in many aspects (time horizon, sample size, etc). (Drummond et al 2005)

As all relevant evidence is rarely available from a single source, the mostly used approach in economic evaluation is modelling: collecting the best available evidence from various sources and synthesising it using appropriate modelling techniques.

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Ethical aspects

Domain description

What is this domain about?

The term “ethics” is broadly used to describe activities relating to the understanding and study of “the moral life”. The term “morality” encompasses beliefs, standards of conduct, principles and rules which may guide personal and professional behaviour and the behaviour of institutions. Morals are standards that are widely shared, and that form some degree of social consensus (Beauchamp and Childress, 2001).

The ethical aspects domain encompasses the ethical issues raised by the health technology itself and by its implementation. The issues stem from the general values of the population, the aims of the healthcare system and from values arising from use of a technology. Ethical analysis also addresses specific issues inherent in the process of health technology assessment (HTA). In carrying out ethical analysis, prevalent norms and values in society relevant to HTA are considered. The weight given to these norms can differ between societies and countries. Socio-political, cultural, legal, religious and economic differences also have a major impact on the moral value societies will attribute to the consequences of implementation of a technology. However, many ethical considerations are common to all countries and societies, and are presented in the core model.

Why is this domain important?

Ethical analysis aims to provide a thorough understanding of norms and values that need to be taken into account during the HTA and in the decision making process. Moral values and norms form the basis of social life and they play a key role in shaping the context in which health technologies are used. Ethical analysis also reflects the fact that HTA is a value-laden process which should not be considered as a purely technical tool for maximising the health benefits of technology, since benefit maximising is of itself a normative aim that carries a priori assumptions about the goals of healthcare and healthcare expenditure.

Although addressing ethical issues is generally accepted as an important component of the HTA process, their integration to date has often been limited. It can be argued that “integration” is not the right word since ethics is already a part of HTA (Hofmann 2008). The challenge is to make it more explicit and visible. The need for, and weight placed, on ethical analysis can differ greatly between technologies depending on the purpose and context of their use (Grunwald 2004). For example, a new test that targets the same biomarker as the one it is intended to replace but does so with better specificity, sensitivity, safety and at lower cost is likely to be less problematic than a new, risky technology for a previously undiagnosable disorder.

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

Ethical considerations are especially relevant to screening, because:

- it targets healthy or asymptomatic persons, or those in whom disease is unsuspected,
- the risk/benefit balance is different from targeted diagnostics,
- test efficacy is reduced in low prevalence populations,
- the balance of risks and benefits of interventions may be different for screened early detected cases than for later diagnosed cases, and because
- screening raises moral questions of overdiagnosis and overtreatment.

Relation to other domains

Although ethical analysis is a separate domain in the HTA Core Model, moral issues are relevant to all HTA domains and the methods of ethical analysis should take this into account. Although some argue that ethical and legal issues should be kept separate from the rest of the HTA process (Duthie & Bond 2011) , it can be important to integrate the ethical analysis in the entire HTA process, including assessment and decision making. Ethical issues, rather than being a "one session" task or an add-on, the various topics and issues described in the assessment element have to be identified and addressed at different phases of the assessment process. This is important in order to ensure that decision-makers are presented with a complete picture, but also because not all ethical considerations are apparent early in the HTA: sometimes they emerge as the clinical or cost-effectiveness evidence emerges. For example, the assessment might indicate that the proposed technology is not cost-effective for subgroups who are protected by equalities legislation.

Specific features in finding, interpreting or implementing information for this domain

Values are inseparable from HTA (Hofmann 2005a), 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 (Hofmann 2005b; 2008). The more the technology presents new, severe or fundamental value conflicts, or challenges to everyday norms or beliefs, the more emphasis should be placed on the ethical analysis. Methods and significance of integrating ethical analysis in HTA have been explored and actively advocated in the INAHTA ethics working group (Andersen et al 2005; Burns et al 2011).

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 bearings of the recommendations. If the HTA organisation is clearly separated from decision-makers, it may be enough to describe the different norms, values, attitudes and arguments that should be considered by the decision-makers. The “first” ethical question to emerge – whether to select a topic for HTA – might also be outside the scope of some HTA organisations. Furthermore, successful integration of ethical analysis into the HTA process depends on recognising its importance and aligning its processes with those of the entire HTA organisation, not carrying it out as an add-on to selected HTA projects (ten Have 2004). HTA organisations will need the appropriate skills, understanding and resources to do this. According to recent study, only 17% of Canadian HTA reports addressed ethical issues (DeJean 2009). Separate sections on ethical aspects were rare in the reports: instead, superficial remarks about possible ethical issues were more common, or ethical issues were raised but not solved. Further, use of ethical experts was rare.

Integration of ethical analysis may take various forms in HTA organizations. Some methods align well with the more traditional approach of conducting HTA, e.g. hiring a bioethicist to conduct a separate chapter on ethics, 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.

Issues specific for (diagnostic technologies in) screening programmes

Screening technologies bring many ethical questions to participants, their relatives, health care system and the society as stated in the criteria for a screening programme (Wilson 1968 and the Danish council of ethics 2002). The condition sought should be a sufficiently important health problem both to the individual and to society to warrant considering allocating resources to a screening programme, but the decision to define a disease as an important health problem is of itself a value-laden one (Hofmann 2001). Ethical considerations will vary depending on whether the subject of the HTA is a diagnostic test used in primary or secondary screening. Primary screening deals with asymptomatic populations in which disease is possible if not actually yet suspected. In secondary screening, the population has already come into contact with the healthcare system because symptoms have arisen. In secondary screening for conditions with known adverse effects there may therefore be a greater imperative to identify and treat the condition, because the natural history of the disease, once it has been found, might dictate early treatment. For primary screening, the test is being given to an asymptomatic individual and this raises significant ethical issues that are discussed further below.
There are a number of considerations that govern the introduction of organised screening programmes. Some bodies have criteria to determine the appropriateness of programmes being considered for introduction across the population (eg UK National Screening Programme criteria, criteria for screening programmes in Finland). Such criteria can form a useful basis for the classification of issues to consider when initiating HTA on screening technologies. Some of these considerations are now discussed in more detail.

Organised screening programmes are usually targeted at healthy individuals, and involve the health care system contacting an individual and proposing an intervention to prevent disease and promote health. This implies a special responsibility for the health care system; the effectiveness and the safety of the screening must be guaranteed as well as the treatment that follows if the patient is found to have the disease. It increases the importance of clear and balanced patient information and decision aids in order to ensure informed consent to participation. The participants need to be well informed about the options they may face if the test is positive. Ethical analysis needs to be applied to the consequences of "false positive" and "false negative" test results as well as consequences of possible over-diagnosis and over-treatment have to be carefully evaluated and weighed against the expected benefits. Any of these may affect the medical, economic or legal status of individuals who participate in the programme.

There should be a suitable test or examination for screening, for which the following characteristics are known (eg UK national screening programme criteria):

- validity of the testing system
- sensitivity and specificity
- predictive value of the test(s)
- any concerns about safety or adverse events.

The screening test should be acceptable to the population. Where to set the limits for test accuracy (sensitivity and specificity) and who to include in the assessment of this (i.e. the acceptability to the population) are normative issues. If the proposed screening is for a disease that the programme planners wish to have identified at a latent or early symptomatic stage, it will result in people who feel healthy learning that they have a “disease”. The natural history of the condition, including development from latent to declared disease, should therefore be adequately understood.

Equity of access is a further consideration. Some technologies may be expressly addressed to reduce inequalities (for example, self sampling HPV tests or mobile mammography), while other technologies may carry a risk of decreased equity of access, such as regionalised assessment or colonoscopy vs. faecal occult blood testing. Information materials may, in attempting to be scientifically correct, be too difficult to understand, and thus act as a barrier for less educated people. The evaluation should also consider whether participating in the screening programme might stigmatize the participants or the test positive individuals.

Ethical evaluation of a screening programme has multiple perspectives as it may encompass the health care system from primary to tertiary level. General and technology specific ethical issues and consequences for various stakeholders (e.g. participants, their relatives in case of hereditary disorders, various levels of health care organization, screening test providers, screening health care professionals) need to be identified both before and during the HTA process. For each stakeholder, possible consequences of proceeding with or refraining from the implementation of the screening technology have to be identified.

There may be different ethical considerations for “case-finding” and screening carried out with the intention of treating. If screening is being carried out with the purpose of finding patients who need treatment, there needs to be an effective treatment available for the condition being screened for, and a clear referral protocol for subsequent treatment (as measured on, for example, physiological or other characteristics which may be found by the test). The costs of both screening and subsequent treatment will form part of the HTA

Assessment elements

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
F0001	Ethical analysis	**Principal questions about the ethical aspects of technology**	Is the technology a new, innovative mode of care, an add-on to or modification of a standard mode of care or a replacement of a standard?	The consequences of totally new screening programmes are likely to be more difficult to predict than the consequences of changing methods within an existing screening programme (breast screening and digital imaging), for individual values, attitudes and expectations as well as for health care systems. Novel screening programmes (screening for rare metabolic disorders in newborn), improved specificity of screening methods (ultrasound for fetal abormalities), or totally new screening tests (screening for maternal drug and alcohol abuse from hair or meconium) - 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	DTC, Organisational domains
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. Finding other acceptable possibilities for 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. screening for fetal abnormalities and on the other hand the concept of “design babys” through development of preimplantation diagnostics).	3	2	Literature search. Expert opinion. Stakeholder hearing	Ogletree 2004	Social

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
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.	The technology may be used for other purposes and have side-effects in addition to those following from the intended use. E.g. screening for fetal abnormalities may give information on gender. Unintended consequences may be difficult to predict (eg abortion due to unwished gender), but the intended purpose and uses of the technology should be evaluated against the likely uses and consequences of the technology. New technologies give rise to new ethical questions (e.g. screening for metabolic disorders in newborn with non-existing early treatment options). As pre-symptomatic screening tests have become available, the health care system has to be prepared to handle moral issues raised by true positive and false negative findings. Screening positive and being diagnosed with the disease may have effects on relatives as a all diagnoses of hereditary disorders, also provide knowledge of relatives. Screening positive may also affect social relations. In screening programmes by definition diagnostic information necessitates further action, so all screening programmes may have large impact on the health care processes and systems and on individuals. They may even change the concepts of disease if the definition of whom to treat as a patient is unclear (eg screening for aorta aneurysm).	3	2	Literature search. Expert opinion. Stakeholder	Ogletree 2004, Hofmann 2005b, Hofmann 2002b	
F0004	Ethical analysis	**Autonomy**	Does the implementation or use of the technology challenge patient autonomy?	Patients have in most cases a right to autonomy. This means both the right to decide, but also right to relevant information. The information should enable understanding the issues, enable considering it in relation to personal values, and deciding accordingly. Screening programmes represent complex technologies that may be difficult to be understandably explained to the patient (e.g.meaning of screening positive or negative and the possible risks associated with diagnostic tests and/or treatment) , as are screening programmes that require patients to behave in a certain way (e.g.dietary restrictions for fecal blood test). The practical challenge with screening programmes is that in order to be fully autonomous, the participating person should understand all alternatives following different test results and be able to make informed consent at every step.	3	2	Literature search. Expert opinion. Stakeholder hearing	Miller 2004	
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 cannot give informed consent to it?	3	3	Literature search. Expert opinion. Stakeholder hearing	Miller 2004	

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
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? Screening programmes to be used for early identification of life-threatening situations may have life-threatening side effects (e.g. treatment is invasive surgery with risk of death). Technology used to get exact diagnostic information for those screening positive may have unexpected severe side-effects (e.g. miscarriage due to amniocentesis).	3	3	Literature search. Expert opinion. Registers	Miller 2004	Safety
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 (eg. screening for drug abuse when use is denied). Technologies that align with professional ethics are more likely to be implemented successfully. For example, people may require a test or intervention for many reasons, even if the professionals think them unnecessary and potentially harmful (eg whole body MRI scans).	3	2	Expert opinion	Hofmann 2005b. Medical Professionalism Project 2002	DTC, Organisational.
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 (eg. screening children for fetal alcohol spectrum disorders). Some screening tests may label healthy people as sick (eg PSA for prostate cancer) or otherwise less worthy (screening for a non-dominant gene defect in fertile aged, screening for STD in school aged girls). Handicapped people may be labelled by prenatal screening programmes which imply that their handicap is an indication for abortion.	3	2	Literature search. Expert opinion. Stakeholder hearing	Kilner 2004	

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
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 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. Institutions that discourage honesty or ethical conduct are detrimental to integrity; for example, systems where lying about one's health state might lead to better treatment than being honest. Prenatal screening programmes might challenge the integrity of people who value new life as gift; screening for cervical cancer and/or HPV may be problematic for some religious groups.	3	2	Literature search. Expert opinion. Stakeholder hearing	Kilner 2004	
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 a 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 to participate at every possible step. 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.and Effectiveness

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
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, 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 prenatal screening and screening for metabolic disorders in newborn 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 treatment facilities may significantly alter the requirements placed on the health care system.	3	2	Literature search. Expert opinion. Stakeholder hearing	Autti-Rämö 2007 Beauchamp and Childress 2001	Organisational, Social
F0012	Ethical analysis	**Justice and Equity**	What are the consequences of implementing / not implementing the technology on justice in the health care system? Are principles of fairness, justness and solidarity respected?	A new intervention may require reallocation of human resources, funding and training. A large reallocation of resources may seriously jeopardize other patient groups. 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 and who would equally benefit for the programme? How can this be guaranteed? Could potential discrimination or other inequalities (geographic, gender, ethnic, religious, employment, insurance) prevent access? Are specific safeguards needed? If the technology is obsolete, does it possibly hinder some other, more effective innovative technology to be implemented? How will possible caregivers' burden and well-being be influenced? Potential inequalities and discrimination should be justified. Screening technologies sometimes acquire significant symbolic value (e.g. fetal ultrasound, PSA) that may create demands for tests that are not justified on health or public health grounds.	3	2	Literature search. Expert opinion. Stakeholder hearing	Sterba 2004 Daniels 2001	Cost-effectiveness. Organisational. Social

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
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	
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 screening programmes, issues of access to screening and diagnostic tests and treatments as well as labelling and potential discrimination of diagnosed persons may be relevant issues.	3	3	Literature search. Law, rules and regulations. Expert opinion. Stakeholder hearing	Marks 2004	Social. Legal
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. Screening and 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 assessment 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? Is legislation needed to ensure equal access? What kind of rules and regulations are needed to ensure good quality of high risk diagnostic tests and treatments.	2	1	Law, rules and regulations. Stakeholder hearing. Expert opinion	Capron 2004	Legal

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
F0017	Ethical analysis	**Questions about effectiveness and accuracy**	What are the proper end-points for assessment and how should they be investigated?	The acceptable and feasible endpoints must be carefully considered early in the analysis. The context must be especially considered; some technologies require extensive interpretative skills, and sometimes the consequences will depend on the target population. This is especially true in disorders related to life style. The importance of context relates to what kinds of studies are deemed acceptable. For diagnostic technologies and screening programmes, clinical effectiveness – improved health outcome -should ideally be directly investigated. This is not always possible so other endpoints may have to be used. In addition, screening programmes may have several aims (e.g. screening for hearing disorder in newborn - early institution of therapy and possibility for cochlear implant)The validity of patient reported outcomes need to be discussed especially in screening programmes where the outcome may not be disease free (eg. prenatal screening for congenital heart disorder requiring serial surgery postnatally)	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 (sensitivity and specificity) 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		

Methodology

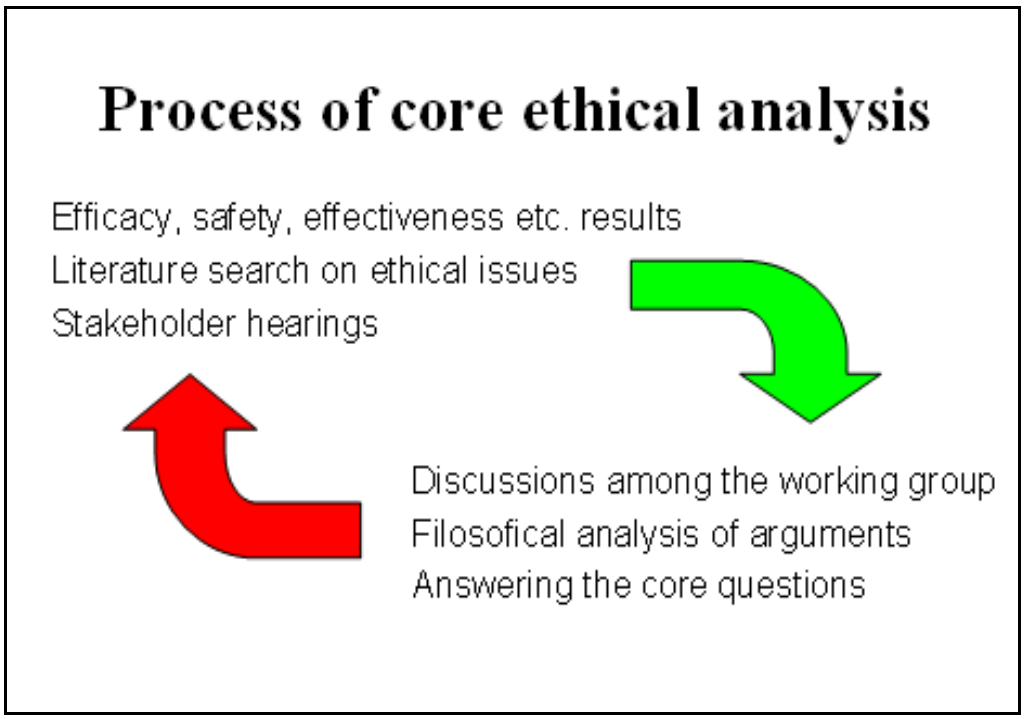
Where to find information?

Issues requiring ethical analysis should be identified systematically at the start of the HTA but assessors and decision-makers should be prepared to consider relevant issues that arise at any point in the HTA process. Information and evidence required to carry out ethical analysis in HTAs of screening technologies may need to be gathered from a number of sources, using various procedures. These may include:

- standard literature searching, which for ethical analysis will need to be carried out in a broader range of sources than for standard HTA;
- expert opinion, elicitation and professional guidelines;
- patient/service user opinion;
- views of organisational stakeholders, for example, the health system within which the technology is to be used.

The information gathering phase may require several iterations, where previous phases identify new needs and questions that might then be answered from other sources (Figure 1). Thus, it may be useful to repeat some phases following new insights.

Figure 1. Process of ethical analysis



Databases and search strategies

Evaluation of the principal questions about the technology, and the consequences of implementing or not implementing it are based on the information received from ongoing research on efficacy, safety, effectiveness and cost-implications of the technology. Organisations carrying out ethical analysis in HTA will need to consult a wider range of sources of literature than would normally be considered for scientific

evidence on clinical effectiveness. Academic sources encompassing philosophy, particularly ethics, law and social sciences should be searched. Grey literature, including legal case law, books and other monographs may also be of interest. Information retrieval for ethical assessment is likely to require more hand searching than information retrieval for effectiveness assessments. If these sources do not contain suitable literature in relation to the screening technology under consideration, searching should be extended to include other related technologies with similar ethical challenges (see casuistry below). A suggestion for databases and MeSH terms that can be useful has been identified by Droste et al (Droste 2003). Droste et al (Droste 2011) propose a methodological approach to literature searching for ethical analysis in HTA.

Expert and stakeholder opinion

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

What kind of information is required?

The focus of the assessment, 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 are defined by the entire working group, and may be incorporated into a formal scope or decision problem document. 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, even before any factual considerations about consequences of implementing or not implementing the related technology. For example, some types of screening may introduce gender bias or be used in conditions that are considered by some to be “self-inflicted”, which could lead to debates about access to treatment. Furthermore, some screening tests involve complex relationships, interests and outcomes: for example, prenatal screening tests may raise fundamental questions about the value of life and autonomy, and highlight competing interests of the embryo, mother, father, siblings or future possible siblings.

Some issues in the Assessment elements table deal with the direct consequences of the implementation of a technology (e.g. can the technology harm the patient?). Others relate to questions of value that need to be addressed when deciding on implementation, such as the impact of the technology on availability of healthcare resources for different patient groups, or the balance of benefit and harm for the population as a whole. Competing ethical considerations generally do not lead to clear conclusions and therefore judgement must be applied by assessors and decision-makers. Philosophical techniques such as deductive reasoning may be helpful in testing the logic and coherence of the arguments for stakeholders’ different viewpoints.

The perspective of all relevant stakeholders should be reflected in the process. It is usually fairly easy to identify the primary stakeholders for each technology - patients, clinicians, patient organizations, industry, providers etc. Making HTA project plans public as early as possible and allowing for public consultation may help identify relevant stakeholders and their fears early in the process. It is equally important to identify those stakeholders who will be indirectly affected if the technology is implemented, such as patient groups with competing interests in accessing healthcare resources. The views of stakeholders are best acknowledged early on in the process rather than during the external peer review process.

Ethical assessment and analysis

As we have seen, 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 still analysing other aspects of the technology. The results and insights gathered for the other domains guide ethical analysis. However, the ethical analysis phase should add to the process in a way that the other domains cannot. For each Core HTA project there should be a person responsible for facilitating and reporting the ethical analysis. For a successful ethical analysis, it is necessary that it is done together with scientific and clinical experts. If expert ethical advice is available within the HTA organisation this resource should be used. If it is not available, it should be acquired if possible at least for the application of the methods.

Although there is wide consensus that ethical analysis should be a mandatory element of HTA, there has been no generally accepted, structured method for performing ethical analysis. Identifying and defining the various methodological approaches has been conducted by the INAHTA ethics working group (Andersen 2005). Most of them emphasise the need to consider issues extending past utilitarian maximisation of cost-benefits of technology.

The methods must be tailored to suit the HTA organisation, the topic under study as well as the local culture and health care system. Standard HTA practices such as evidence grading are redundant in this context. 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. The following aspects determine the relative importance of ethical analysis in HTA:
   - The intervention is innovative, or appears to challenge commonly held values or societal beliefs. For example, HPV-screening is seen by some groups as “promiscuity testing”; prenatal screening (PND) and preimplantation genetic screening (PGS) are considered to be offensive by some people with the conditions that are screened for (the so-called expressivist argument).
   - In cases where screening (encompassing diagnosis and treatment) of an individual may have an impact on the health or treatment of relatives.
   - In cases where there is a pre-treatment test to identify a responding subgroup (stratified or personalised medicine), which may lead to restricted access to treatment.
   - When there are uncertainties about safe use of the technology or the long-term outcomes of both the diagnostic and the subsequent therapeutic technology
   - In cases where the intervention predominately affects a group protected by equalities legislation.
   - The accuracy level of the diagnostic test

b) The role and authority of the HTA organisation in the national decision making procedure. Decision making bodies and agencies providing guidance may have more explicit requirements for transparency for their stakeholders than academic or other bodies carrying out HTA. They may also have legal duties requiring them to avoid discrimination and promote equality. This may affect their approach to ethical analysis.

c) The methodological expertise and experience with ethical analysis that are available within or to the organisation.

d) Time and resource constraints for the assessment.

Methods for ethical analysis

The following approaches have been presented (and used) for ethical analysis in HTA.

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 underlie 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 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 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,
- Beneficience: 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 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 inter-subjective 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.

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 2005, 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).

Axiological (Socratic) approach

The axiological approach is based on the insight that science and technology is a social activity governed by a wide variety of norms and values. Health technology is applied in a social setting where there is interplay of different kinds of norms and values, HTA should highlight and address the norms and values involved in the implementation and use of a health technology. The reason why it is also called a Socratic method, is because it is based on a set of questions which are aimed at highlighting normative issues in the HTA as well as in the decision making process.
The (32) questions relate to:

- General moral issues, such as integrity, human rights, patient autonomy, benefit, harm, respecting social and religious convictions
- Moral issues related to stakeholders (patients, relatives, health care providers, industry, policy makers)
- Moral issues due to methodological challenges (end-point selection, quality assessment of study design)
- Issues typical to the technology (function, purpose, intention)
- Moral issues related to the HTA process itself.

The axiological/Socratic approach consists in six steps (Hofmann 2008).

1. Identify and analyze the moral challenges that are typical for the health technology.
2. Identify stakeholders.
3. Select a set of morally relevant questions by selecting from a list of questions (Hofmann 2005a; 2008) which highlight value issues in regard to the implementation of health technology. Justify the selection.
4. Perform literature search on the basis of the steps 1-3.
5. Analyze the selected questions (in step 3) on the basis of the literature search (step 4), hearings with stakeholders, and results from qualitative research.
6. Summarize the analysis and highlight the most important value issues.

The aim with addressing norms and values through the set of morally relevant questions is to provide an open, transparent and informed decision making process.

The axiological/Socratic approach has been applied to bariatric surgery (Hofmann 2010), newborn screening (Vist et al 2007; Heiberg 2009; Hofmann 2010), HPV-vaccine (Hofmann 2008; 2009), welfare technology (Hofmann 2008;2009), palliative surgery (Hofmann et al 2005), obstibation treatment in cancer care (Movik et al 2009), ICSI (Holte et al 2007), amalgam replacement (Håheim et al 2006), autologous stem cell transplantation in advanced breast cancer (Droste 2011), and other technologies. Moreover several HTAs include subsets of the questions in the axiological approach (DeJean et al 2009).

Examples of local application of these and other methods, see Appendix 2

Qualitative synthesis

The methods described above can be used to guide the elicitation of information, but their main use will be in presenting, analysing and balancing that information so that conclusions may be drawn, and the presentation can be used by decision-makers. The core set of questions in the Assessment element table is intended especially for identifying ethically relevant issues. The morally relevant issues and moral conflicts have to be synthesized and reported transparently so that they can be considered when deciding whether to implement a 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 variation in morals and values found within most societies. 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 both 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 or not implementing the technology may be handled using an open framework (Autti-Rämö 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 1). 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 1. 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				
Healthcare organisations (ie the organisations that own hospitals and provide healthcare)				
Other patient groups within the specialty				
Primary Health care providers				
Secondary Health care providers				
Tertiary health care providers				
Non-governmental organisations (NGO) representing patients who need the technology				
NGOs representing patients needing another technology which is withdrawn due to implementing the technology in question				
Payers				
Society				
Producers/Industry				
Decision makers				
HTA organisations				

It is important to identify also those areas where values may differ significantly between the various stakeholders (eg. attitude towards the care of patients with non-treatable diseases, treatments of extreme cost or conditions perceived as ‘self-inflicted’). The main areas of ethical controversy and competing interests should be clearly stated in the final document.

Reporting and interpreting

The results of the ethical assessment or analysis will usually be reported as a separate chapter, in order to assure transparent reporting of value issues. The ethical implications of implementing or refraining from the implementation of 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 set them out transparently.

Overlap with legal and social aspects

The results of the ethical assessment or analysis closely relate to the evaluation of legal and social aspects, although Duthie and Bond (2011) argue they should be clearly distinguished from one another. 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 social 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.

Transferability of ethical analysis

The ethical assessment or 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, and will crucially relate to factors such as the ‘social contract’, the funding system used for the country’s healthcare and the country’s GDP growth prospects. 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.

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Organisational aspects

Domain description

What is this domain about?

The organisational aspects domain considers what kind of resources (e.g. material artefacts, human skills and knowledge, money, attitudes, work culture) have to be mobilised and organised when implementing a technology, and the consequences they may further produce in the organisation and the health care system as a whole. The issues include e.g. quality and sustainability assurance, centralization, communication, managerial structure, and acceptance.

There are three levels to consider organisational aspects: Intra-organisational (e.g. how information about the new technology is provided to the patients in the organisation), inter-organisational (e.g. how the communications between different organisations occur), and health care system level (e.g. how to set down national objectives). There are various stakeholders, besides staff and patients, at various levels, e.g. payers, providers and suppliers. These groups have usually different aims and expectations of the technology. Some issues are relevant at all levels (e.g. approval of a new technology), and some mostly at one level. Viewpoints may be different in the various levels.

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)

Why is this domain important?

Organizational aspects have not been a visible part of HTA: focus has been more on the clinical aspects (Banta 2003, Draborg 2005). The growing focus of organisational issues in HTA indicates a recognition that many decisions on resource allocation in provision of technologies are of crucial importance. Organisational aspects in an HTA influence the behaviour 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. Organisational aspects in HTA may clarify challenges and barriers in implementing health technologies.

Relation to other domains

The organisational domain might overlap with most other domains: current use, effectiveness (through e.g. adherence), cost and economic evaluation (e.g. budget impact), ethical aspects (e.g. acceptance and accessibility), social (e.g. participant/patient aspects), and legal domains (e.g. privacy).

Specific features in finding, interpreting or implementing information for this domain

The complexity of health care systems and processes challenges the assessment of organisational issues. Due to the multiplicity of objectives and criteria in organisational analysis, it will be less pre-determined and more variable than for example economic 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 of assessment should be guided by the information needs of the end users of HTA (e.g. regional health authorities' focus may differ from that of hospital managers).

Issues specific for screening technologies

A screening program is a system incorporating all necessary steps, from identifying and providing information to the eligible population, through actual screening, to diagnostic testing and treatment. The assessment of a screening technology implies thus an assessment of a complex organization where organisational changes and relations within and between organisations are considered.

The screening technology under assessment can have various objectives and thus various implications for organisational aspects assessment. For example, when assessing mammography screening program, the focus can be either in a new screening test (digital mammography), or population eligible for screening (screening for women less than 50 years old), or varying screening interval (1 to 3 years), or the way to deliver the test (e.g. calling people to attend the fecal test versus mailing the test kit to them in colorectal cancer screening).

Regarding the population eligible for screening, the extent of the use of screening and waiting times defined in the Health problem and current use Domain, are of importance to the Organisational Domain. In the Description and technical characteristics Domain issues concerning definitions of the screening test and further investigations (diagnostic tests) are important also in the organisational domain.

Assessment elements

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
G0001	Organisational aspects	**Process**	What kind of work flow, participant flow and other processes are needed?	Current tasks and work processes and participant path should be described. Preparations of participants need to do before and after the intervention (e.g. diet before bariatric surgery) must be taken into account, as well as need for self/home monitoring. There are many actors at different levels (intra-organisational, inter-organisational and health care system level) in the process. Continuity should be ensured so that there will be no gaps between the steps of the process. It has to be described how the screening process has been organised, e.g.: 1) how the target population is chosen, 2) how and by whom the invitation is carried out (open/fixed invitation, announcement/personal invitation letter), 3) how and by whom the information for consent is given, 4) how, where and by whom the test is executed, 5) how, where and by whom the further investigations and treatment are carried out, 6) how, when, and by whom the follow up services are carried out (e.g notifying results, recalls, reminders).	3	2	Literature search, guidelines, annual reports and statistics, reports and own study (e.g. questionnaires and interviews of different actors)	Kristensen 2001, Kristensen 2007, Lee 2007	Mandatory: A0007, A0023, A0011, A0013, A0014, A0015, A0016, A0017. Other: B0004, B0005, B0016. Order of doing: to be answered prior to E0001

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
G0012	Organisational aspects	Process	What kind of quality assurance is needed and how should it be organised?	A new technology usually have an effect on current quality assurance not only inside the organization but also outside in different health care levels. To assure the quality, a monitoring system with standards and indicators are needed. It should notice how quality assurance affects the management or effectiveness. Screening involves asymptomatic participants and therefore quality control is crucial. There are national, regional and/or (cross)organisational (screening unit) demands for quality assurance. Quality control needs to be systematic at every step of the screening process steps and throughout the screening programme. Acceptable delay from screening test to test positive result and finally to treatment must be specify. Special attention has to be paid to the control when the programme is provided by several providers (e.g. a combination of private and public health care organisations) when test and further investigations are separated.	3	2	Literature search, annual reports and statistics reports of hospitals and own study: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratories). Information from manufacturers.		B0012, C0007, E0001
G0002	Organisational aspects	Process	What kind of involvement has to be mobilized for participants and important others?	The technology may require distribution of tasks among the people involved in the treatment and care. Participants and their important others may be more actively involved in own care and treatment – or tasks they used to carry out may be taken over by health professionals. The screening has to be organised in the way that the test and the further investigations are easily attainable e.g. mobile mammography.	3	1	Literature search, annual reports and statistics reports, hospital documents and own study: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory, participants).	Kristensen 2007, Lee 2007	A0006, A0007, A0023, B0014, B0015, H0002, H0003

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
G0003	Organisational aspects	Process	What kind of staff, training and other human resources are required?	How much staff is needed and what kind? How much trained resources are needed to ensure proper functioning? Different health care levels (e.g. primary and secondary care) should be taken into account. What are the needs for training and expert advice? Are there national, regional or in-house registries and criteria for personnel and training? How training affects the effectiveness? Implementing a technology can change the job and have thus influence on job satisfaction.	3	2	Literature search, guidelines, reports and documents of the hospital or hospital districts and own study: interview or questionnaires of different actors of the process.	Busse 2002, Kristensen 2001, Kristensen 2007	B0013, C0063, E0001
G0004	Organisational aspects	Process	What kind of co-operation and communication of activities have to be mobilised?	Implementing a technology can demand new co-operation and communication in- and outside the organization, e.g. other hospitals, pharmacies. Also interaction and communication with patients/participants and their important others will change. Adaptation of self/home monitoring needs close co-operation and fluent communication. Screening needs close co-operation and fluent communication between all actors of the screening process in all steps (e.g. screening unit, laboratory, hospital, registry, participants). There are actors at different levels which make the communication and co-operation challenging, especially when making up a new screening. The information must be fluent and electronic communication (software) is crucial. Adequate communication with participants and their important others must be taken into account. Different kinds of "patient information" could be defined for screening. For example: 1. "promotional/educational information" with the aim to involve target population and to promote participation 2. "screening related information" to communicate with participant the "phase related information" in the different phases of the process (e.g. sending invitation; communicating the test results etc.). Information strategies should be tailored to the specific subgroup of the target population (depending on socio-economic status, cultural background, epidemiological features, etc.). Risk families need special information.	3	2	Literature search, guidelines, reports and documents of hospital and hospital districts, guidelines, own study: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory, participants).	Kristensen 2001, Kristensen 2007, Senter för Medisinsk metodevurdering (SMM) 2003	B0015, C0063, E0001, H0007, H0008

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
G0005	Organisational aspects	**Structure**	How does de-centralisation or centralization requirements influence the implementation of the technology?	The setting (primary - secondary - tertiary care) can vary between different countries depending on the health care system. (De)centralisation could have some economical and qualitative benefits. Centralisation could make the technology more difficult to access. Sometimes screening test (for example maternal ultrasound) needs special experience from personnel which is possible after education and sufficient amount of patients. Centralisation could make screening or further investigation more difficult to access. For example timing is important in foetal screening. Decentralisation makes screening more attainable but the quality can weaken.	3	1	Literature search, guidelines, reports and documents of hospital and hospital districts, health information databases (DRG etc.), own study: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory, participants).	Busse 2002, Kristensen 2001, Kristensen 2007, Senter för Medisinsk metodevurdering (SMM) 2003	B0005, E0001
G0006	Organisational aspects	Structure	What kinds of investments are needed (material or premises) and who are responsible for those?	Implementing the required changes in e.g. premises may be costly for the organisation. High costs can influence the decision of purchasing the new technology. There may be division of costs so that some organisation(s) take the acquisition costs and others the running costs. Investments of all steps and actors of the process must be perceived. When building up a new screening programme, there's need for many investments (e.g. equipments, education and implementation support, training).	3	2	Literature search, guidelines, reports and documents of hospitals and hospital districts and manufacturers (e.g. producer handbook), own study: questionnaires and interviews of different actors of the screening process (monitoring authorities, hospitals, hospital districts, laboratory)	Kristensen 2007	A0011, A0012, A0019, B0008,, D0023, E0001, E0002. Order of doing: to be answered prior to E0001.

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
G0007	Organisational aspects	Structure	What is the budget impact of implementingthe technology?	Budget impact analysis is primarily intended to inform decision-making and budget planning, and thus the recommended perspective is that of the health are budget holder (on national, regional or local level). Variations of the health care systems of different countries influence this issue as there might be different payers (government/region/ municipalities/employer/insurance company) and the payer could change during the management process (e.g. municipality pays screening test but hospital district pays further investigations). When implementing a new technology initial costs are needed. Incentives are connected to this issue: What kind of incentives the budget impact imposes on different actors? How this potentially impact on the organization? National screenings are usually free of charge for people, but sometimes participants have to pay e.g. hospital fee for further investigations.	3	1	Literature search, reports questionnaires and interviews of different actors of the screening process (monitoring authorities, hospitals, hospital districts, laboratory), information from manufacturers.	Mauskopf 2007 , Kristensen 2007	A0011, E0001, E0002

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
G0008	Organisational aspects	**Management**	What management problems and opportunities are attached to the technology?	The issue concerns the administrative / managerial questions of technology: management of resources (e.g. investments), co-ordination (in relation to different levels and different steps of the process), establishment of objectives, monitoring and control, evaluation and sanctioning. Data/information management systems connected to each of these points have to take account.	3	2	Literature search, guidelines, reports and documents of hospitals, own study: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory).	Kristensen 2007, Weinstein 2003	A0011, A0012, A0015, A0016, A0017, H0009
G0013	Organisational aspects	Management	What kind of monitoring requirements and opportunities are there for the technology?	There may be different monitoring systems for different phases of the process where the technology is used (e.g. personnel registry or quality control system). These registries are part of quality assurance. It is necessary to define validated/recommended indicators (guidelines for QA, or other documents). A core data set is needed to monitor the phases and to produce the recommended indicators. The information flow should be analysed.	3	2	Literature search, reports and documents of hospitals and hospital districts, guidelines, own study: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory).		A0013, A0014,

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
G0009	Organisational aspects	Management	Who decides which people are eligible for the technology and on what basis?	Information about the possible variations in the decision level and criteria has ethical implications. Decisions about the people eligible for screening is done in the beginning of the screening. Usually, it has been made nationally or regionally (in municipalities) but also locally (by employers). In systematic screening, the screening unit does not make decisions about who is eligible for screening. The management of positive test result needs systems to guarantee proper follow up and sometimes case specific evaluation. In this topic responsibilities should be identified.	2	2	Literature search, guidelines, documents of hospitals, own study: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory).	Kristensen 2007	F0012, I0012
G0010	Organisational aspects	**Culture**	How is the technology accepted?	Acceptance should be looked at by different perspectives: by organisation, by personnel and by participants. Organisational view can be separated out intra-organisational (primary care), inter-organisational (secondary care) and health care system level. In allthese actors/views acceptance could vary. Alternative ways to introduce a new technology into the organisation could influence problems e.g. resistance among staff and dysfunction of processes. Acceptance could vary in the same screening process for example in foetal screening someone accepts ultrasound but not chromosomal (serum) test. Example of organisational acceptance: Sometimes screening could consist of elements which are not suitable for the image of the organisation. Screening is voluntary and for persons eligible for screening both decisions are right decisions: to participate or not. Giving understandable information on pros and cons of screening is important. Communicational skills of personnel may have an influence on acceptance of screening.	3	2	Literature search, own study: questionnaires and interviews of different actors of the screening process (monitoring authorities, hospitals, hospital districts, screening units, laboratory, staff, participants).	Kristensen 2007	F0007, H0006

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
G0011	Organisational aspects	Culture	How are the other interest groups taken into account in the planning / implementation of the technology?	It may be useful to know who are the possible stakeholders, as well as what kind of co-operation exists and what kind of interaction is needed. The stakeholders could be e.g. the pharmaceutical industry and companies offering technologies for screening, authorities (national / regional), registry, administrative parties, municipalities, policy makers / decision makers, staff groups, GPs/primary care physicians and patient organisation. One can also ask: Has the patient organisation taken part into the evaluation process? Has it been involved from the beginning (in the planning) or in the later stages for example as commentator?	2	1	Literature search, reports and documents of hospitals, own study: questionnaires and interviews of different actors of the screening process (monitoring authorities, hospitals, hospital districts, screening units, laboratory, manufacturers, registry, participants).	Kristensen 2001, Kristensen 2007, Senter för Medisinsk metodevurdering (SMM) 2003	F0003, F0011

Methodology

Where to find information?

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. Sometimes it is needed to carry out primary study about specific issues for example work processes.

Databases and search strategies

Organisational studies could be found in different databases. Selection of databases depends on the context. The most important databases are:

- Medical databases: Medline, Medline in Process, Cochrane Library, HTA, DARE, NHS EED, Cinahl
- Social Science databases: Sociological Abstracts, Social Services Abstracts, Social Care on line / Caredata and SocINDEX, PsycInfo, ASSIA (Applied Social Sciences Index and Abstracts)
- Administrative studies: General science publishers' databases such as Emerald Library, Science Direct and Ebsco Academic Search Elite, Pub Med Central (PMC) and Bio Med Central (BMC), ProQuest Health Management
- Educational database: ERIC
- Gray literature: Dissertational Abstracts, conference proceedings (Web of Science database); Scirus (reports of hospital studies and doctoral thesis), OAIster
- GIN guidelines

Other useful sources and links

- Registers, e.g. national screening registry;
- international, national and regional routine collected statistics (Health Information Database DRG);
- national and regional health care providers and authorities;
- national and regional guidelines;
- expert opinions;
- patient associations;
- experience of organisations e.g. NHS Technology Adoption Centre http://www.technologyadoptionhub.nhs.uk/; and
- manufacturers' handbooks and direct contacts.

Own research

When necessary, primary research could be carried out according to the co-production approach, but it will usually be very time-consuming. There are several possible 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.

What kind of information is required?

Framework

In a complex system, such as health care, the boundaries are typically fuzzy and activities of different agents are not predictable. Multiple approaches are needed in this kind of systems (Pselk 2001). Through different theoretical frameworks we can understand how various organisational functions operate.

One approach to address health care systems is to divide them into micro level (patient interaction), meso level (health care organization and community) and the macro level (health policy). All these levels have been taken into account while defining the issues of the organisational domain. 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 relation between technology and organisation can be tackled in different ways. At least two different and incompatible views on causality and transferability can be differentiated with respect to the organisational issues: the diffusion model and the translation model, see Appendix 3 (Kristensen 2001, Latour 1987). Parallel viewpoint is seen in the social domain.

The definition of organizational analysis in this document 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 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).

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.

Study types, design, outcome measures

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 involve qualitative methods such as interviews or observations, or quantitative methods such as surveys (Kristensen 2001).

Qualitative study is the mostly used study type in organisational domain (Table 1). In this kind of research approach the scope of relevant evidence is not known in advance and therefore the search method is usually iterative. The collected information of iterative search could be systematic only if the search steps have been documented carefully.

The review question should be based on PICO (Patient, Interventions, Control, Outcomes), see Appendix 3. Within qualitative evidence synthesis SPICE (Setting, Perspective, Intervention/Interest, Comparison, Evaluation) (Booth, 2004) or PICo (Population, phenomena of Interest, Context, outcome) (Joanna Briggs Institute 2008) could be more eligible for formulating a question.

It depends on the research question what kind of study design gives the most reliable answer to it. Both quantitative and qualitative studies and their synthesis are essential in the organisational domain. Although the most important sources of information are observational and qualitative studies, it is good to check if there are controlled or quasi-experimental studies available. Other types of relevant information for organisational issues can be found in national and international guidelines, statistics and registers and handbooks.

Issues specific for screening technologies

Policy measures, such as the choice between organised and opportunistic screening, or the reimbursement/funding strategies are implemented at the macro level and are likely assessed more appropriately by observational/qualitative studies; the organisation of screening services delivery at the institutional (meso- level) might be studied using qualitative research designs, but experimental studies may offer valuable and crucial information; similarly at the micro level of the interaction between provider and patients both experimental and qualitative evidence are important to assess screening technology.

Of course there are interactions across the levels and different actors may be involved at more than one level (i.e. the provider is involved both at the meso and at the micro level).

Tools for critical appraisal

There are different study types used in the organisational domain and therefore the range of quality assessment and appraisal instruments available to assess studies is wide. These are presented in table 1. Examples of quality assessment and checklists of different study types are shown in the appendix 3. Some of the appraisal instruments are generic and others targeted to specified contexts. For quantitative studies assessment of quality is clearer than for qualitative studies. It has been claimed that quality of qualitative study cannot be determined by prescribed instruments. Therefore using checklist or scales on quality assessment of observational or especially of qualitative studies is not always relevant.

Table 1

Issue	Study type	Quality assessment	Systematic vs other	Synthesis
What kind of work flow, participant flow and other processes are needed?	Guidelines, observational, mostly qualitative	AGREE, or other methods to evaluate guideline quality, tools for qualitative study appraisal	Not necessarily systematic	narrative
What kind of quality assurance is needed and how it should be organised?	Obervational, qualitative and quantitative. Intervention studies are possible, usually not controlled (pre-post), randomisation is not possible for most of the interventios	Relevant. Tools for RCT and observational study evaluation, tools for qualitative study appraisal	Not necessarily systematic, systematic for national and regional reports	narrative
What kind of involvement has to be mobilized for participants and important others?	RCT or systematic reviews of RCTs; observational quantitative and qualitative. Guidelines.	Relevant. Tools for RCT evaluation. AGREE.	Systematic	meta-analysis for most commonly evaluated intervention, narrative for less common and complex interventions
What kind of staff, training and other human resources are required?	Guidelines, scientific soc. consensus, Obervational, qualitative and quantitative	Not relevant, tools for qualitative study appraisal	Not necessarily systematic, systematic for national and regional reports	narrative
What kind of co-operation and communication of activities have to be mobilised ?	Observational, mostly qualitative. Guidelines.	Not relevant, tools for qualitative study appraisal.	not necessarily systematic, systematic for national and regional reports	narrative
What influence decentralisation or centralization of the technology will have?	Guidelines, observational, mostly qualitative. Health Information Databases (DRG etc.)	Not relevant, tools for qualitative study appraisal	not necessarily systematic	narrative
What kinds of investments are needed (material or premises)?	Guidelines, producer technical handbooks.	Not relevant	systematic at least for technical requirements	narrative
What is the budget impact of implementing the technology?	Costing and budget impact analyses	Tools for the evaluation of economic studies	systematic	narrative
What management problems and opportunities are attached to the technology?	guidelines, observational studies mostly qualitative	Not relevant, tools for qualitative study appraisal	not necessarily systematic	narrative
What kind of monitoring systems are there for the technology?	guidelines, consensus, registries	AGREE, or other methods to evaluate guideline quality	systematic	narrative
Who decides which people are eligible for the technology and on what basis?	guidelines, consensus, protocols	AGREE, or other methods to evaluate guideline quality	not necessarily systematic, systematic for national and regional reports	narrative
How is the technology accepted?	observational, mostly qualitative. Scientific societies websites	Not relevant, tools for qualitative study appraisal	not necessarily systematic, systematic for national and regional reports	narrative
How are the other interest groups taken into account in the planning / implementation of the technology?	observational, mostly qualitative. Scientific societies websites	Not relevant, tools for qualitative study appraisal	not necessarily systematic, systematic for national and regional reports	narrative

Analysing and synthesizing evidence

Data extraction

Data extraction approach must be appropriate to the review question, the type of review and the available evidence. It needs to be systematic and transparent. Data extraction can be a subjective process and therefore the design of these forms should be undertaken carefully (CRD guidance 2009). The amount of information to be extracted should be directly related to the questions posed and must be balanced detail with usefulness (overly inclusive / minimalist data extraction form).

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. Example of data extraction form for qualitative studies is SUMARI done by Joanna Briggs institute (Joanna Briggs Institute 2008).

Biases

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)

Synthesis

Meta-analysis is rarely used in the organisational domain because most of studies are qualitative. 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 a focus on the same topic of interest. It can be an aggregative or interpretive process which requires authors to identify and extract evidence: categorizing the evidence, and combine categories to develop synthesized findings. Important is to understand why people feel or behave certain way and not just make a description of it (Noyes 2008).

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

Synthesis methods are classified in different ways and it has been argued weather it is acceptable to conduct syntheses of qualitative evidence at all, and whether it is acceptable to synthesize qualitative studies derived from different traditions. (Thomas 2008, Dixon-Woods 2007, CRD Guidance 2009)

Qualitative and quantitative findings could be synthesized in two ways: multilevel synthesis (separate and combined synthesis) and parallel (separate and juxtaposed synthesis) (Noyes 2008). Quantitative and qualitative studies can be synthesize together, one example is systematic review on teenage pregnancy and social disadvantage (Harden 2009)

Reporting and interpreting

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.

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Social aspects

Domain description

What is this domain about?

Social domain takes the patient or individual as a point of departure in an HTA. A technology may be practiced in hospital, primary care or at home. Implications for patients may though extend far beyond the original setting of the technology. The patient is not just a passive target for interventions in health care. He is also a human being with different roles – a family member, a citizen, an employee, a consumer etc. (Hansen 2007). His life takes place in various arenas: everyday life, homes, schools, workplace, health services, etc. The use of the technology may change the roles, skills and positions in both negative and positive ways. A new role can strongly affect all the arenas of one's everyday life and all the important others. Considerations of power, empowerment and stigmatisation are therefore essential (Hastrup 1997, Goffman 1990, Devereux 1963, Rose 1993).

Patients and carers give specific meanings and significance for health technologies. Perceptions are attached to feelings of hope, fear, or perhaps uncertainty as well as values of society (Hansen 2007, Lehoux 2006, Whyte 1997, Bech 1992, Douglas 1996). The social analysis is interested in all these aspects.

The analysis of social aspects of health technology can include at least two kinds of questions. The first set of issues focuses on the kinds of resources (people, support, money and so on) that have to be enacted and mobilised from the point of view of a patient before, during and after the implementation of the technology. The other set of issues focuses on the experiences, actions and reactions of patients with respect to the technologies as well as on the changes and consequences that the enactment of the technologies may further generate. These are for example changes that occur 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 social analysis of a health technology can be considered at two levels: micro and macro sociological. The first is related to the individual (inter-individual relationship, direct environment of a person, direct effects on an individual), while the second focuses on the society as a whole (views, attitudes, culture, norms and values). From a macro sociological point of view core questions are aimed at understanding the benefits and consequences of the technology for the target population, for specific groups (religious, ethnic etc.) and for the general population.

Figure 1 provides a view of different social aspects that are relevant from a patient's perspective (Hansen 2007). The model intends to show and map different aspects, which could be considered of relevance for a specific HTA analysis. Social domain chooses 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 1.

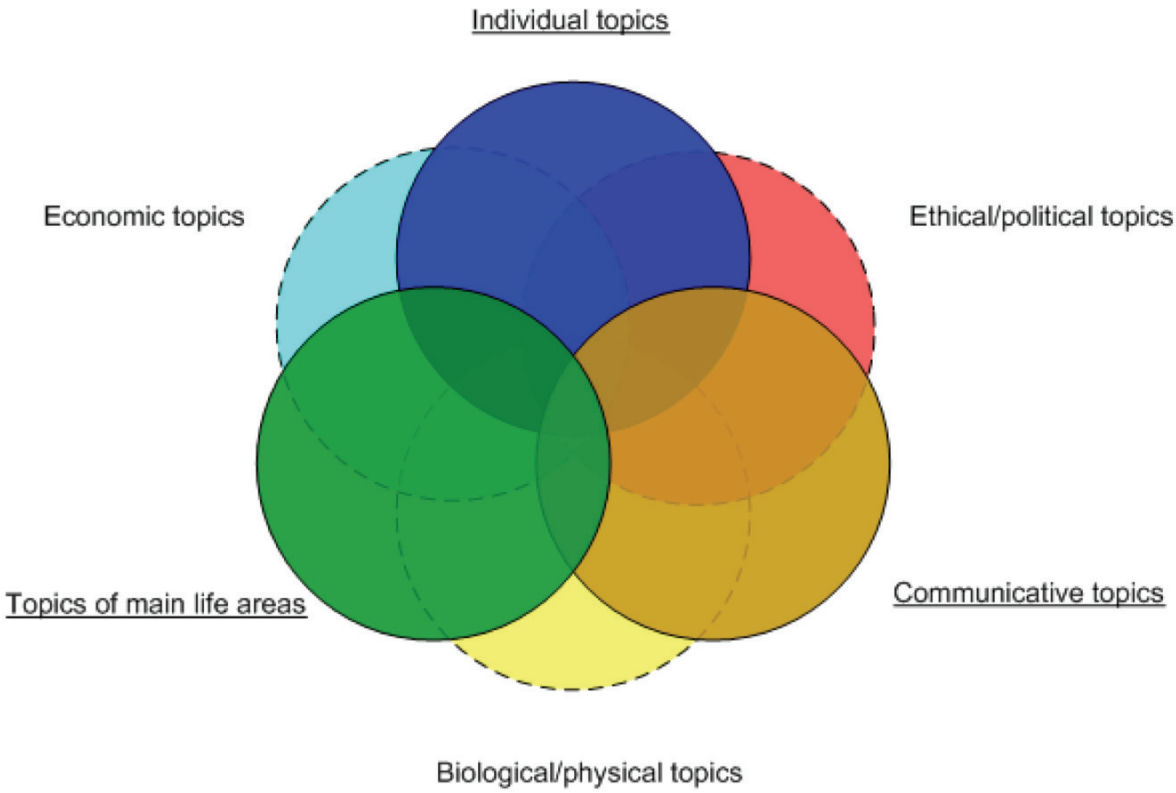


Figure 1. Social aspects of relevance from a patient perspective in HTA. Modified from (Hansen 2007).

Issues specific for screening technologies

Issues important in screening:

- attendance/participation to screening
- compliance to further assessment tests and treatment protocols
- patient and operator preference for the screening organisation and setting (in particular the between organised and spontaneous screening)
- acceptability of intervals (longer or shorter)
- attitude of the patient organisations to propose very aggressive and invasive screening protocols
- attitudes of clinicians to apply clinical protocol for differential diagnosis to screening protocols.

All these issues should be seen - from a social point of view - as in the aspects of the Council Conclusions on Common values and principles in European Union Health Systems (2006/C 146/01)that include quality, safety, care based on evidence and ethics, patient involvement, redress, privacy and confidentially.

Why is this domain important?

The technology does not produce the good results alone. Social analysis reveals the resources needed in individual's daily activities in order to achieve satisfactory results. Being satisfactory depends on the technology and its defined outcomes. The use of technology always produces some kind of changes or consequences in different spheres of social life, which should be anticipated. These can be positive or negative, or even unexpected (Rapp 1999, Kaufert 2000, Cambrosio 2000). The different meanings individuals give to a technology and its implication are important to recognize (Dreier 2000, Bourdieu 2000).

Relations to other domains

Patient perspectives are present in several other Domains:

- Ethical analysis domain
- Effectiveness and safety domains

- Costs and economic evaluation domain
- Legal domain.

The information from Social domain can guide the other domains e.g in defining important endpoints for assessment, Coordination is needed across the domains to cross feed and avoid overlap when preparing a Core HTA.

Specific features in finding, interpreting or implementing information for this domain

Technologies are not applicable everywhere. They work within networks of different human and non-human elements. Implementing a technology means that the technology and its entailing network has to be re-built in a new place (Koivisto 2007, Koivisto 2008). This is equally true for simple technologies, such as a single drug or a single device, as for complex interventions like screening or disease management programmes. Transferability of the social analysis results requires careful consideration of the comparability of the social and cultural circumstances presented in the published literature to the circumstances at hand.

Furthermore, social implications change over time as people put the technology to use, get accustomed to it, and find new ways of using it in combination with other technologies or practices. 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 consideration.

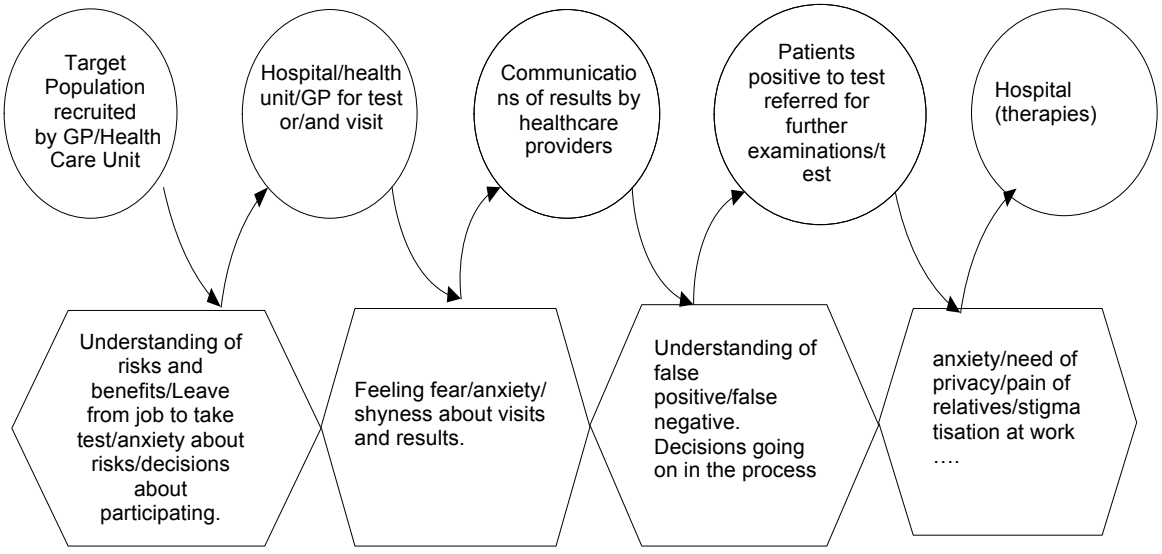
Issues specific for screening technologies

Equity in access is essential for the participation in the screening and thus the success of the screening program. The delivery modes of screening may have an impact on this. Self-sampler devices and the possibility to mail the sample instead of clinic visit and telephone reminder messages can affect participation, as well as mass media campaigns.

Correct and balanced information on benefits and harms of screening is essential for an individual to be able to make informed decision to participate screening.

Figure 2 illustrates the scope of social analysis by an example of the individual's itinerary in and outside the health services during screening procedure.

Figure 2.



Assessment elements

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
H0001	Social aspects	**Major life areas**	Which social areas does the use of the technology influence?	Map the major life areas of the patients or citizens using the technology, and their important others. Major life areas include family life, day care, school, work, leisure time, lifestyle, or other daily activities. The use of the technology can affect the final decision of the individual about participating.	3	2	Search for existing literature review, or collect primary studies and if possible conduct a litterateur review, or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals, patients, citizens, or important others can be consulted.	Hansen 2007	
H0002	Social aspects	Major life areas	Who are the important others that may be affected, in addition to the individual using the technology?	E.g. the results of screening or genetic and prenatal testing, may affect relatives.	3	2	Search for existing literature review, or collect primary studies and if possible conduct a litterateur review, or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals, patients, citizens, or important others can be consulted.		Ethical and Legal domains
H0004	Social aspects	Major life areas	What kind of changes may the use of the technology generate in the individual'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 (associated by the social norms and values defining the role) manner in major life areas.	3	2	Search for existing literature review, or collect primary studies and if possible conduct a litterateur review, or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals, patients, citizens, or important others can be consulted	ICF 2001: activities and participation, interpersonal interactions and relationships (chapter 7, d710-779), community, social and civic life (chapter 9:d910-d999). Douglas 1996, Goffman 1990, Hoffman 2005, Becker 1997	Ethical, Effectiveness, Safety and Legal domains

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
H0003	Social aspects	Major life areas	What kind of support and resources are needed for the patient or citizen as the technology is introduced?	This issue is about any kind of support and resources (practical, physical, emotional, information, personal, social, nurturing, financial etc.) to ensure the access and satisfactory results. It covers all arrangements or adjustments that may be needed in the major life areas (e.g. alteration of special tasks, working time, adjustments in the physical environment, emotional support, attitudes, reasons for (non)-participation.	3	2	Search for existing literature review, or collect primary studies and if possible conduct a litterateur review, or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals, patients, citizens, or important others can be consulted.	ICF 2001: environmental factors: support and relationships (chapter 3: e310-399); " activities and participation, chapter 6: d698, structural arrangements of patient's environment. Dreier 2000 Rapp 1999 Kaufert 2000	Organisational and Costs domains
H0010	Social aspects	Major life areas	What kind of social support and resources are needed for the providers as the technology is introduced?	This issue is about any kind of support and resources (attitude of providers, social gap between providers and patients, number of providers, time, documentation, flow for additional diagnostic or treatment, financial etc.) that need to be mobilized, and organized - or might be released to use the technology with satisfactory results.	3	2	Search for existing literature review, or collect primary studies and if possible conduct a litterateur review, or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals, patients, citizens, or important others can be consulted.		Organisational domain
H0011	Social aspects	Major life areas	What kinds of reactions and consequences can the introduction of the technology cause at the overall societal level?	Macro sociological aspect: This issue is about the broader society. What social reactions can be expected for example from religious groups, specific patients and citizens organisations and associations and from any other stakeholder groups (social burden with accepted versus stigmatising diseases)? Are special (social) risk groups defined (ethnic, age etc.) and their possible reactions assessed?	3	2	Search for existing literature review, or collect primary studies and if possible conduct a litterateur review, or, if relevant data is not available, conduct a stakeholder analysis and a qualitative/quantitative primary study; if there's no time the systematic collection of opinion of some of the involved stakeholders and interest groups can be done. Patients, citizens and important others can be consulted.		Ethical, organizational and Legal domains

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
H0012	Social aspects	**Individual**	Are there factors that could prevent a group or persons to participate?	Do providers select? Are special groups discriminated? It should reflect how the legal regulation takes place in practice. Ethical and social issues have often been considered in academic articles and discussions in the HTA field, but they have rarely been translated into practice.	3	1	Implement the best available evidence about social restrictions, social pressure, social attitudes		Legal domain
H0005	Social aspects	Individual	What kind of physical and psychological changes does the implementation and use of the technology bring about and what kind of changes do patients or citizens expect?	This issue covers whether, from a patient perspective, the technology leads to improvements or harms, or generates any other unexpected effects on functioning.	3	2	Search for existing literature review, or collect primary studies and if possible conduct a litterateur review, or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals, patients, citizens, or important others can be consulted.	ICF 2001, Good 1994	Effectiveness and Safety Domains
H0006	Social aspects	Individual	How do patients, citizens and the important others using the technology react and act upon the technology?	Micro sociological aspect: This issue is about the attitudes, perceptions, preferences, and satisfaction of the patients, citizens using the technology and their important other in relation to the technology. This covers whether, from a patient perspective, any positive or negative issues arise as a consequence of using the technology e.g. feelings of unity or empowerment and existential experiences, e.g. insecurity, worries, hope, anxiety, stigmatisation, person's value as a human being or social status, courage to face life, satisfaction, changes in self-conception.	3	2	Search for existing literature review, or collect primary studies and if possible conduct a litterateur review, or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals, patients, citizens, or important others can be consulted.	ICF 2001: body functions: mental functions (chapter 1:b110-b199), environmental factors: attitudes (chapter 4:, e410-499), Whyte 1997	Effectiveness and Ethical Domains

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
H0007	Social aspects	**Communication**	What is the knowledge and understanding of the technology in patients and citizens?	This issue explores the understanding of the technology in order to describe and decide what guidance and help (e.g. patient information leaflets, counselling processes, need of follow up consultation or help from other professionals) is needed before, during and after the use of the technology.	3	2	Search for existing literature review, or collect primary studies and if possible conduct a litterateur review, or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals, patients, citizens, or important others can be consulted.		Health problem and current use, Safety, and Organisational Domains
H0008	Social aspects	Communication	How do patients and citizens perceive the information they receive or require about the technology?	This issue is about the exchange of information from the patients' and important others' perspectives. What are their questions? How do they receive answers?	3	2	Search for existing literature review, or collect primary studies and if possible conduct a litterateur review,or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals, patients, citizens, or important others can be consulted.		Organisational Domain, B0014, B0015
H0013	Social aspects	Communication	What are the social obstacles or prospects in the communication about the technology?	E.g. limitations to decision making in participating or using the technology (dependent, passive user), and possibilities (empowered, active user)..	3	2	Search for existing literature review, or collect primary studies and if possible conduct a litterateur review,or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals, patients, citizens, or important others can be consulted.		Organisational and Ethical Domains

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
H0009	Social aspects	Communication	What influences patients' or citizens' decisions to use the technology?	What kind of societal influences lead patients to decide to participate? How do the provisional perceptions about the outcome influence the use of the technology?	3	2	Search for existing literature review, or collect primary studies and if possible conduct a litterateur review, about what works and what does not.		Ethical,Effectiveness and Legal Domains

Methodology

Where to find information?

Issues on the social aspects of technologies can be subject of the following fields:

- Medical Anthropology,
- Medical Decision-Making,
- Medical Sociology,
- Science and Technology Studies,
- Governance of Innovation Studies,
- Medical Ethics,
- Social Psychology,
- Communication science, and
- Health Services Research
- Health Sociology

Examples of relevant scientific journals: Health Expectations, Medical Anthropology Quarterly, Social Science and Medicine, Anthropology and Medicine, Sociology of Health and Illness, Qualitative Health Research, Values in Health, Medical Decision Making.

Databases and search strategies

Psychological/sociological databases such as

- Psychinfo,
- ASSIA (Applied Social Sciences Index and Abstracts),
- Sociological Abstracts and
- ISI Web of Science
- Social Services Abstracts,
- Social Care on line / Caredata
- SocINDEX

Euroethics (European Database Network on Ethics in Medicine, including:

- Biogea (Italy),
- Cendibem (Spanish),
- CRIB (Belgium),
- ETHINSERM (France),
- ETHMED (Austria, Germany, Switzerland),
- EUROETHIK (Germany),
- MIKS (Sweden).

Medical databases such as

- Medline,
- Embase,
- Cinahl**.**

Suggested search terms include: "social aspects of", "medical decision making process", "patient education", depending on the PICO question.

Useful other sources

Other sources of qualitative studies can be

- Citizens and patients associations
- WHO, OECD, ILO, UNESCO homepages and databases
- Citizens and patients associations
- Patients' (virtual) forums
- Structured systematic content analysis of Patients' (virtual) forums
- Structured systematic content analysis of Mass media

The use of qualitative sources should always be done in caution do to the high possibility for the subjective bias.

Own research

Primary study

If no relevant studies could be identified, it could be worthwhile to carry out primary studies, e.g. interviews and questionnaires. Timing of the primary study must be considered thoroughly. Appropriate time point for assessing the patient experience will be different with different technologies. Both ethical and practical considerations must be taken into account when deciding on whether to study people before, during or after using the technology. This choice may also have considerable significance for the results. Primary study, as any intervention, affects behaviour and practice. There must be clarity whether the effects noticed in e.g. an interview are related to the implementation of the technology or to the interview itself.

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 amount of knowledge on the views of respondents may be limited as it reflects participants' willingness to listen and talk. Even when talking the information is influenced by the positions and power relations of the professionals and patients, knowledge asymmetry, patient's dependency on doctor's goodwill and time constraints. Stakeholders may represent patient's perspective, but the evaluator should be critical to any political agenda.

Social analysis is both theoretically and empirically complex and demanding. Advanced skills in social analysis are required from the person conducting this part of the HTA. An assessment of patient and social aspects should not be a separate process within an HTA. Co-operation and interaction between the HTA team members is essential.

What kind of information is required?

Analytical framework

At least two different approaches can be differentiated with respect to the assessment of the social sphere. The approaches are 1) the diffusion model and 2) the translation model (see also Appendix 3). They imply different study questions and methods for the analysis of social issues. They were originally characterized by Latour (1987) and elaborated by Tryggestad & Borum (2001).

Diffusion model

The diffusion model bases on a linear, one-directional conception of causality. This model supposes that a technology has an inner causal power that can affect and change the individuals' life (micro-level), the organizations such as hospitals or health care centers (meso-level) or the national and international systems

(macro-level). From the point of view of citizens the model implies that a health technology can cause the people to work longer, it can change the way people live and it can improve the quality of life of people.

The adoption process of a technology typically includes (Rogers 2003):

- Technical knowledge about the technology
- Persuasion for the participation
- Decision for the participation or use
- Implementation of changes to decrease risk
- Confirmation for further use according to the time schedule of the program

According to the diffusion model, it can be asked

- which social impact will the implementation of the technology have?
- how does the technology change the social or working life of people?
- which strategies should be adopted to facilitate diffusion of the technology?

Translation model

The translation model sees technology as something endogenous. It cannot be separated from the health system, its users, and the context of use; it is not an independent and stable entity. Technology is a network of human and non-human elements that produces change. From the point of view of a citizen it is up to the perceptions and discretion of the people what they make with the technology or with the possibilities it offers. Constant interaction between the technology and people determines whether, in what ways, and how often the technology is used. Therefore the actual implementation of the technology may be different from policy makers' analytical expectations. The task of the evaluator is to reconstruct the chains of empirical events which are related to the implementation and utilization of the technology.

According to the translation model, it can be asked

- how much and what kind of resources (material entities, time, money, people, etc.) must be mobilized and organized in order to produce satisfactory result?
- what kind of behavioral patterns (such as resistance or compliance) or attitudes can influence/interfere use of the technology?
- how do potential users perceive its benefits and risks?

Study types, design, outcome measures

When estimating the applicability of published literature, it is important to consider contextual factors. There is no hierarchy in study designs of social research. Studies have to be evaluated according to their relevance for the issue at stake and quality.

A number of study designs, both quantitative and qualitative, are relevant. These include randomized or non randomized controlled trials, observational studies and open or semi structured individual or group interviews. For qualitative studies the relevance refers to the 'transferability' of the concepts to our setting, in knowing how far the findings help us to understand 'what is going on' in our setting (Green & Thorogood 2005).

Patient related outcomes are relevant also for many questions in 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 major consideration and impact on the content and conclusions of a HTA report. The technology may for instance have other patient related consequences than intended.

Tools for critical appraisal

Quality assessments should evaluate (Facey 2010).

- the purpose of the study and relevance to study question,
- context (population/setting/values),
- appropriateness of methods and theoretical framework,
- transparency of data generation, analysis and interpretation (avoidance of bias),
- connection between research question and conclusions (internal consistency in relation to the theoretical framework of the study) and
- the account of the knowledge generated given the methods (relevance for practice)

Quality assessment of qualitative research

In assessing qualitative studies it should be noted that generalizability of findings in statistical terms is often not the aim. In qualitative works study samples are rarely randomly selected because the logic of generalizability is here different. The aim is to provide in-depth ('thick') descriptions or to address particularities rather than to provide generalizable findings (Greeen & Thorogood 2005).

Another point is that researchers' judgment sometimes applies to the interpretations provided by qualitative studies. Although the researcher describes a certain issue from the point of view of participants, s/he simultaneously unpacks the issue in such a way that broader meanings and connections can be elicited. Therefore, the presence of researcher's perspective does not per se discredit the study. So long as the judgment is made consciously and articulated explicitly in the study, it may not be considered as a source of bias.

Guidelines for standards on qualitative research vary and are currently debated and developed. For further guidance, see e.g. Malterud et al 2001 or Hansen et al 2007. Another tool can be found in Green & Thorogood 2005, page 241 and Tong 2007.

Analysing and synthesizing evidence

Data extraction

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	

Qualitative synthesis

- **Thematic mapping**

Qualitative studies often involve generating evidence in the form of certain themes, concepts and trends. Thematic mapping means mapping out relevant sub-themes, and the assessment of the quantity, quality of existing literature related to them. Applicability of published information depends on its ability to give insight into social processes. Examples of sub-themes may be: how do illness or risk perceptions change family relations, roles, people's interaction with technology, unforeseen and unintended social consequences, or risk management. A thorough description of relevant themes and dimensions is more important than finding all relevant studies. It is also important to define the questions that cannot be answered on basis of the existing literature.

- **Other methods**

The synthesis of qualitative studies can be done according to different methods such as meta-ethnography (Noblitt 1988) or narrative analyses (Popay 2004). Guidance for making synthesis of qualitative literature can be found in method books (Petticrew 2006, Coren 2006, Social Care Institute for Excellence 2006). A critical interpretive synthesis on literature considering access to healthcare by vulnerable groups provides one example (Dixon-Woods 2006).

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Legal Domain

Domain description

What is this domain about?

The focus of the legal domain in a Core HTA is to detect rules and regulations that have been established to protect the patients' rights and societal interests. They may be part of patient rights legislation, data protection legislation, or provisions concerning health care personnel and their rights and duties in general. They may also incorporate prior approval processes by competent bodies.

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

1. Issues related to the central question of who the end-user of the diagnostic technology is;
2. 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;
3. Issues related to health care professionals rights and duties;
4. 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
5. Issues related to the process of acquisition of the technology; and
6. Issues related to the health care policy at the local, national, European and/or international level, such as distribution of health services.

Why is this domain important?

Legal issues form a substantial part of HTA in the future, since norms of professional ethics are continuously codified into statutes and European Union is producing ever more health technology related legislation. At the same time one must bear in mind national characteristics of legal systems and health care systems and policies, and thus 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).

Legal domain helps identifying the legal barriers which hinder the export and import of HTA results (Drummond & Weatherly 2000, Henshall et al. 2002, Hofman 2005, Terry 2004). It gives insight into the areas of health care legislation where harmonisation is needed, and provides tools for legislative and policy reforms.

Relations to other domains

Issues in Legal domain may overlap with

- Ethical/ social aspects: How to deal with the socio-economic impact of an adverse event? How are relatives and their legal rights affected?
- Costs: What is the impact of the legislation? Are there further costs to fulfill legal acts?

Specific features in finding, interpreting or implementing information for this domain

The systematic consideration of legal aspects is expected to contribute to the implementation of HTA results across the Europe. Information sources are contents of relevant international law, EU law and national law. The interpretation of “evidence” in the legal aspects depends on whether a legal regulation exists or not (i.e. for quality), or is planned. Sometimes existence of governmental guidelines and other soft law material makes detection of de facto applicable legal sources challenging.

Assessment elements

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
I0002	Legal aspects	**Autonomy of the patient**	Is the voluntary participation of patients guaranteed properly?	What kind of informed consent procedure is required by the law/binding rules? The use of screening programs is for symptom free (and probably healthy) people, therefore it must not compromise patient safety. Patients should not be pressured into such programs.	3	1	National, international, databases, legal binding guidelines, published laws, related or affected laws	EU Charter of fundamental rights (2000/C 364/01) Art 3;	Organisational domain
I0034	Legal aspects	Autonomy of the patient	Who is allowed to give consent for minors and incompetent persons?		3	2	National law	Convention on Human Rights and Biomedicine, Art 6 and 7	
I0036	Legal aspects	Autonomy of the patient	Do laws/ binding rules require appropriate counseling and information to be given to the user or patient?	It is important to provide information on the consequences of using the technology in such a manner that the patient can truly understand it.	2	2		Convention on Human Rights and Biomedicine, Art 5; Art 12	B0004
I0008	Legal aspects	**Privacy of the patient**	Do laws/ binding rules require informing relatives about the results?	The results of a test, or the incidental findings related to use any technology, may indicate that the relatives of a patient may have a medical condition that would need to be addressed. Do the laws/binding rules require breaking the privacy of the original patient in order to inform the relatives of their situation.	2	2		Directive 95/46/EC; Convention on Human Rights and Biomedicine Art 10. ECHR Case Law: Z. v. Finland Appl. 22009/93.	Ethical aspects, B0004

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
I0009	Legal aspects	Privacy of the patient	Do laws/ binding rules require appropriate measures for securing patient data?	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. Data security has to be provided within a national legal framework when processing claims data or therapeutic information.	2	1		Directive 95/46/EC; Convention on Human Rights and Biomedicine Art 10,	Organisational aspects
I0011	Legal aspects	**Equality in health care**	Do laws/ binding rules require appropriate processes or resources to guarantee equal access to the technology?	Is equitable access prescribed in the law or in practice, both at national and international level? The technology can be part of a public program or opportunistic. In many Constitutions equality of citizens covers also access to health care.	3	1		European Social Charter, 1996, ETS No. 163, Art 11 (1., 3.); Convention on Human Rights and Biomedicine Art 3; UN Covenant on Economic, Social and Cultural Rights (1966), Art 12. (Universal declaration Bioethics UNESCO (2005).)	Social, Ethical and Organisational Domains
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. Does subsidization enhance equal access?	2	1		Charter of Fundamental Rights of the European Union (2000/C 364/01). Art 35	Organisational and Costs Domains
I0035	Legal aspects	Equality in health care	Do laws/ binding rules require appropriate preventive or treatment measures available for all?	A screening program without the infrastructure to treat the detected diseases appropriately (and with equal access) would be unethical and senseless.	2	1		Additional protocol to the Convention on human rights and biomedicine on Genetic testing, Art 19 Genetic screening for public health purposes. CETS No 203 (2008).	In screening model only
I0015	Legal aspects	**Authorisation and safety**	Has the technology national/EU level authorisation (marketing authorisation, registration, certification of safety, monitoring, qualification control, quality control)?	Does the technology require approval and evaluation of a certain committee? Which? How are professional competences and quality of laboratories being governed? A European database of medical devices (EUDAMED) is under construction.	3	2		In vitro diagnostic directive (98/79/EC); EUDAMED;	Safety domain, B0004, B0011

Element ID	Domain	Topic	Issue	Clarification	Importance 3=critical 2=important 1=optional	Transferability 3=completely 2=partly 1=not	Information sources	Reference	Relations
I0019	Legal aspects	**Ownership and liability**	Does the technology infringe some intellectual property right?	Infringement of intellectual property rights can reduce the use of the 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; C-317/05 (ECJ), C-283/03 (ECJ).	2004/18/EC on public contracts.	

Methodology

Where to find the information?

International level/ European Union level

- Human Rights and Biomedicine Convention with its Additional Protocols
- European Human Rights Convention
- European Court of Human Rights
- internet database EurLex
- decisions of the European Court of Justice

National level:

- national legislation
- precedents of national High Courts

Contract level:

- provider/ payer

In addition to these, a survey on legal literature may be conducted. At European level such journals as e.g. European Journal of Health Law, Medical Law International, Medical Law Review and Medicine and Law may be scrutinised. It is also advised that national libraries' electronic databases are used to search for relevant international and national monographs and articles on the issue in question. Especially for medical issues and legal aspects articles can be searched in medical databases like Pubmed, where the term "legal" or "legal issues" can be combined with AND for the medical issue.

Interpreting and reporting

The report should follow the different levels of legal sources according to their power of influence on the implementation of the technology under assessment.

i) International law, particularly generated by the **Council of Europe.** The most important document in the field of medicine is the Human Rights and Biomedicine Convention with its Additional Protocols. However, these has not been ratified by all European countries, so their applicability needs to be checked in each case. Also various recommendations given by the parliamentary assembly of the Council of Europe may need to be considered. In addition, it may be necessary to investigate whether the European Court of Human Rights has given a relevant decision on the matter based on the European Convention on Human Rights. As new judgements arise in constant manner, knowledge of these needs to be updated regularly.

ii) The **level of European Union**. While the doctor-patient relationship does not directly fall under the authority of the Union, the Union may, however, issue health care related legislation regarding e.g. patient safety, free movement of (health care) goods and personnel etc. Hence, a search of relevant EC legislation is needed. Also, regulation related to free markets and competition law may become relevant in i.e., public procurement.

iii) The **level of national legislation**. As most of the EC legislation is given in a form of directives, it is necessary in each country to know the relevant national legislation in order to evaluate the exact manner of implementation. Also much of the health care related EC legislation is given as minimum directives and hence a stricter national control may apply.

iv) Agreements with and documentation provided by the technology supplier (**Contract level**). 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 it is advised that the scrutiny of these documents is made by a legally educated person.

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- http://curia.europa.eu/jurisp/cgi-bin/form.pl?lang=en
- COUNCIL OF EUROPE Treaty Office
- http://conventions.coe.int/
- EMEA Product Safety Announcements
- http://www.emea.europa.eu/htms/human/drugalert/drugalert.htm
- EMEA 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
- 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 searh page for the case law of the European Court of Human Rights)
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Council of Europe

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

Appendix 1 Information sources

Comment from coordinator: This appendix is in construction. This version includes some of the information sources clipped from the domain methodology sections. Its is not yet a comprehensive presentation of useful information sources for Core HTA doers. It will be updated and amended in the future versions.

Registers

Registers may act as an important information source for those involved in the conduct of HTA. Registers are usually managed by medical societies, scientific associations or government institutions; industry-managed registers also exist. Registers collect data for a defined geographical area, usually a single country. However, regional or even European registers also exist.

Registries commonly release periodic reports for disseminating findings and results. The reports are often open-access and downloadable free of charge from the homepage of the registry. Dissemination is also achieved by publishing specific studies or reports in specialised peer-reviewed journals. Registers include technology, procedure and disease registers.

Technology and procedure registers

Technology and procedure registers gather information on the use of specific technologies and procedures (e.g., knee arthroplasty register). A new case is registered in the database every time the technology is used (i.e. a procedure is undertaken, an intervention takes place). In some countries, there is an obligation to report the indications and consequences of using a technology before it is approved, for example when there is no high quality evidence to establish effectiveness and, or the safety of the technology.

Disease registers

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).

Regulatory institutions

EMA

The European Medicines Agency EMA www.ema.europa.eu is responsible for the scientific evaluation of applications for European marketing authorisations for both human and veterinary medicines (centralised procedure). It comprises over 40 national Competent Authorities in 30 EU and EEA-EFTA countries, the European Commission, the European Parliament and a number of other decentralised EU agencies.

- Once a medicine has been granted a Community marketing authorisation by the European Commission, the EMA publishes a full scientific assessment report called a **European Public Assessment Report** (EPAR)
  http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125&jsenabled=true

- All medicines for human and animal use derived from biotechnology and other high-tech processes must be approved via the centralised procedure. The same applies to all advanced-therapy medicines and human medicines intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases, as well as to all designated orphan medicines intended for the treatment of rare diseases.
- The EMA assesses medicines that do not require a centralised procedure - in cases where they have been referred to the Agency due to a disagreement in authorisation or use of the medicine between two or more Member States, or due to some other issue that requires resolution in the interest of protecting public health.
- The EMA monitors the safety of authorised medicines through a pharmacovigilance network, and takes appropriate actions if adverse drug reaction reports suggest that the benefit-risk balance of a medicine has changed since it was authorised.

Standardisation and regulatory concerns of medical devices

The government of each European Member State is required to appoint a **Competent Authority** responsible for medical devices. The Competent Authority (CA) is a body with authority to act on behalf of the government of the Member State to ensure that the requirements of the Medical Device Directives are transposed into National Law and are applied. The CA reports to the Minister of Health in the Member State. The CA in one Member State does not have jurisdiction in any other Member State, but they do exchange information and try to reach common positions.

In the EU, all approved medical devices are identified with the CE mark.

The ISO standards for medical devices are covered by

- ICS 11.100.20 standard for biological evaluation of medical devices http://www.iso.org/iso/products/standards/catalogue_ics_browse.htm?ICS1=11&ICS2=100&ICS3=20& and
- ICS 11.040.01 standard for medical equipment http://www.iso.org/iso/iso_catalogue/catalogue_ics/catalogue_ics_browse.htm?ICS1=11&ICS2=040 .

The quality and risk management regarding the topic for regulatory purposes is convened by ISO 13485 and ISO 14971. Further standards are IEC 60601-1, for electrical devices (mains-powered as well as battery powered) and IEC 62304 for medical software. The US FDA also publishes guidance for industry regarding this topic.

Medical Device Directives

The Medical Device Directive (Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, OJ No L 169/1 of 1993-07-12) is intended to harmonise the laws relating to medical devices within the European Union. The MD Directive is a 'New Approach' Directive and consequently in order for a manufacturer to legally place a medical device on the European market the requirements of the MD Directive have to be met. Manufacturers' products meeting 'harmonised standards'[2] have a presumption of conformity to the Directive. Products conforming with the MD Directive must have a CE mark applied. The Directive was most recently reviewed and amended by the 2007/47/EC and a number of changes were made. Compliance with the revised directive became mandatory on March 21, 2010. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31993L0042:EN:HTML

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

Other sources

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

Appendix 2: Examples of local approaches to ethical analysis

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 "c*omprehensive" 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 seperate 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.

Appendix 3. Shared methodologies

Comment from coordinator: This appendix is in construction. This version includes some of the methodologies clipped from the domain methodology sections. It is not yet a comprehensive presentation of useful methodologiesfor Core HTA doers. This work will continue during EUnetHTA JA2

Diffusion and translation models

The relation between technology and organisation can be tackled in different ways. At least two different and incompatible views on causality and transferability can be differentiated with respect to the organisational issues: the diffusion model and the translation model (Kristensen 2001, Latour 1987). Parallel viewpoint is seen in the social domain.

Diffusion model

- bases on a linear, unidirectional conception of causality
- considers technology as an exogenous and independent entity
- seen as a given object which stands outside or above the society, its organisations and actors
- supposes that technology stays constant
- sees technology be diffused and transferred from the innovator to different users

(Leavitt 1965)

Translation model (Leavitt 1965):

- sees technology as endogenous, as a part of the organisational and use process
- technology can't be separated from the organisation and its users
- technology does not stay constant during the implementation process
- human activity is a part of the technology in question
- asks "how many and what kind of resources (material entities, time, money, people, etc.) must be mobilised and organized in order to produce satisfactory results from a health technology."
- technology does not causally affect the organisation and change its social structures
- organisation and its work processes and social structures have to be organized so that good results can be produced from the technology.

(Leavitt 1965)

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Leavitt HJ. Applying Organisational Change in Industry: Structural, Technological and Humanistic Approaches. In Handbook of Organisations, edited by James G March. Chicago: Rand McNally. 1965.

General guidance to critical appraisal of published studies and other information

Critical appraisal of HTAs

[to be added]

Critical appraisal of systematic reviews

[to be added]

Critical appraisal of guidelines

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

Critical appraisal of trials

[to be added]

Critical appraisal of observational studies

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

- Newcastle Ottawa Scale http://www.cochrane.org/training/cochrane-handbook
- AHRQ: Systems to Rate the Strength Of Scientific Evidence http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=erta47
- Checklist of items that should be included in reports of observational studies (actually not meant for assessing quality): STROBE http://www.strobe-statement.org

Critical appraisal of diagnostic accuracy studies

QUADAS-2

Critical appraisal of modelling studies

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

References:

Weinstein et al. Principles of Good Practice for Decision Analytic Modeling in Health-Care Evaluation: Report of the ISPOR Task Force on Good Research Practices - Modeling Studies. Value in Health 2003;6:9-17. http://www.ispor.org/workpaper/healthscience/TFModeling.asp

Critical appraisal of economic evaluation

There are several methodological characteristics to consider, when assessing the quality of an economic evaluation. Several checklists have been published for reporting an economic evaluation, but also to help in identifying the strengths and weaknesses of different studies (e.g. Drummond 1996, Drummond 2005). An example of a checklist (by Drummond 2005) is:

11. Was a well-defined question posed in answerable form?
12. Was a comprehensive description of the competing alternatives given?
13. Was the effectiveness of the programmes or services established?
14. Were all the important and relevant costs and consequences for each alternative identified?
15. Were costs and consequences measured accurately in appropriate physical units?
16. Were costs and consequences valued credibly?
17. Were costs and consequences adjusted for differential timing?
18. Was an incremental analysis of costs and consequences of alternatives performed?
19. Was allowance made for uncertainty in the estimates of costs and consequences?
20. Did the presentation and discussion of study results include all issues of concern to users?

References:

Drummond M, Manca A, Sculpher M. Increasing the generalizability of economic evaluations: Recommendations for the design, analysis, and reporting of studies. International Journal of Technology Assessment in Health Care 2005;21: 165-71.

Drummond MF, Jefferson TO, on behalf of the British Medical Journal Economic Evaluation Working Party. Guidelines for authors and peer reviewers of economic submissions to the BMJ. British Medical Journal 1996;313:275-283

Critical appraisal of qualitative studies

Examples of quality assessment instruments:

- Critical Appraisal Skills Programme – CASP www.phru.nhs.uk/Doc_links/Qualitative%20Appraisal%20Tool.pdf
- QARI software by Joanna Briggs Institute. www.joannabriggs.edu.au/services/sumari.php
- EPPI-review by the EPPI Centre. http://eppi.ioe.ac.uk/eppireviewer/login.aspx
- Quality Framework UK Cabinet Office http://www.gsr.gov.uk/downloads/evaluating_policy/a_quality_framework.pdf
- Checklist of items that should be included in reports of qualitative studies (not checklist for assessing quality) COREQ http://www.aaz.hr/dokumenti/odjel-raz-ist-i-zdra-teh/edukativni-materijali/smjernice/7.%20Guidelines%20for%20qualitative%20research.pdf
- Popay et al (1998)
- The Mays & Pope criteria (2000)

Quality assessment of routine collected statistics and administrative data

Routine collected administrative data (e.g. DRG, discharge databases, reimbursement claims databases) can be useful too, when available. For example sickness funds collect great amounts of information which could be used to analyse utilisation of technology etc. However, analysis of this kind of data might be very time consuming, since data need to be “prepared” before analysis. By definition, these data has been collected for other purposes than research and they cannot be used to answer scientific questions without previous processing. This might not be feasible in the context of an HTA project, due to resource constraints.

The use of routine collected statistics has several limitations. The reliability of the diagnosis varies and usually it is not possible to differentiate between different stages of the disease. Even the validity of the coding of causes of death may be variable, and in some countries it is known to be very limited.

Own analysis of administrative data often requires authorization from the data owner, which in some countries might be difficult to obtain due to issues of privacy protection and confidentiality.

Critical appraisal of register data

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

General guidance to conducting own research

Guidance for modelling

International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has published an article describing the basic guidelines for conducting and reporting modelling studies. ISPOR is also developing more specific guidelines on different modelling methods.

References

Weinstein et al. Principles of Good Practice for Decision Analytic Modeling in Health-Care Evaluation: Report of the ISPOR Task Force on Good Research Practices - Modeling Studies. Value in Health 2003;6:9-17. http://www.ispor.org/workpaper/healthscience/TFModeling.asp

Guidance for conducting a register study

[to be added]

Guidance for conducting survey (questionnaire, interview)

[to be added]

General guidance for synthesis

Meta analyses of accuracy studies

No heterogeneity

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

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

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

Heterogeneity present

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

Paired estimates of sensitivity and 1 - specificity in original studies are plotted in a ROC plane. Regression model is used to fit the SROC curve (Moses 1993). If the SROC curve is symmetrical around the line where sensitivity equals specificity, the studies share one common DOR, and any variability is due to differences in the test threshold. In statistical terms, if in the model the slope b (estimated regression coefficient) is not statistically significant and approaches zero, The SROC will be symmetrical.

Spearman's test for a nonparametric distribution has also been used to test for a threshold effect. Using this method, the correlation between sensitivity and 1-specificity for each study is measured and a Spearman rank correlation coefficient > 0.6 is used to confirm variation across studies due to a threshold effect (Moses 1993). If the correlation is poor (Spearman rank correlation coefficient < 0.6) the variation between studies is attributed to other differences. This is a crude measure and is not generally recommended.

Threshold effect only

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

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

Heterogeneity that is more than just threshold effect

If the slope b in the SROC model is statistically significant, the SROC will be asymmetrical and the DOR changes along the threshold. In such cases advanced methods for fitting the SROC is used. Advanced methods to pool are indicated if heterogeneity in the results can be attributed to known sources of variation (see above Chapter Assessing heterogeneity). Otherwise the interpretation of the summary estimate is not possible (Lijmer 2002).

Possible sources of variation include

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

If differences in the results can not be attributed to these known sources of heterogeneity, then pooling of the results to one summary estimate should not be attempted, because its interpretation will be impossible (Lijmer 2002).

Methods to test for heterogeneity (Medical Services Advisory Committee 2005):

1. Plot the sensitivity and specificity from each study with their 96% confidence interval in a table and/or forest plot to illustrate the range of estimates and identify outliers.
2. If sufficient data are available, plot the paired sensitivity and 1-specificity results for each study on the ROC plane to detect heterogeneity and identify outliers. A small number of studies will limit the power of regression to detect heterogeneity.
3. Use a chi-square test for heterogeneity (Cochran's Q test) or Fischer's exact test for small studies to test the hypothesis that there is no statistically significant difference in the sensitivity and specificity reported.

Advanced models enable incorporation of covariates, e.g. population subtype in the meta-regression analysis. Poor reporting of primary studies may though lead to biased estimates. The two main advanced models are hierarchical SROC and bivariate meta-regression, and they are mathematically identical (Harbord 2007). Syntax to run these models in SAS, STATA, WINBUGS, S-PLUS and R are or will be available. Hierarchical SROC (HSROC) produces informative summary measures with confidence ellipses (Reitsma 2005). Model is infrequently used, probably due to complex fitting.
More reading: (Deeks 2001, Deville 2002, Kester 2000, Irwig 1995)

References:

Harbord RM, Deeks JJ, Egger M, Whiting P, Sterne JAC. A unification of models for meta-analysis of diagnostic accuracy studies. Biostat 2007 April 1;8(2):239-251.

Lijmer JG, Bossuyt PM, Heisterkamp SH. Exploring sources of heterogeneity in systematic reviews of diagnostic tests. Stat.Med. 2002 Jun 15;21(11):1525-1537.

Medical Services Advisory Committee. Guidelines for the assessment of diagnostic technologies. August 2005.

Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. Stat.Med. 1993 Jul 30;12(14):1293-1316.

Reitsma JB, Glas AS, Rutjes AWS, Scholten RJPM, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. Journal of Clinical Epidemiology, 2005 10;58(10):982-990.

General guidance for interpretation

Guidance for assessing applicability

Atkins et al. (2011):

- Step 1. Determine the most important factors that may affect applicability
- Step 2. Systematically abstract and report key characteristics that may affect applicability in evidence tables (highlight studies with a pragmatic approach and data on effect size of effect modification).
- Step 3. Make and report judgements about major limitations to applicability of individual studies.
- Step 4. Consider and summarize the applicability of a body of evidence

General guidance for reporting

EUnetHTA WP4 Policy Survey 2011

INSTRUCTIONS

WHAT IS THE SURVEY ABOUT?

We have identified 35 questions about the HTA Core Model and any information produced through using the Model. Answers to these questions define policies that steer the utilization of the HTA Core Model in the future. By now we have produced a document that lists various options for each policy, as well as some pros and cons of each option. At this point we want to hear EUnetHTA agencies' opinion on the policy options, so that we can define policies that as many agencies as possible can agree on.

WHO SHOULD RESPOND AND WHEN?

This task has been budgeted to WP4 Strand A, hence all WP4 Strand A agencies are expected to respond. All other EUnetHTA member agencies (partners and associates) are encouraged to participate to ensure wide variety of views. **Deadline for submitting your response is 16th of September 2011**.

WHO DECIDES ON THE POLICIES?

The set of policies is an official deliverable of WP4. Lead Partner of the work package will consider and discuss the results of this survey first within WP4 and makes then a proposal of a policy set to the Executive Committee. The EC may bring the set also to the Plenary Assembly for endorsement. WP4 Stakeholder Advisory Group will be consulted during the process.

WHAT SHOULD WE DO IN PRACTICE?

Please first read pages 1-5 of the document "Policies-2011-07-13.pdf", which contains more detailed information on the topic. Then rate each policy option with the following scale:

- Preferred = Your agency finds this a very good policy. You can assign this value to more than one options of one policy.
- OK = Your agency finds this policy acceptable, but another option would be clearly better.
- Bad = Your agency would not want to see this policy implemented
- Cannot say = Your agency is not sure if this policy is good or bad

As there are many policies and several options for each, we recommend that you first record your ratings in a paper copy of this pdf. After you have completed all policies, submit your response through an online questionnaire at the following address:

http://www.webropolsurveys.com//S/043E9F65E196AF04.par

This URL is common for all respondents. You can share it with your colleagues, but please send only one response per agency. The questionnaire is divided into 5 pages, each containing one section of policies. You can move between pages with buttons "next" and "previous". You can interrupt answering at any point by

selecting the “break” button. You will then receive a URL though which you can continue at a later point**. Be sure to submit your response after you have finished. Check the confirmation box on the last page and press “submit”.**

When preparing your response, please notice the following important aspects:

- Please respond by the 16th of September 2011.
- Your response should reflect your agency’s opinion on the policies, not your personal opinion. However, please observe that responding to this survey does not constitute a commitment on behalf of your agency with regard to the final decisions on the policies. We hope that you can in any case give us a realistic indication of your agency’s preferences.
- Please send only one response per agency. The invitation has been sent to several contact persons so please coordinate within you agency.
- Several of the policies may be strongly connected to the EUnetHTA business model and those policies may be affected by whatever choices are done within the business model development.
- Most policy options are presented in an order that changes from “open use” to “restricted use”. Hence in many cases the options are mutually exclusive, i.e. only one option can be selected as the final policy. In some cases, however, it may be possible to combine two or more options into a single policy that is well accepted.
- Please rate as many options as possible.
- You can write comments on each policy in the questionnaire.

If you have any questions or problems with the survey, please send an email to eunethta@thl.fi. Please notice that due to the summer vacation period, our response may take longer than normally. We will respond in the beginning of August the latest.